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# Cost of severe haemophilia in Toronto

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**Summary.** Our objective was to determine costs and trends in treating boys with severe haemophilia A before our centre routinely used prophylaxis. One reviewer extracted data from patient charts to determine resource consumption for 17 boys with severe haemophilia A from 1978 to 1998 at Toronto's Hospital for Sick Children. Resources included factor concentrate, doctors and health care professionals (physiotherapists/social workers), tests (laboratory, radiological and diagnostic) and hospitalizations. Subgroup analysis on those patients infected with HIV and/or hepatitis were also performed. Costs in Canadian Dollars were taken from standard lists and discounted at 3%. Total average cost (range) \$62 292 (3339–121 738) per year patient$^{-1}$; the largest fraction, \$59 910 (3103–119 480), 96.2% was accounted for by factor VIII. Hospitalizations accounted for \$1832 (0–5217) per patient year$^{-1}$ including drugs, nursing care and stay. Doctor and health care professionals visits averaged \$252 (36–462) and \$72 (0–175) per patient year$^{-1}$, laboratory and other tests cost \$201 (22–377) and \$26 (2–60) per patient year$^{-1}$, respectively. The average number of bleeds was 12.9 (2.0–22.0) per patient year$^{-1}$, decreasing since 1977 by 0.68 per patient year$^{-1}$ ($R^2 = 0.56$). Hospitalizations averaged 0.22 (0–4) per patient year$^{-1}$, lasting 2.3 days. From 1984, hospitalizations decreased by 0.025 patient$^{-1}$ year$^{-1}$ ($R^2 = 0.76$). Concurrently, the average treatment costs increased by \$5456 patient$^{-1}$ year$^{-1}$ ($R^2 = 0.81$). Clotting factor concentrate cost per patient increased by \$5521 year$^{-1}$ ($R^2 = 0.82$). Patients with virally transmitted diseases had considerable higher costs. The cost per year was substantial. Costs increased with virally transmitted diseases. Number of bleeds and hospitalizations over the period of study decreased and costs increased because of factor use in secondary prophylaxis.

**Keywords:** cost of illness, economic burden, factor VIII, haemophilia

## Introduction

The treatment of severe haemophilia A is associated with considerable costs [1,2]. The most important treatment for this disease, factor VIII concentrate, ranks among the most expensive drugs available.

In the period 1977–1998, several developments occurred, which had a large impact on the economic burden of haemophilia A. During this period, FVIII became available in larger quantities and with higher purity. Practitioners and researchers developed new insights into the management of the disease. However, many patients became infected with one or more viral diseases transmitted along with the clotting factor. All of these developments had a great effect on the treatment of haemophilia A.

The disaster in the haemophilia community stimulated a search for safe clotting factor concentrates. Initially, dry heat-treated concentrates were introduced, quickly followed by the introduction of high purity, plasma-derived concentrates treated during preparation with methods (e.g. solvent-detergent treatment) known to inactivate lipid-coated viruses such as hepatitis C and HIV. The high purity, plasma-derived FVIII and FIX concentrates were

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introduced in the late 1980s. In the early 1990s, recombinant FVIII (rFVIII) concentrates were introduced into Canada. These remarkable advances in haemophilia treatment have essentially eliminated the risk of transfusion-transmitted hepatitis C and HIV in persons with haemophilia. Reflecting these technological advances, the management of boys with severe haemophilia has now switched to the use of prophylaxis to prevent joint damage and ensure an excellent musculoskeletal outcome. Boys with severe haemophilia managed in this way have a much improved quality of life and a normal life-expectancy [3].

Several studies have calculated the incremental costs associated with prophylaxis vs. on-demand therapy, or utilization of different purities of FVIII products. Miners *et al.* [4] calculated an incremental cost of UK£547 (1998) per bleed averted associated with prophylactic treatment as opposed to on-demand treatment. Smith *et al.* [5] reported similar incremental costs (USD $1100) per bleed averted for patients using prophylactic therapy from 3 to 20 years of age. In a recent quality of life-based cost-study by Molho *et al.* [6] the authors reported mean annual treatment costs of USD $73 029 patient$^{-1}$ with severe haemophilia. These results clearly demonstrate the high costs of modern haemophilia treatment.

