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ORIGINAL ARTICLE *Clinical haemophilia*

First analysis of 10-year trends in national factor concentrates usage in haemophilia: data from CHARMS, the Canadian Hemophilia Assessment and Resource Management System

A. N. TRAORE,* A. K. C. CHAN,† K. E. WEBERT,‡ N. HEDDLE,‡ B. RITCHIE,§ J. ST-LOUIS,¶ J. TEITEL,‖ D. LILLICRAP,** A. IORIO†† and I. WALKER‡

**McMaster Transfusion Research Program; †Department of Pediatrics; ‡Department of Medicine McMaster University, Hamilton, Ontario; §Department of Medicine University of Alberta, Edmonton, Alberta; ¶Department of Hematology Hôpital Maisonneuve-Rosemont and Université de Montréal, Montreal, Quebec; ‖St. Michael's Hospital, Toronto & Central Ontario Hemophilia Program, Toronto; **Department of Pathology and Molecular Medicine Queen's University, Kingston; and ††Clinical Epidemiology and Biostatistics McMaster University, Hamilton, Ontario, Canada*

Summary. The Canadian Hemophilia Assessment and Resource Management System (CHARMS) tracks factor concentrates (FC) from the sole suppliers, Canadian Blood Services (CBS) and Hema-Quebec (HQ), to hospitals and to patients' homes. Patients FC infusion data are entered into CHARMS at Canadian Hemophilia Treatment Centres (HTCs) then exported to the national database (CentrePoint). From 2000 to 2009, 2260 registered haemophilia A or B patients received FVIII (1 009 097 765 IU) and FIX (272 406 859 IU). Over 91% of FVIII and over 84% of FIX was infused at home. Utilization of FVIII progressively increased; this was accounted for by an increase in the number of patients treated ($r = 0.97$; $P < 0.001$), there being a linear relationship between the increase in utilization and the increase in number of patients treated ($P < 0.001$). There was also a correlation with the annual amount used per patient ($r = 0.95$; $P < 0.001$). Utilization of FIX did not increase over time. The highest proportional utilization of both FVIII and FIX was for prophylaxis, and this proportion progressively increased being, in year 10 (2009), 77% and 66% for FVIII and FIX respectively. The proportion used for bleeding remained steady; in year 10 that proportion was 14% for FVIII and 26% for FIX, the use per patient for bleeding decreasing. The HTC-based CHARMS tracking system is essential, in Canada, for analysing indications for infusion, for predicting utilization and planning for future needs.

Keywords: Canada, coagulation factor concentrate, haemophilia, home infusion, prophylaxis

Introduction

Haemophilia is a chronic disease characterized by bleeding in joints, muscles and soft tissues [1]. The high frequency of bleeding in severely affected individuals leads to significant morbidity and risk of early mortality, and is associated with high treatment costs; therefore both patient care and resource utilization need to be monitored. Prerequisites for effective care and monitoring include specialized haemophilia treatment centres (HTCs) and a national haemophilia registry [2–5]; both are established in many countries [6–8].

The mainstay of effective care is an adequate supply of coagulation factor concentrates (FC) [9,10]. FC is infused for a variety of indications, for treatment of bleeds, for prophylaxis, both short term and long term, and for immune tolerance induction (ITI) [9,11–18]. These treatments can be provided in hospitals, at home or elsewhere [19–22].

To monitor patient outcomes and the appropriate use of FC, it is essential to have a system to track utilization, both the indications for and amounts used [23]. The combination of a national haemophilia registry and FC utilization data can improve the quality of care and support research [24].

The Canadian Hemophilia Registry (CHR) was formed in 1988 to define the population [8,23,25,26].

Correspondence: Dr Irwin Walker, 711 Concession St., Hamilton, ON L8V 1C3, Canada.
Tel.: 1-905-648-3373; fax: 1-905-575-7320;
e-mail: walkeri@mcmaster.ca

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In 1997 Canadian authorities, in response to the transfusion-transmitted AIDS epidemic [19,27], recommended the introduction of a blood product tracking system. The Association of Hemophilia Clinic Directors of Canada (AHCDC; www.ahcdc.ca) responded by developing the Canadian Hemophilia Assessment and Resource Management System (CHARMS), designed to assist in patient management and to track FC from the suppliers, Canadian Blood Services (CBS) and Hema-Quebec (HQ), to hospitals and, from there, to patients' homes [23]. Data collection commenced in 2000 and a pilot project was completed soon after [19,28]. Clinic directors supported the formation of this tracking system as it has helped to validate the accuracy of patient diaries, the amount being received by patients not having been well validated.

In this study, the first 10 years of data were analysed, with the specific aim of tracking utilization of factor concentrates used by patients with haemophilia A or B, the amounts used, indications, and the locations of infusions. The following concentrates were used during this period: Factor VIII (FVIII), factor IX (FIX), recombinant activated factor VII (rFVIIa), FEIBA® (Factor Eight Inhibitor Bypassing Activity). Use of the von Willebrand factor concentrates, Humate-P and Wilate, were documented in this study only for patients with haemophilia A or B.

Materials and methods

Computer facilities

CHR has previously been described and validated as representing the Canadian haemophilia population [8,23,25]. Patients with inherited bleeding disorders attending the 26 Canadian HTCs are registered and assigned a unique computer-generated identification number (CHR number). CHARMS is a purpose-specific software program resident within HTCs that records a wide variety of data related to haemophilia care.[19,23]. Data relating to patients FC infusions are uploaded from CHARMS by each HTC to a central database called CentrePoint. Both CHR and CHARMS are provided with oversight by a subcommittee of AHCDC and both have been given ethics approval by university and hospital ethics committees. Data sent from HTCs are non-nominal and only collated data are made available. Patient consent has till this time been deemed unnecessary.