In North America, however, most patients have used prophylactic therapy following on-demand therapy or have used a combination of both approaches, in which on-demand therapy was followed by prophylactic therapy after target joint bleeding. The costs for these mixed treatment regimens of severe haemophiliacs have not yet been reported. When considering the current costs of using prophylaxis from a very early age (i.e. primary prophylaxis) the comparison should be to these mixed treatment regimens that have been widely used in North America.

In haemophilia A, the severity of the disease is a strong predictor of health-related quality of life. Patients with severe haemophilia A generally experience severe bleeding into muscles and joints and have the poorest musculoskeletal outcomes [7]. However, the treatment of haemophilia A is itself also considered to decrease the health-related quality of life [8]. This effect is probably related to the numerous i.v. injections for prevention or treatment of bleeding and the risk for infections, such as hepatitis C or HIV and also catheter-related infections. Consequently, we have chosen to examine only patients with severe haemophilia A in this study.

The purpose of this study was to determine the average total costs per year for the treatment of patients with severe haemophilia A between 1977 and 1998. Trends in the costs for the haemophilia treatments over these years were examined. Subanalyses were performed to contrast patients with and without virally transmitted diseases.

## Materials and methods

### *General analysis*

In order to calculate the total costs incurred with all aspects of the treatment of severe patients with haemophilia between 1977 and 1998, we performed a retrospective patient chart review. The analysis was conducted from the perspective of the Ontario Ministry of Health in Canada.

Data were collected from patient charts in the Hospital for Sick Children in Toronto, Canada. We included boys born between 1972 and 1981 with a diagnosis of severe haemophilia A (defined by a circulating FVIII level of <1%), who received clotting factor concentrate. All patients were followed until they were 17–19 years of age; therefore, we required that patient charts had to be complete for that time period. Patients with serious complications (e.g. inhibitors to FVIII, viral infections such as hepatitis or HIV), were not excluded from the study. The patients all attended the paediatric comprehensive care haemophilia clinic at the Hospital for Sick Children. During this time period, patients were usually treated with FVIII on-demand until their situation worsened or they developed a target joint (defined for the purposes of this study as any joint in which three bleeds occurred within a 3-month period). After development of a target joint, patients were treated with prophylactic FVIII for a period of 3 months or longer.

One reviewer (MK) extracted information from all patient charts; in case of uncertainties, a second reviewer verified the data. The extracted information about resources used was categorized and analysed according to five different groups, namely, factor use, hospitalization, doctor visits, health care professional visits and diagnostic tests. For clotting factor consumption, the number of units used per year per patient was calculated and multiplied by a price per unit. In a subanalysis, corrections for weight have been made by dividing the FVIII utilization by the average weight of the patient for each year. Hospitalizations were charged at a fixed rate per day, as is standard in Ontario. This charge included all hotel costs (i.e. bed and meals), nursing and other hospital services. Only doctors' consultations were charged separately.

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Consultations to doctors were counted and calculated per patient per year. For the first time a patient sees a doctor, a charge for a consultation is made, which is generally higher. After this visit, charges for general re-assessments are made. Costs for a consultation with a haematologist, rheumatologist, orthopaedic surgeon, infectious disease specialist or other specialists were calculated separately. Consultations to other doctors, such as a neurologist, hepatologist, dermatologist or gastroenterologist were calculated together using an average price per consult.

Health care professionals included clinical nurses, social workers and physiotherapists. Visits to these professionals were counted and costs were calculated per patient per year. Several tests were performed on the patients in the study period. We divided these tests into two types. The first type included laboratory tests, such as blood chemistry, haematology, virology and coagulation. The second type included other diagnostic tests, such as X-rays, magnetic resonance imaging and ultrasound examinations.

### *Subgroup analysis*

To investigate the influence of virally transmitted diseases on the resource consumption of severe haemophiliacs with virally transmitted diseases, subanalyses have been performed. Because most patients had combinations of HIV and hepatitis, these analyses have been done based on the state of disease per patient-year. For that reason, the total number of patient-years was divided into four groups: (i) without any virally transmitted disease, (ii) with HIV only, (iii) hepatitis (B and/or C) only and (iv) with combinations of HIV and hepatitis (B and/or C). Costs and consumption for these patient-groups have been calculated with the method described above.