Distribution of FC

All FC are distributed to hospitals by CBS and, in Quebec, by HQ. Hospitals infuse a minor proportion of most FC, distributing the bulk to patients for home use. Home use is voluntarily documented by patients in diaries, either paper or electronic [29]. Patients are trained, and required, since their first visit to an HTC, to provide specific data on each infusion; specific formats are provided. Most patients submit data electronically [EZ-Log® (Bayer Healthcare, Toronto, Canada), Advoy® (Baxter Inc, Deerfield, IL, USA) or Helitrax® (CSL Behring, Ottawa, Canada)], the remainder on paper diaries submitted by post, in person, or via email. HTCs track the products from CBS and HQ, to hospitals, and then to patients. HTCs receive data from CBS and HQ (distribution data), regional hospitals (utilization, distribution and inventory data) and patients (utilization and inventory data). HTCs electronically export their data once a month to CentrePoint which is validated with respect to discrepancies and missing information. CHARMS is an AHCDC priority program; HTC personnel received training at a national workshop, are provided with dedicated phone support, and receive updates and reports at the annual AHCDC meeting.

Data management

For each infusion, the following data were recorded: HTC, CHR number, date of birth, gender, diagnosis, type and severity of disorder, date of infusion, amount/units infused, manufacturer, type of product, brand name, location of infusion (home, HTC or hospital) and indications for infusion. Indications for infusion were either on demand (bleeding), ITI therapy, surgery, prophylaxis or other (open response, referred to as unclassified). Prophylaxis included six subcategories: prophylaxis–long term, prophylaxis–sports, prophylaxis–physiotherapy, prophylaxis–dental and prophylaxis–surgery.

Some data logs were received incomplete. In these cases, total use for the period in question was entered after reviewing the patient's receipt logs and current inventory. For this reason neither frequency of infusions nor doses in units/kg could be accurately presented. Also, when the indications for infusions were not described, infusions were categorized as 'unclassified'.

Patients

Only patients with haemophilia A or B were included in this analysis.

Data analysis

Data from CentrePoint were exported for analysis to SAS for Microsoft Windows (Statistical Analysis Software, Version 9.2, SAS Institute, Cary, NC, USA).

Indications and locations of infusions recorded as '*other*' were reclassified whenever possible into the specific categories. Total units were calculated for each type of FC and compared by age group (adult

>17 vs. pediatric ≤17 years). The trend in the severe haemophilia population alone also was analysed.

For the total units of FVIII infused annually, a Pearson correlation coefficient was used for assessing the correlation of the number of patients and the units infused per patient per year. The correlated predictive variable was then included in a linear regression model. We also assessed the underlying temporal trends of the proportion of unclassified indications to improve the quality of the recording process.

Results

Patients

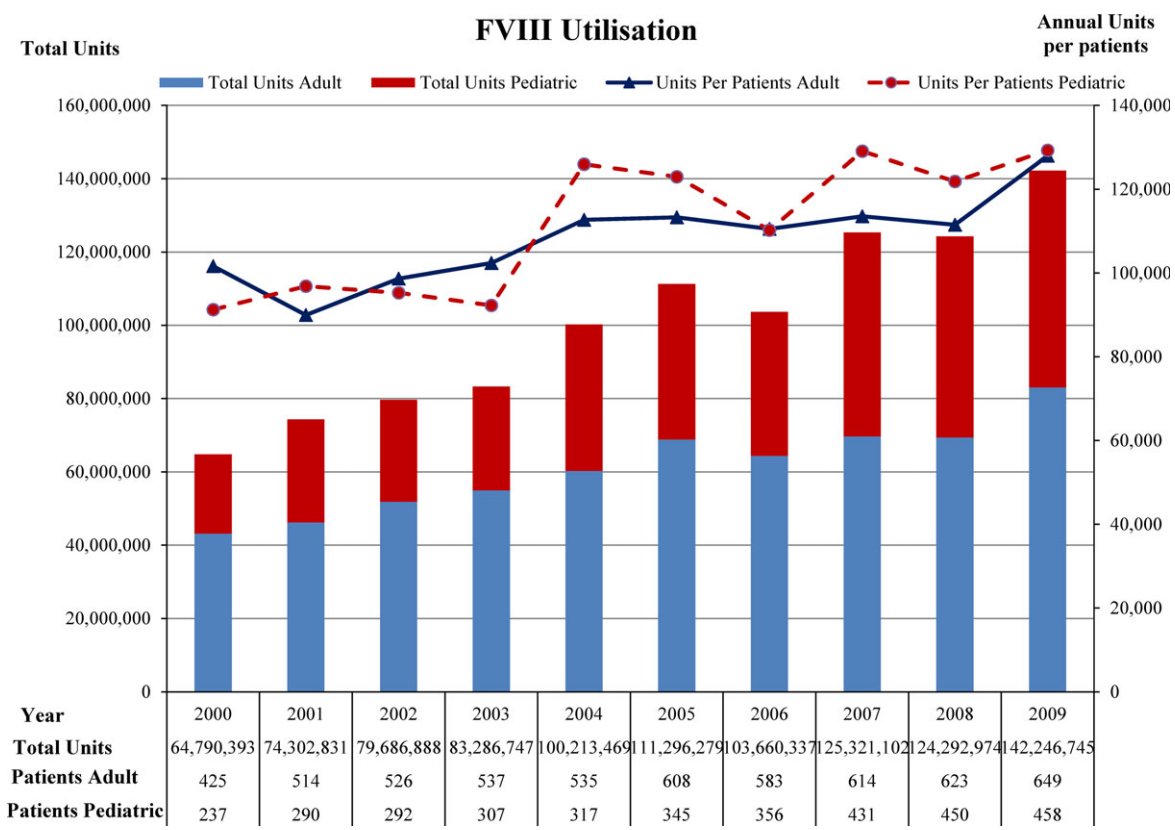
From 2000 to 2009, a total of 2260 registered haemophilia A (1750) or B (510) patients received FVIII, FIX, rFVIIa or FEIBA. The majority of patients, 2199 (97%), were male. The proportion of pediatric patients varied between 34% and 39%. The mean and median ages of 329 severely affected patients first registered after study commencement were 1 year and 6 years respectively The majority (90%) of all 986 severe haemophilia A or B patients continuously provided diary data after starting; among them, 50% providing data for all 10 years and 80% provided diaries for at least 5 years. By comparing CHS and CHARMS databases, we were able to determine that 93% (697/750) and 90% (140/157) of individuals with severe haemophilia A and B, respectively, received at least one infusion of FC during 2009.

Total FC infused

Over 10 years, CHARMS was able to track the infusions of 1 009 097 765 IU of FVIII. The overall proportion of plasma-derived FVIII was 2.2% (minimum 0.2% in 2000 and maximum 4.8% in 2009). All 272 406 859 IU of FIX were recombinant. The majority of FC was infused by severely affected individuals: 86% for FVIII, 70% for FIX, 90% for FEIBA and 94% for rFVIIa.

Trends in FC utilization

The annual usage of FVIII increased over the period of observation (Fig. 1). This increase was significantly and positively correlated with the mean amount of units infused yearly per patient (Pearson correlation coefficient $r = 0.95$; $P < 0.001$) as well as to the number of treated patients ($r = 0.97$; $P < 0.001$). Furthermore, there was a linear relationship between an



Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Total Units	64,790,393	74,302,831	79,686,888	83,286,747	100,213,469	111,296,279	103,660,337	125,321,102	124,292,974	142,246,745
Patients Adult	425	514	526	537	535	608	583	614	623	649
Patients Pediatric	237	290	292	307	317	345	356	431	450	458

Fig. 1. Total annual and per patient amounts of FVIII infused from 2001 to 2009.

increase in the number of patients and increased utilization, each additional patient predicting for an increased utilization of 108 002 IU ($P < 0.001$). These results were similar in both adult and paediatric populations.

The annual use of FIX did not increase, in contrast to the trend with FVIII above. There was an increase in the number of patients but the usage per patient decreased in both adult and paediatric population (Fig. 2). The trends in FVIII and FIX utilization paralleled annual total distributions from CBS and HQ (data not shown).

Indications for infusions

The proportion of FVIII used for prophylaxis predominated throughout the survey period, rising progressively (Fig. 3). For adults the increase was from 59% to 73% and in children the increase was from 52% to 82%. There was an increase in total utilization annually, due both to an increase in the numbers of severely affected individuals and to an increase use per patient, predominantly for prophylaxis (Table 1 and Fig. 3). In contrast, the proportion of FVIII used for bleeding was constant, ranging between 13% and 19% annually for all haemophilia A patients and between 12% and 17% for severe patients. The proportion of severe patients who infused for bleeding decreased from 13% in 2001 to 5% in 2009. Surgery accounted for only 1% to 3% of infusions for all haemophilia A patients. Documentation of indications for infusions improved over the period of the study, with only 5% of infusions in 2009 being unclassified.

FIX likewise was infused mainly for prophylaxis, the proportion rising from 45% to 66%, both among adults (30–64%) and children (61–76%). Use for bleeding decreased from 42% to 26% (Fig. 4). The proportion used for surgery was between 2% and 6%.

For both FVIII and FIX, the proportions of units infused for unclassified reasons were higher than 10% until 2004. Diaries data documentation improved subsequently and the decrease after 2005 paralleled an increase in use for prophylaxis. Indeed, there is negative and significant correlation between unclassified infusions of FVIII and infusions for prophylaxis ($r = -0.74$; $P = 0.02$); when the proportions of unclassified infusions decreased, the proportion for prophylaxis increased, showing the impact of improved documentation of reasons for infusion.

Among bypass treatments FEIBA was mainly infused for prophylaxis whereas rFVIIa was predominantly infused for bleeding (Fig. 5). These trends were seen in