We did not, however, assess the extra direct costs (such as antiretroviral drugs, etc.) because of viral infections such as HIV or hepatitis. About a decade ago, virus transmission was problematic in the blood supply system. However, manufacturers have implemented a number of safety measures that have eliminated that danger and most FVIII concentrates presently used recombinant, or high purity virus inactivated plasma-derived concentrates. Therefore, such blood transfusion-associated problems are unlikely to occur again in Canada.

### *Data analysis*

In the analysis, the costs within each group were calculated per patient per year. Costs were corrected for inflation using the Canadian Consumer Price Index and discounted at a rate of 3% per year, as suggested by Gold *et al.* [9]. From these numbers, total costs of treatment per subcategory and per calendar year, as well as averages, were calculated. Using linear regression, we calculated trends in costs for the period 1977–1998 [9]. All costs shown are in 2002 Canadian Dollars, unless otherwise stated.

Sensitivity analyses have been performed on the general results. Both the FVIII price and the discount factor have been varied. In this analysis, the prices of FVIII were varied in steps of 5 to +20 and −20% of the original price. The discount rate has been varied from the original 3 to 0 and 10%.

## Results

### *General analysis*

In total, 17 subjects met the criteria for inclusion in the study. Because of incomplete data from before 1977, we decided to limit our study to the period 1977–1998. Consequently, we followed up a cohort of 17 patients over a time frame of 22 years. In this period, patients were followed from the time of diagnosis up to the age of 18 years, representing a total of 297 person-years.

Of the 17 boys, the majority ($n = 11$; 65%) started receiving clotting factor soon after birth, five patients started at the age of 1, and one patient began at the age of 2. These patients used on average 70 160 units of clotting factor per patient per year or 1816 units $kg^{-1}$ $year^{-1}$. Over the period of study, there was a gradual linear increase in the usage by about 5864 units $patient^{-1}$ $year^{-1}$ (Utilization of factor units per patient = $\$5863.81 \times$ Year − \$879.62; $R^2 = 0.82$). The amount administered per kg did not show a trend over the years. There was no information available on the type or manufacturer of the clotting factor concentrate.

Fifteen of the 17 boys used their factor concentrate prophylactically during one or more periods. Prophylactic use was defined as a period in which clotting factor was administered three or more times a week for a period of more than 3 months. The average number of prophylactic episodes was eight times per subject (for these 15 boys). The average duration of the prophylactic therapy was 192 days (range: 90–547).

In Canada, all patients used plasma-derived clotting factor before 1992 and rFVIII after 1992. The recombinant clotting factor was slightly more expensive than the plasma-derived product. Prices of rFVIII varied between CAD\$0.75 and CAD\$1.70,

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depending on the source of the product (i.e. Canadian Blood Services 1997, Bayer 2000, Aventis Behring 2003).

**Table 1.** Unit costs in this analysis and their sources.

| Item | Unit cost | Year | Source |
|---|---|---|---|
| Clotting factor | \$0.24–\$0.76 | 1997 | CBS |
| Hospitalization (per day) | \$880.20 | 2002 | HSC |
| Haematologist consult | | | |
| First visit | \$111.25 | 2001 | SOB |
| Reassessment | \$40.75 | 2001 | SOB |
| Rheumatologist consult | | | |
| First visit | \$111.25 | 2001 | SOB |
| Reassessment | \$40.75 | 2001 | SOB |
| Orthopaedic surgeon consult | | | |
| First visit | \$55.60 | 2001 | SOB |
| Reassessment | \$24.40 | 2001 | SOB |
| Infectious disease specialist consult | | | |
| First visit | \$111.25 | 2001 | SOB |
| Reassessment | \$40.75 | 2001 | SOB |
| Other doctor consult | | | |
| First visit | \$111.25 | 2001 | Average |
| Reassessment | \$40.75 | 2001 | Average |
| Social worker consult | \$35.00 | 1996 | Estimate |
| Physiotherapist consult | \$35.00 | 1996 | Estimate |
| Blood chemistry laboratory test | \$40.56 | 2002 | HSC |
| Haematology laboratory test | \$11.96 | 2002 | HSC |
| Virology laboratory test | \$31.42 | 2002 | PHL |
| Coagulation laboratory test | \$28.60 | 2002 | PHL |
| X-ray | \$15.15 | 2001 | SOB |
| MRI | \$62.80 | 2001 | SOB |
| Ultrasound | \$24.05 | 2001 | SOB |
| Other tests (average) (e.g. bone scan, immunology test) | \$30.65 | 2001 | Average |

CBS, Canadian Blood Services; SOB, Schedule of Benefits [12]; HSC, Hospital for Sick Children, Toronto, Canada; PHL, Ontario Provincial Health Laboratories; MRI, magnetic resonance imaging.