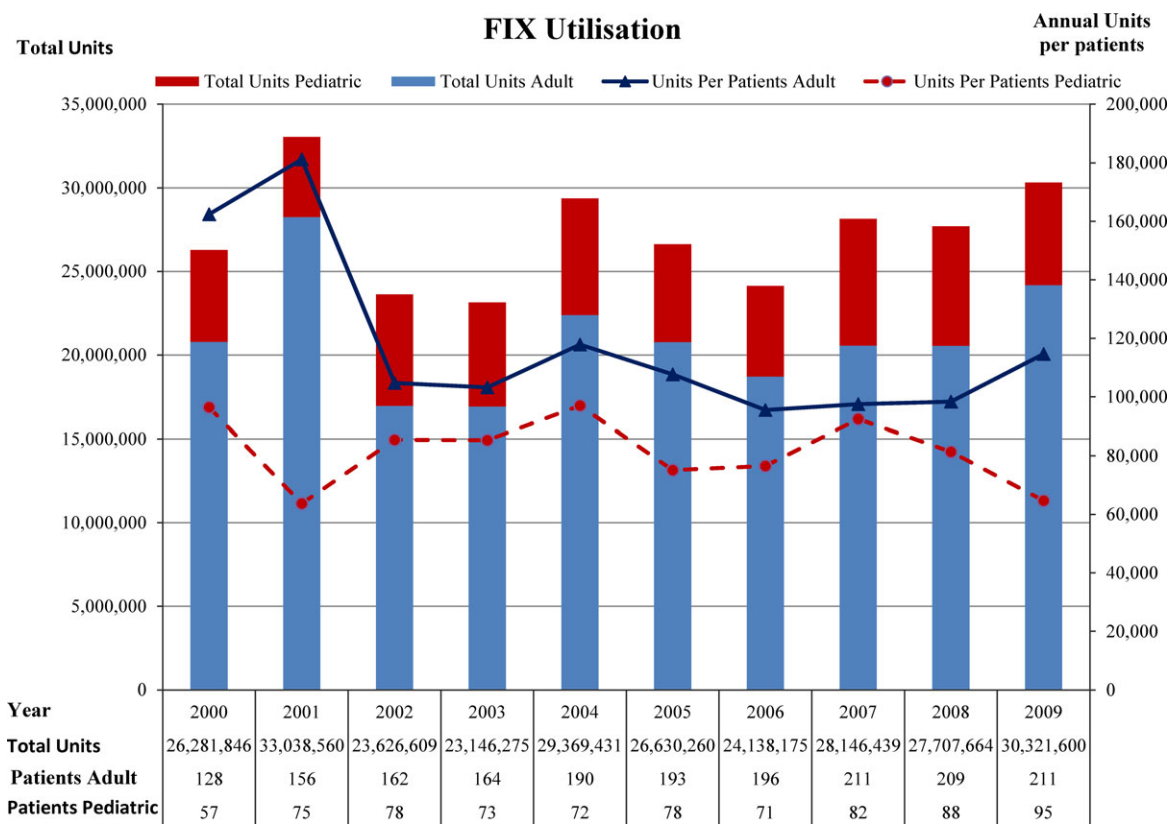


Fig. 2. Total annual and per patient amounts of FIX infused from 2001 to 2009.

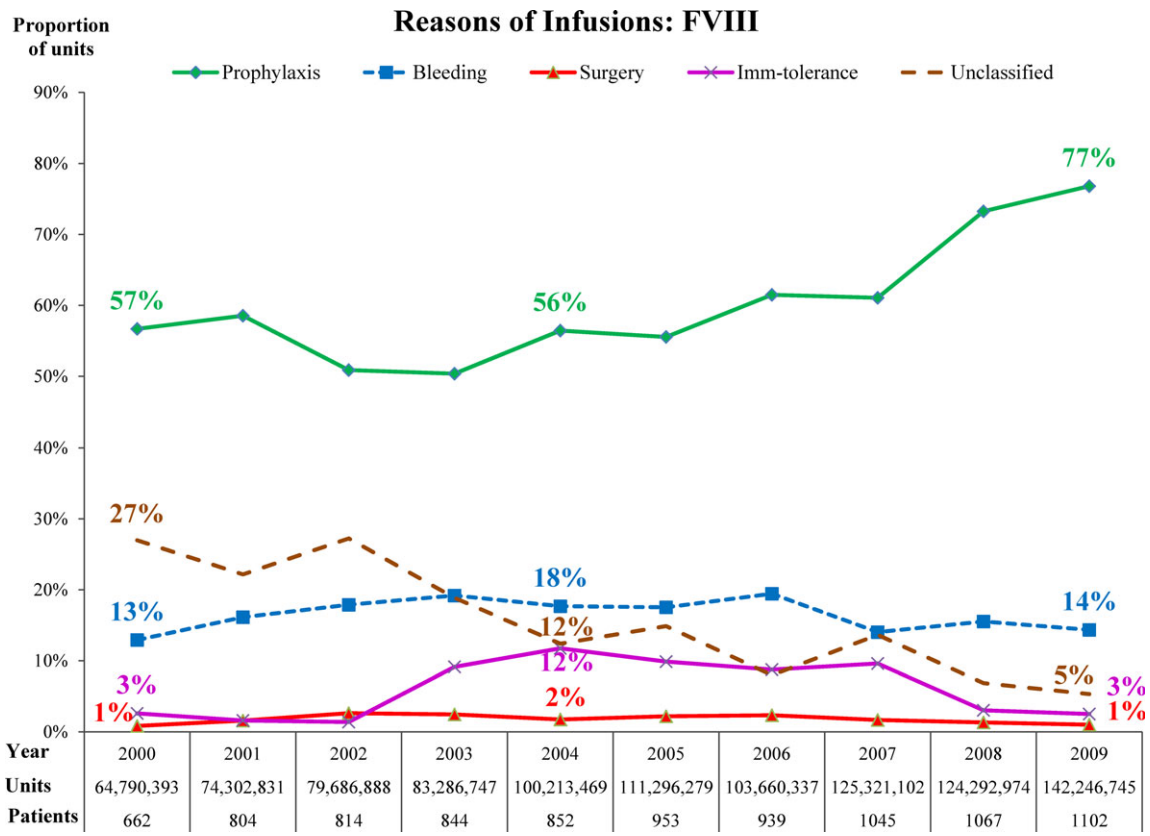


Fig. 3. Indications for FVIII infusions.

Table 1. FVIII utilization trends among severe haemophilia A patients.

		Severe haemophilia A patients						
Year	Total haemophilia A patients	Total patients	Total units infused	% units infused for prophylaxis	% units infused for bleeding	% who infused for prophylaxis only	% who infused for bleeding only	% who infused for both
2000	667	425	49 487 758	60%	12%	42%	8%	28%
2001	811	530	60 507 937	61%	15%	35%	13%	41%
2002	819	530	69 458 696	53%	16%	27%	15%	46%
2003	847	543	72 876 699	52%	17%	28%	17%	43%
2004	863	558	88 823 502	58%	15%	26%	14%	57%
2005	963	594	96 778 560	58%	15%	27%	11%	58%
2006	947	600	91 025 847	63%	17%	25%	6%	67%
2007	1051	662	109 671 498	62%	12%	33%	6%	58%
2008	1073	686	107 650 533	74%	14%	31%	6%	62%
2009	1104	697	120 922 686	77%	13%	33%	5%	60%

both adults and children. For FEIBA, the proportion of units infused for prophylaxis by adults was steady around 52% during these 10 years. However, in the paediatric population, the proportion used for prophylaxis went from 6% to 82%. For rFVIIa, the proportion of units infused for bleeding by adults patients varied between 22% and 68%. Among paediatric patients, that proportion varied between 36% and 96%.With respect to the proportion of patients requiring treatment, a confounding influence is the changing identity of the population, inhibitors both developing and resolving and inhibitor status at any point in time was not always certain. Currently, the proportions of patients in CHR with FVIII inhibitors are 8% (n = 70), 3% (n = 9) and 0.5% (n = 9) in those previously having had severe, moderate and mild FVIII deficiency respectively (www.ahcdc.ca). Figure 5 shows the number of patients receiving FEIBA and the number receiving rFVIIa during each of the last 5 years of the study. The number of patients receiving rFVIIa and/or FEIBA over 10 years and during the last year of the study was 150 and 67 (37 adult and 30 pediatric)

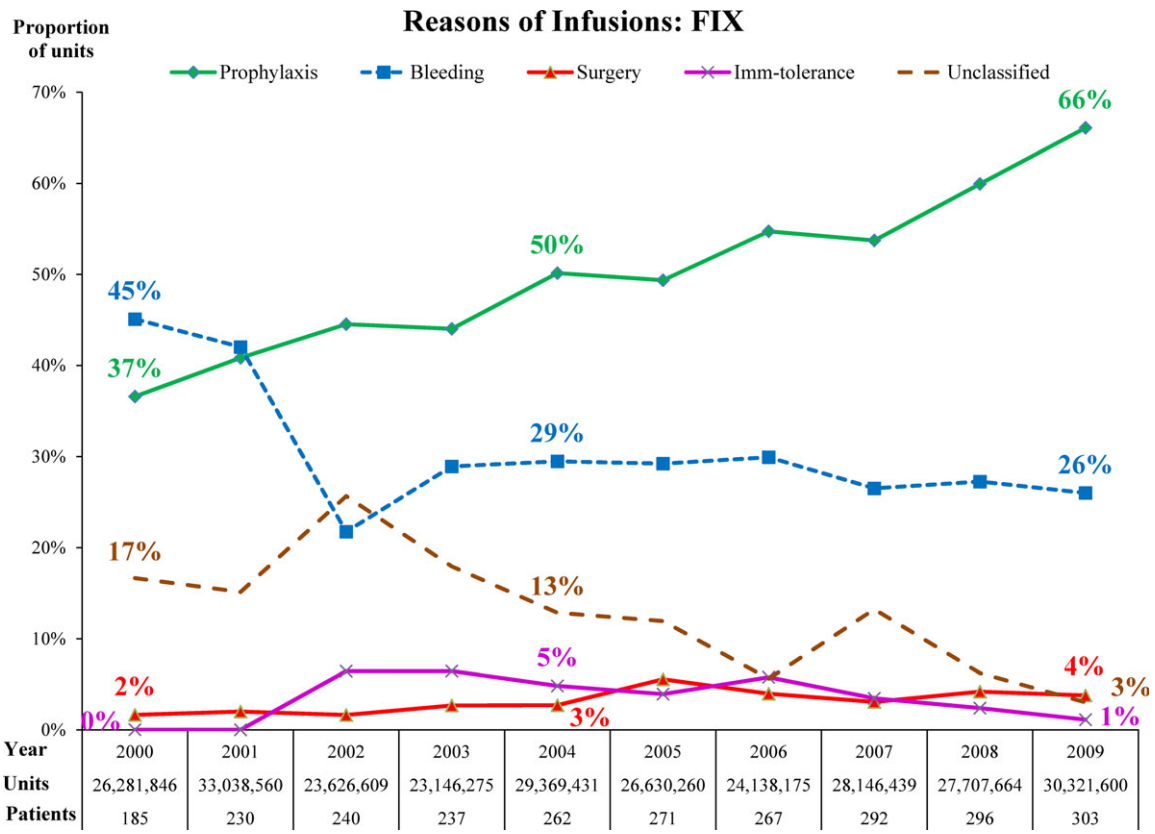


Fig. 4. Indications for FIX infusions.

respectively. Based on the number receiving product in the last year of the study and the number of patients with inhibitors in CHR, about 24% (21 out of 88) of patients with inhibitors did not require bypass therapy.

Locations of infusions

For all products, most of the infusions were performed at home, the proportions being 91–96% for FVIII and 84–95% for FIX. Home infusion predominated also for rFVIIa (58–90%) and for FEIBA (74–90%).

Validations

Infusion data over the period of the study were compared with distribution data over the same period supplied by the distributors CBS and HQ. Infusion data were 90% and 87% of distribution data for FVIII and FIX respectively, and 92% and 89% if taking into account expected wastage, as previously assessed [28]. A previous publication validates the Canadian Hemophilia Registry as truly representing the entire population of severely affected individuals, and hence those using the vast amount of concentrates [23]. There were 270 new registrants with severe haemophilia A and 37 with haemophilia B during the 10-year study period. Most of these were young children; indeed, the median age was 1 year, 73% were less than 5 years at registration and 81% were aged ten or less, for both deficiencies.