We were able to obtain prices for clotting factor for several years from different studies that have been published (1996, US\$0.53 [5]; 1999/2000, GB£1.45 [10]). These data provided values for clotting factor prices from 1997 to the current time; however, it was not possible to obtain the prices of the FVIII concentrate that was used before 1997. Before 1992, human plasma-derived FVIII was used, which was generally slightly cheaper. For that reason, we decided to use the price of 1997 (i.e. CAD\$0.75) and made corrections for inflation using the Canadian Consumer Price Index for all the years studied (i.e. 1977–1998). With this method, prices varied from CAD\$0.24 in 1977 to CAD\$0.76 in 1998. Unit costs of all the resources in this analysis are displayed in Table 1.

The total overall cost (range) of all haemophilia-related treatments and services per year per patient were \$62 292 (range: \$3339–\$121 738). These costs increased from 1977 to 1998 by about \$5456 patient$^{-1}$ year$^{-1}$ (Average costs per patient = \$5455.9 × Year − \$3821.5; $R^2 = 0.81$). These results are graphically shown in Fig. 1 and displayed in Table 2. In the period with the greatest rise in costs, 1978–1995, they rose steadily by \$6919 year$^{-1}$ (Average costs per patient = \$9619.3 × Year − \$14 710.0; $R^2 = 0.95$), indicating a considerable increase in costs during the years in which all the innovations such as high purity plasma-derived and recombinant clotting factor concentrates and prophylactic therapy were introduced. This increase seems to be caused primarily by an increase in the use of clotting factor. There was a small decrease in the costs between 1995 and 1998.

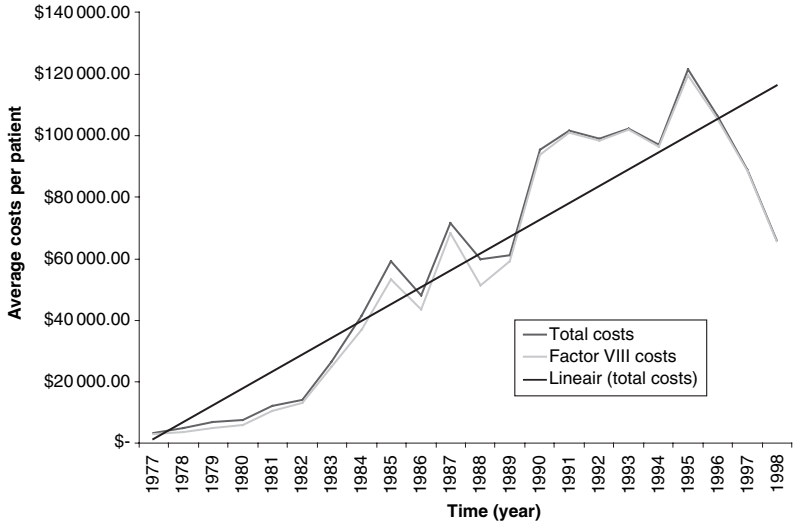


**Fig. 1.** Total cost and factor VIII cost per patient. Total costs per patient = \$455.9 × Year − \$3821.5 ($R^2 = 0.81$).