Discussion

CHARMS and CHR together were valuable in cross-checking data, these databases being independent; as an example, the proportion of adults (67%) to children was identical. As well, we were able to determine the proportions of patients who received concentrate.

Almost all (90%) of severe haemophilia A or B patients continuously provided diary data after entry and CHR and CHARMS together provide a valuable cross check on data quality. Diary submission is a long established practice in Canada and each patient receives training by the clinic coordinator. The practice of submitting diaries has been agreed to by the Canadian Hemophilia Society as a policy statement. While return of diaries is often imperfect, validations were available. First, the supply of concentrate to each patient is ordered by the HTC and confirmed by electronic download from CBS and HQ. Thus, data on the supply of concentrate to each patient are accurate. With regard to utilization, with each diary submitted

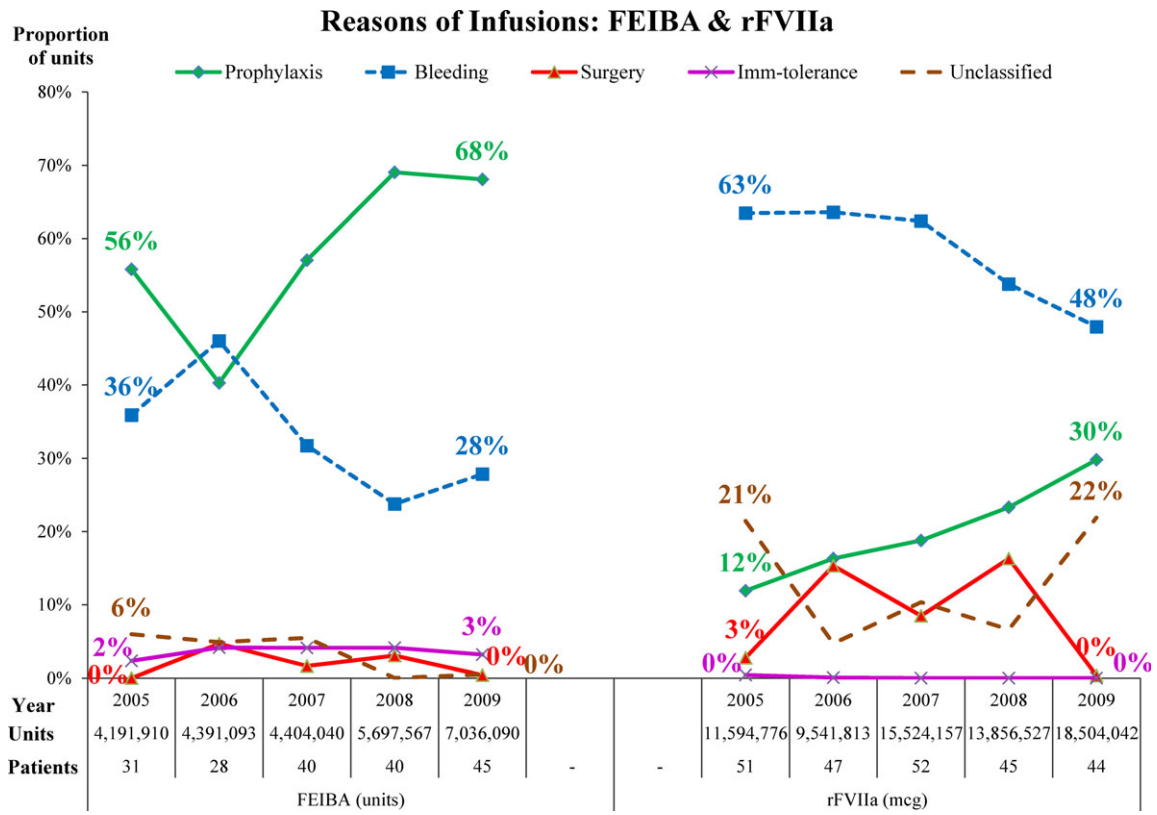


Fig. 5. Indications for bypassing products infusions.

patients are to provide their current inventory, so that together with supply and inventory details, the diaries can be validated. Patients can be contacted when data cannot be reconciled. Even so, complete accuracy cannot be assumed. We have therefore compared the total amount sent to patients with the utilization data returned by patients over 10 years. This comparison reveals a deficit of 10% for FVIII and 13% for FIX FC in total units used compared with that supplied.

The steep rise in concentrate used during the first 3 years may be a rebound from decreased utilization during a world-wide shortage. At that time, AHCDC and the Canadian Hemophilia Society addressed this shortage with guidelines. One of the recommendations was for delay of non-urgent surgery. The decrease in overall utilization was for most indications, however, there are actual data in this paper supporting the changing use for surgery. In this study, the annual usage of FVIII concentrate for surgery during this period of shortage (2000–2001) was 536 412 IU in 2000 and 1 173 145 IU in 2001. In the following 2 years the figures were 2 090 311 IU in 2002 and 2 040 511 IU in 2003. A sharp increase during the same period was seen also in the previous pilot study [19,28].