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**Table 2.** Overview of average costs per patient group.

| | | Subgroup analysis | | | |
|---|---|---|---|---|---|
| Resource costs per year | General analysis | No viral transmission | HIV only | Hepatitis (B and/or C) only | HIV and hepatitis (B and/or C) |
| Number of person-years | 297 | 153 | 24 | 73 | 47 |
| Average weight (kg) | 36.5 | 22.1 | 52.8 | 50.4 | 53.0 |
| Factor VIII | $59 910 (3103–119 480) | $25 629 (3103–78 867) | $85 448 (72 578–113 689) | $91 618 (13 205–147 111) | $109 213 (30 349–189 787) |
| Hospitalization | $1832 (0–5217) | $1319 (0–5424) | $6079 (0–29 797) | $1598 (0–22 169) | $1668 (0–5677) |
| Doctors consultations | $252 (36–462) | $249 (93–512) | $350 (133–749) | $135 (0–268) | $366 (215–696) |
| Health care professionals consultations | $72 (0–175) | $65 (0–137) | $113 (89–159) | $44 (0–186) | $118 (18–103) |
| Laboratory tests | $201 (22–377) | $130 (22–249) | $315 (131–451) | $188 (0–272) | $380 (104–586) |
| Other diagnostic tests | $26 (2–60) | $16 (0–39) | $209 (6–53) | $21 (0–192) | $63 (8–176) |
| Total costs | $62 292 (3339–121 738) | $27 409 (3339–79 218) | $92 336 (73 417–122 750) | $93 602 (13 770–155 433) | $111 809 (31 267–193 835) |

The discounted and inflation corrected costs for the use of clotting factor were on average \$59 910 year$^{-1}$ patient$^{-1}$, ranging from \$3103 in 1977 to \$119 480 in 1995. After 1995, costs decreased slightly. The increase in costs over the period 1977–1998 was about \$5521 year$^{-1}$ patient$^{-1}$, and occurred in an approximately linear fashion (Clotting factor costs = \$5521.1 × Year − \$6651.5; $R^2 = 0.82$). As with the total costs, for the clotting factor costs the period 1977–1995 had the most dramatic rise in costs, with an annual increase of \$6921 patient$^{-1}$ (Clotting factor costs = \$6920.5 × Year − \$17 073.0; $R^2 = 0.94$). The costs of FVIII per kg was \$1492 (range: \$275–\$2283) per year. These weight corrected figures for FVIII are displayed in Table 3.

During the same period, the average number of bleeds per patient per year varied from 21.9 in 1986 to 2.0 in 1998. There was a weak linear decrease in the number of bleeds in this period by 0.69 bleeds per year per patient (Number of bleeds = −0.69 × Year + 20.51; $R^2 = 0.58$; see Fig. 2). This trend indicates progress in the prevention of bleeds in haemophilia patients.

Of the 17 patients studied, 11 required hospitalization for 1 or more days. There were in total 673 hospital days over 62 hospitalizations in the study period, with an average of 2.01 days (range: 0–8.65) in hospital per patient per year or 0.20 (range: 0–0.57) hospitalizations per patient per year. The number of hospitalizations per patient decreased from 1978 to 1998 by approximately 0.02 year$^{-1}$ patient$^{-1}$ ($y = -0.02 \times$ Year + 0.49; $R^2 = 0.76$). The discounted costs incurred with hospitalizations were on average \$1832 year$^{-1}$ patient$^{-1}$ (range: \$0–\$5217).

The costs for doctor and health care professional consultations, laboratory tests and diagnostic tests are displayed in Table 2. These costs, \$551 patient$^{-1}$ year$^{-1}$ (range: \$79–\$820), account for 0.9% of the total costs and hospitalization for another 2.9%. However, clotting factor concentrate accounted for 96.2% of the total costs per year per patient.

### *Subgroup analysis*

Of this group of patients, none of the subjects was hepatitis A-positive, but four were positive for hepatitis B and 12 for hepatitis C. HIV infection had occurred in eight patients. Patient-years were divided into four groups and costs were calculated. The average costs per year of the patients in these groups are shown in Table 2. Costs were higher for patients infected with more diseases. The average


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**Table 3.** Factor VIII utilization corrected for weight.

| | | Subgroup analysis | | | |
|---|---|---|---|---|---|
| Factor VIII utilization | General analysis | No viral transmission | HIV only | Hepatitis (B and/or C) only | HIV and hepatitis (B and/or C) |
| Number of person-years | 297 | 153 | 24 | 73 | 47 |
| IU $kg^{-1}$ $year^{-1}$ | 1816 (539–2869) | 1320 (539–2281) | 2018 (1594–3689) | 2328 (493–7000) | 2533 (506–4929) |
| Costs $kg^{-1}$ $year^{-1}$ | $1492 (275–2283) | $1000 (275–1985) | $1744 (1472–2982) | $1978 (413–5402) | $2206 (433–4342) |

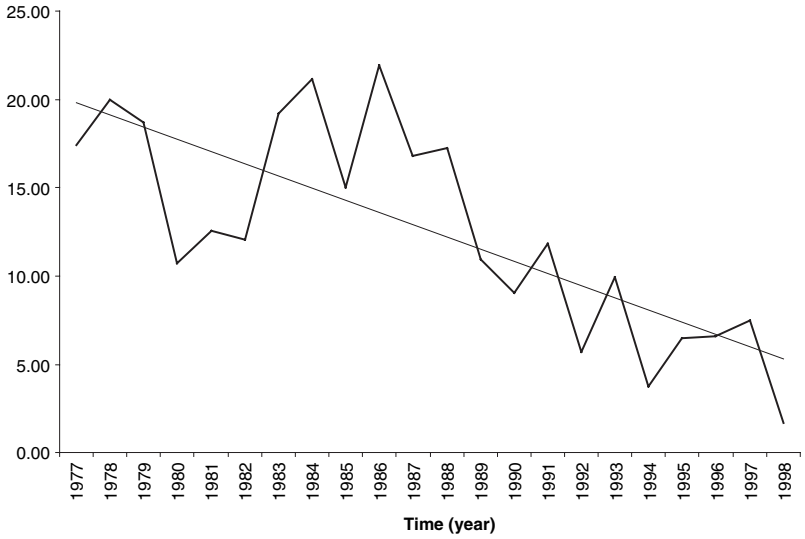


**Fig. 2.** Total bleeds per patient over time. Total bleeds per patient = $-0.69 \times \text{Year} + 20.5$ ($R^2 = 0.58$).

utilization and costs per kg per year are shown in Table 3. Both utilization and costs increased with more transmitted diseases.

### *Sensitivity analysis*

As the clotting factor accounts for 96.2% of all the costs, the results are likely to be highly dependent on the clotting factor price per unit. For a reduction of the FVIII price with 10%, the total average costs per year, decreased from $62 292 to $56 301. This is a reduction of 9.6%. For a cost reduction of 20%, an overall decrease of 19.6% was found. The same applied to increases of the clotting factor price with 10% and 20%. These numbers imply that the results are highly sensitive to the clotting factor price per unit.

We also conducted a sensitivity analysis varying the discount factor. For a standard discount factor of 3%, the overall average cost was $62 292. For the sensitivity analysis, we used a discount factor of 0%, in which case the costs became $44 770 and a discount factor of 10%, for which the costs became $137 594. This analysis shows that the results of this study are highly sensitive to both the discount factor and the clotting factor price.

## Discussion

This study affirms that the costs for the treatment of haemophilia A in Canada, even prior to the institution of primary prophylaxis, were considerable. Over all the studied years, we found a total average cost per patient of CAD$62 292, with clotting factor as the major price driver. This was in the same order of magnitude as the figure of USD$57 046 for full prophylaxis and USD$48 820 for partial prophylaxis reported by Bohn *et al.* [11]. Patients with one or more viral diseases had even higher costs than those without these diseases. Costs and utilization of resources in the treatment of haemophilia A were seen to increase with each newly diagnosed virally transmitted disease.

The costs calculated per year in this study were not corrected for the weight gain of the patients. FVIII is a drug that is usually administered based on the bodyweight of the subject. When the patients grow, the utilization of FVIII will increase. However, this research was done to study the costs for the utilization of FVIII and other services during a specified time interval, i.e. 1977–1998. It was not conducted to study the increase in utilization of these services during a patients' life. For reasons of

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comparability, we have however, made corrections for weight on the clotting factor utilization. The results of these calculations affirm the assumption of the higher costs and utilization of FVIII in patients with virally transmitted diseases.