Prophylaxis was the dominant indication, particularly with respect to FVIII. These results are very similar to, and confirm, an earlier study that was restricted to South-Central region of Ontario [28]. This is in keeping with the policy statements of the World Federation of Hemophilia, that 'prevention of bleeding is the goal in haemophilia care' and that 'prophylaxis must be the goal of all haemophilia care programs until a cure is available' [30]. Data in this survey indicate that medical practice in Canada is in line with these policy statements and with the literature [10,14,17,18,31–34]. As expected the proportion of FC used for prophylaxis is higher among children as the primary purpose of prophylaxis has been the prevention of joint damage [17,31,35–37].

It would be expected that the increase in use of concentrate for prophylaxis would result in a decrease in use for bleeding. This was in fact the observation for FIX concentrate but not so for FVIII. The reason for this counter-intuitive finding for FVIII concentrate is not clear, but the same trends were observed in a previous regional study [28]. We suspect that this finding could be explained by an increase in units infused per bleed over time, due both to the increased practice of giving multiple infusions per bleed, and the increase in vial sizes. As well bleeding would not decrease in those not on prophylaxis. As indicated in Table 1, there was in fact a decrease in the proportion of patients with severe haemophilia who infused for bleeding despite the fact that many adults are not on prophylaxis, supporting the idea of increased use of FC per bleed.

Prior to 2004 there was a higher proportion of unclassified use of FC. This aspect of data documentation improved following a workshop on CHARMS during the AHCDC general meeting in April 2004. The proportion of FIX infused for prophylaxis is lower than that of FVIII, likely a reflection of the perceived decrease in bleed frequency for haemophilia B and the lack of supporting clinical trials supporting prophylaxis [17].

Regarding bypassing products, a much higher proportion of FEIBA was used for prophylaxis than rFVIIa, the commonest indication for the latter being bleeding. This is in keeping with other studies [13,15,38,39]. A proportion of FEIBA, but not rFVIIa, was used during ITI therapy in accord with existing practices elsewhere [12,13,15,38–41].

Weaknesses in this article relate firstly to the 10% gap between figures for utilization and distribution. Part of this gap is due to waste, another is likely to represent use by hospitals (10%) from which receipt of data is less certain. A second weakness relates to occasional uncertainties regarding designation of indications for infusion. There may be ambiguities regarding whether joint pain may be from bleeding or arthritis, and in this situation an infusion may even be designated as for prophylaxis if that had been scheduled for that time.

This survey shows that the bulk of FVIII and FIX concentrate is infused outside health-care institutions as expected with the trends toward self-infusion and prophylaxis [20–22].

Conclusion

Tracking the use of concentrates validates patient diaries, thereby making patient assessments more accurate, identifies trends in utilization and changes in practices, provides an early warning system for side effects, and helps manage resources in a nationalized subsidized system. CHARMS is therefore useful both for the clinician and the suppliers. The AHCDC-based data collection systems, having shown usefulness in documenting the haemophilia population[23] and recording both clinical[26,42] and survival data[43] now demonstrates, as well, usefulness for documenting trends in factor concentrate use. CHR and CHARMS are powerful resources for collecting data on Canadian haemophilia patients and their treatment [8,19,23,25,43].

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Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

1 Kaushansky K, Lichtman M, Beutler E, Kipps T, Prchal J, Seligsohn U. Williams Hematology. 8th ed. New York: McGraw-Hill, 2010.
2 Soucie JM, Nuss R, Evatt B *et al.* Mortality among males with hemophilia: relations with source of medical care. The Hemophilia Surveillance System Project Investigators. *Blood* 2000; **96**: 437–42.
3 Smith PS, Levine PH. The benefits of comprehensive care of hemophilia: a five-year study of outcomes. *Am J Public Health* 1984; **74**: 616–7.
4 Hoots WK. Comprehensive care for hemophilia and related inherited bleeding disorders: why it matters. *Curr Hematol Rep* 2003; **2**: 395–401.
5 Soucie JM, Symons J, Evatt B, Brettler D, Huszti H, Linden J. Home-based factor infusion therapy and hospitalization for bleeding complications among males with haemophilia. *Haemophilia* 2001; **7**: 198–206.
6 Hay CR. The UK Haemophilia Database: a tool for reasearch, audit and healthcare planning. *Haemophilia* 2004; **10**: 21.
7 Kar A, Potnis-Lele M. Haemophilia data collection in developing countries: example of the haemophilia database of Maharashtra. *Haemophilia* 2004; **10**: 301–4.
8 Walker I. The Canadian Hemophilia Registry. *Haemophilia* 2004; **10**: 21–2.
9 Petrini P. Identifying and overcoming barriers to prophylaxis in the management of haemophilia. *Haemophilia* 2007; **13**: 16–22.
10 Manco-Johnson M. Comparing prophylaxis with episodic treatment in haemophilia A: implications for clinical practice. *Haemophilia* 2007; **13**: 4–9.
11 Oldenburg J. Prophylaxis in bleeding disorders. *Thromb Res* 2011; **127**: S14–7.
12 Carcao M, Lambert T. Prophylaxis in haemophilia with inhibitors: update from international experience. *Haemophilia* 2010; **16**: 16–23.
13 Ettingshausen CE, Kreuz W. Early long-term FEIBA prophylaxis in haemophilia A patients with inhibitor after failing immune tolerance induction: a prospective clinical case series. *Haemophilia* 2010; **16**: 90–100.
14 Den Uijl I, Mauser-Bunschoten EP, Roosendaal G, Schutgens R, Fischer K. Efficacy assessment of a new clotting factor concentrate in haemophilia A patients, including prophylactic treatment. *Haemophilia* 2009; **15**: 1215–8.
15 Valentino LA, Carcao M, Mathew P *et al.* The application of bypassing-agent prophylaxis in haemophilia A patients with inhibitors: a meeting report. *Haemophilia* 2009; **15**: 959–65.
16 Berntorp E. Prophylaxis in von Willebrand disease. *Haemophilia* 2008; **14**: 47–53.
17 Biss TT, Chan AK, Blanchette VS, Iwenofu LN, Mclimont M, Carcao MD. The use of prophylaxis in 2663 children and adults with haemophilia: results of the 2006 Canadian national haemophilia prophylaxis survey. *Haemophilia* 2008; **14**: 923–30.
18 Schlammadinger A, Ilonczai P, Olah Z, Razso K, Boda Z. Low dose factor concentrate prophylaxis in patients with severe haemorrhagic disorders. *Blood Rev* 2007; **21**: S102–S.
19 Walker IR, Sek JT, Almonte TM *et al.* Developing a tracking system for coagulation factor concentrates in southern Ontario. *Transfusion* 2003; **43**: 556–62.
20 Manco-Johnson MJ, Riske B, Kasper CK. Advances in care of children with hemophilia. *Semin Thromb Hemost* 2003; **29**: 585–94.
21 Rosendaal FR, Smit C, Briet E. Hemophilia Treatment in Historical-Perspective - A Review of Medical and Social Developments. *Ann Hematol* 1991; **62**: 5–15.
22 Colvin BT, Astermark J, Fischer K *et al.* European principles of haemophilia care. *Haemophilia* 2008; **14**: 361–74.
23 Walker I, Pai M, Akabutu J *et al.* The Canadian Hemophilia Registry as the basis for a national system for monitoring the