The clear trends that were observed in this study on the increasing costs and utilization of resources over time are not evident when the results are corrected for the weight gain of the patients. This indicates that these increases are purely a result of the increase of clotting factor utilization caused by the greater weight of the patients as they grow. As was stated in the introduction, during the period 1977–1998, the treatment of haemophilia A developed greatly. FVIII became more available and in better, more purified forms. Consequently, it became clear that FVIII is the most effective treatment to prevent or treat bleeding and to minimize bleed-related morbidity, e.g. haemophilic arthropathy. Also, patients were sometimes treated with periods of prophylaxis, varying from several months to several years. Later, rFVIII became available. After the problems with viral transmission in the 1980s, Canadian haematologists switched almost completely in 1992 to this new and safer clotting factor.

The above described developments in this period may have encouraged doctors to administer larger amounts of FVIII to their patients. Our results suggest that even in the early 1980s (when there were known problems with viral transmission) there was little reservation of doctors to use FVIII.

The reason why the costs for the treatment of haemophilia A are decreasing in our study since 1995 may be twofold. First, most of the patients had reached the age of 19 years at the end of this study. It may be possible that the course of the disease in the studied population is improving. Secondly, it is possible that the prescribing doctors have gained more experience in treating the disease and are able to treat haemophilia A with less FVIII than in the recent past. These possibilities merit further study.

In our sensitivity analysis, we found that the results were highly dependent on both the price per International Unit of FVIII and on the discount factor. This restricts comparisons of this study with other studies, as most other related studies have used a discount factor of 5% and different (mostly higher) prices per FVIII unit.

## Conclusions

Overall, we can conclude that the cost related to the treatment of boys with severe haemophilia A is quite high, and primarily related to the purchase of replacement clotting factor concentrates. Patients with one or more virally transmitted diseases result in even higher costs. The increase in use of FVIII in the 1980s and 1990s likely reflects the increased use of factor prophylaxis. Of interest the decreasing cost of treatment in last 3 years of this study (1995–1998) may reflect a reduced use of factor concentrate as boys with haemophilia mature into young adults. Prospective studies are now needed to better delineate the patterns of bleeding in adolescents and young adults with severe haemophilia and to determine the reasons why such individuals either continue or discontinue factor prophylaxis.

## References

1 Aledort LM. Some aspects on the management of hemophilia. *Thromb Haemost* 1995; **74**: 440–3.
2 Szucs T, Offner A, Kroner B *et al.* Resource utilization in haemophiliacs treated in Europe: results from the European study on socio-economic aspects of haemophilia care. *Haemophilia* 1998; **4**: 498–501.
3 Liesner RJ, Khair K, Hann IM. The impact of prophylactic treatment on children with severe haemophilia. *Br J Haematol* 1996; **92**: 973–8.
4 Miners A, Sabin CA, Tolley KH *et al.* Assessing the effectiveness and cost-effectiveness of prophylaxis against bleeding in patients with severe haemophilia and severe von Willebrand's disease. *J Intern Med* 1998; **244**: 515–22.
5 Smith PS, Teutsch SM, Shaffer PA *et al.* Episodic versus prophylactic infusions for hemophilia A: a cost-effectiveness analysis. *J Pediatr* 1996; **129**: 424–31.
6 Molho P, Rolland N, Lebrun T *et al.* Epidemiological survey of the orthopaedic status of severe haemophilia A and B patients in France. *Haemophilia* 2000; **6**: 23–32.
7 Miners A, Sabin CA, Tolley KH *et al.* Assessing health-related quality-of-life in individuals with haemophilia. *Haemophilia* 1999; **5**: 378–85.
8 Naraine VS, Risebrough NA, Oh P *et al.* Health-related quality-of-life treatments for severe haemophilia: utility measurements using the Standard Gamble technique. *Haemophilia* 2002; **8**: 112–20.
9 Gold M, Siegel J, Russel L *et al. Cost-effectiveness in Health and Medicine*. New York, USA: Oxford University Press, 1996.
10 Miners AH, Sabin CA, Tolley KH *et al.* Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe hemophilia. *Pharmacoeconomics* 2002; **20**: 759–74.
11 Bohn RL, Avorn J, Glynn RJ *et al.* Prophylactic use of factor VIII: an economic evaluation. *Thromb Haemost* 1998; **79**: 932–7.
12 Ontario Ministry of Health. *Schedule of Benefits: Physician Services under the Health Insurance Act*. Toronto, Canada: Ontario Ministry of Health, 2001.

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