use of factor concentrates. *Transfusion* 1995; **35**: 548–51.
24 Iorio A, Oliovecchio E, Morfini M, Mannucci PM. Italian Registry of Haemophilia and Allied Disorders. Objectives, methodology and data analysis. *Haemophilia* 2008; **14**: 444–53.
25 Walker I. Survey of the Canadian hemophilia population. *Can J Public Health* 1991; **82**: 13.
26 Association of Hemophilia Clinic Directors of Canada. Effect of using safer blood products on prevalence of HIV infection in haemophilic Canadians. *BMJ* 1993; **306**: 2.
27 Krever Commission. Commission of Inquiry on the Blood System in Canada. 1997. Available at http://epe.lac-bac.gc.ca/100/200/301/hcan-scan/commission_blood_final_rep-e/index.html.Accessed 11 June 2014.
28 Arnold DM, Webert KE, Carruthers J *et al.* Trends in the utilization and wastage of coagulation factor concentrates: the application of a regional tracking programme. *Haemophilia* 2007; **13**: 271–8.
29 Walker I, Sigouin C, Sek J *et al.* Comparing hand-held computers and paper diaries for haemophilia home therapy: a randomized trial. *Haemophilia* 2004; **10**: 698–704.
30 World Federation of Hemophilia. Guidelines for the Management of Hemophilia. World Federation of Hemophilia. 2005. Available at http://www1.wfh.org/publications/files/pdf-1472.pdf. Accessed 11 June 2014.
31 Brackmann HH, Eickhoff HJ, Oldenburg J, Hammerstein U. Long-term therapy and on-demand treatment of children and adolescents with severe haemophilia A: 12 years of experience. *Haemostasis* 1992; **22**: 9.
32 World Health organization. Report of joint WHO/WFH Meeting on the Control of Haemophilia: Delivery of Treatment for Haemophilia. 2002. Available at http://www1.wfh.org/publication/files/pdf-1451.pdf. Accessed 11 June 2014.
33 van den Berg HM, Fischer K, Mauser-Bunschoten EP *et al.* Long-term outcome of individualized prophylactic treatment of children with severe haemophilia. *Br J Haematol* 2001; **112**: 561–5.
34 Lillicrap D. Improvements in factor concentrates. *Curr Opin Hematol* 2010; **17**: 393–7.
35 Blanchette P, Rivard G, Israels S *et al.* A survey of factor prophylaxis in the Canadian haemophilia A population. *Haemophilia* 2004; **10**: 679–83.
36 Blanchette VS, McCready M, Achonu C, Abdolell M, Rivard G, Manco-Johnson MJ. A survey of factor prophylaxis in boys with haemophilia followed in North American haemophilia treatment centres. *Haemophilia* 2003; **9**: 19–26.
37 Blanchette VS. Prophylaxis in the haemophilia population. *Haemophilia* 2010; **16** (Suppl 5): 181–8; 2.
38 Valentino LA. Assessing the benefits of FEIBA prophylaxis in haemophilia patients with inhibitors. *Haemophilia* 2010; **16**: 263–71.
39 Luu H, Ewenstein B. FEIBA (R) safety profile in multiple modes of clinical and home-therapy application. *Haemophilia* 2004; **10**: 10–6.
40 Leissinger CA, Becton DL, Ewing NP, Valentino LA. Prophylactic treatment with activated prothrombin complex concentrate (FEIBA((R))) reduces the frequency of bleeding episodes in paediatric patients with haemophilia A and inhibitors. *Haemophilia* 2007; **13**: 249–55.
41 Dimichele DM, Hoots WK, Pipe SW, Rivard GE, Santagostino E. International workshop on immune tolerance induction: consensus recommendations. *Haemophilia* 2007; **13**(Suppl 1): 1–22.
42 Arnold DM, Julian JA, Walker IR. Mortality rates and causes of death among all HIV-positive individuals with hemophilia in Canada over 21 years of follow-up. *Blood* 2006; **108**: 460–4.
43 Walker IR, Julian JA. Causes of death in Canadians with haemophilia 1980-1995. Association of Hemophilia Clinic Directors of Canada. *Haemophilia* 1998; **4**: 714–20.

