



## The challenge arising from the cost of haemophilia care: an audit of haemophilia treatment at Auckland Hospital

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### Abstract

**Aims** To compare treatment patterns in adults and children with haemophilia and to estimate the financial impact of the changing practice of haemophilia care.

**Methods** A retrospective audit of replacement coagulation factor usage in all patients with haemophilia treated at the Auckland Haemophilia Centre during 2001.

**Results** A total of 69 males with haemophilia were included in the audit. Twelve children under 16 years old (nine on recombinant products) and six adults (all on plasma products) received prophylactic treatment. The remaining patients used treatment on demand. The cohort included eight patients with factor VIII inhibitors. The estimated cost of replacement products used was around \$3 million for the 23 children and \$2.2 million for the 46 adults.

**Conclusions** Children with severe haemophilia are predominantly treated with recombinant products on regular prophylaxis, whereas adults are largely treated on demand with plasma-derived products. This is in line with international practice as regular prophylaxis has been shown to improve the quality of life for people with haemophilia and in the long term is cost effective. The problem in the short term is that prophylaxis is significantly more expensive than on-demand treatment. We estimate that the cost of replacement product will increase by at least 5% per annum as the children with haemophilia grow.

In New Zealand, there are about 350 people with haemophilia A and 90 with haemophilia B. Severe cases (factor VIII or IX of <1%) experience significant bleeding problems ranging from spontaneous joint and muscle bleeds to prolonged bleeding following surgery or trauma. Before adequate treatment for haemophilia was available, people with the disorder developed severe joint and muscle disease, often leading to permanent disability. As recently as 1960, the condition had a high mortality from intracranial bleeding, with life expectancy of less than 30 years.<sup>1</sup>

Over the last 40 years, treatment has changed dramatically. The introduction of cryoprecipitate in the late 1960s was followed by purified plasma-derived factors VIII and IX in the 1980s and more recently by the introduction of recombinant products. Further improvements have been achieved by the use of regular prophylaxis in the form of bolus doses two or three times each week, rather than treating individual bleeding episodes on demand. This has led to a significant reduction in long-term complications, resulting in some young adults with severe haemophilia experiencing few bleeds and minimal chronic joint disease.<sup>2</sup>

Improvements in haemophilia care have had some serious setbacks. Viral transmission of both HIV and hepatitis C has had a devastating effect on the

haemophilia community. In New Zealand, 28 people with haemophilia have been diagnosed with HIV and virtually all patients who received pooled blood products before 1986 developed hepatitis C. The problems with viral transmission have led to improved donor screening and the heat treatment of clotting factor concentrates, but in spite of these advances it remains impossible to give an absolute guarantee on blood-product safety. This need for increased safety has been a driving force in the development of recombinant factor VIII and factor IX, which are now readily available.

Although these improvements have benefited the majority of cases, it still remains difficult to manage patients with factor VIII antibodies (inhibitors). Factor VIII is a protein foreign to a person with severe haemophilia and exposure may induce an antibody response. Inhibitors occur in approximately 10% of people with haemophilia A, but are usually at low concentration.<sup>3,4</sup> However, in a small percentage the antigen evokes a very brisk response and a high titre antibody is formed. In these cases, acute bleeding is difficult to manage, as conventional factor VIII replacement is ineffective. A number of agents are available for the management of acute bleeds, but the treatment of choice is recombinant factor VIIa, which activates coagulation via a pathway independent of factor VIII.<sup>5</sup> An alternative is to use a form of desensitisation to suppress antibody production and develop immune tolerance. This tolerisation process requires daily treatment with high doses of factor VIII for up to 12 months. This is extremely expensive treatment and unfortunately not always successful. Even in the patients who do respond, long-term prophylactic treatment must be continued to prevent recurrence of the antibody.

The introduction of recombinant products, improved viral safety and regular prophylaxis has clearly been of major clinical benefit to people with haemophilia, but has added significantly to the cost of treatment. The challenge for clinicians is to maintain treatment in line with recognised international standards in the presence of rapidly rising costs of treatment. This audit was undertaken to obtain an accurate assessment of treatment patterns, product usage and the true cost of treatment at Auckland Haemophilia Centre to assist future planning.

## Methods

The audit had four aims. The first was to establish the total number of patients registered at Auckland Haemophilia Centre and the total number seen during the audit period (1 January 2001 to 1 January 2002). Patients were categorised by the severity of disease. The second was to establish the patterns of treatment used by various patient groups, in particular the comparison between children (under 16 years old) and adults. The third was to collate the total amount of replacement products used during the audit period and the fourth was to assess the cost of replacement products used.

Patient demographics, severity of disease, frequency of treatment and number of visits during the audit period were obtained from the Haemophilia Centre database and confirmed by review of each patient's hospital notes. The replacement product usage for each individual was also retrieved from the Centre database. This was cross-referenced with information obtained from the National Blood Service, the Hospital Blood Bank database, records from pharmaceutical companies relating to the delivery of recombinant blood products, and records of blood-product stock orders made by the Haemophilia Centre. The product prices were obtained from the National Blood Service database and the relevant pharmaceutical companies.

## Results

**Number of people with haemophilia seen at Auckland Haemophilia Centre** There are 125 people with haemophilia A (47 severe, 18 moderate, 60 mild) and 43 with

haemophilia B (19 severe, 17 moderate, 7 mild) registered at Auckland Haemophilia Centre. The accuracy of the number of cases of mild haemophilia is unreliable, as many of these cases have few bleeds and are not regularly treated. Approximately 40% of all haemophilia patients in New Zealand are seen at the Auckland Centre.

**Patterns of treatment during 2001 (Table 1)** During the audit period, 69 patients (46 with haemophilia A and 23 with haemophilia B) received replacement therapy at Auckland Haemophilia Centre. Fifteen received prophylactic treatment; nine used recombinant products (8 haemophilia A and 1 haemophilia B) and six used plasma-derived products. All patients on recombinant products were under 12 years old and six were less than 7 years old. Of the patients on plasma-derived product only one was under 12 years old. In addition, three patients with factor VIII inhibitors received regular factor VIII three times each week following completion of a tolerisation programme. All three cases were treated with plasma-derived products.

**Table 1. The total amount of blood products used and approximate cost for adults and children: (a) on prophylaxis; (b) receiving on-demand treatment; and (c) with inhibitors**

**(a) Prophylaxis**

	<b>Patients (n)</b>	<b>Product use (units)</b>	<b>Cost (\$)</b>
<b>Plasma-derived products</b>			
Adults	5	660 750	595 000
Children	1	75 000	67 500
<b>Recombinant products</b>			
Adults	0		
Children (8 HA, 1 HB)	9	1 137 100	1 793 000
<b>Total</b>	<b>15</b>	<b>1 872 850</b>	<b>2 455 500</b>

HA = haemophilia A; HB = haemophilia B

**(b) On-demand treatment**

	<b>Patients (n)</b>	<b>Product use (units)</b>	<b>Cost (\$)</b>
<b>Haemophilia A</b>			
<b>Plasma-derived products</b>			
Adults	13	386 750	348 000
Children	1	2000	1800
<b>Recombinant products</b>			
Adults	3	56 000	90 000
Children	7	85 870	140 000
<b>Total</b>	<b>24</b>	<b>530 620</b>	<b>579 800</b>
<b>Haemophilia B</b>			
<b>MonoFIX<sup>®</sup></b>			
Adults	9	415 500	313 400
Children	0		
<b>Prothrombinex<sup>™</sup></b>			
Adults	12	239 000	90 400
Children	1	33 000	12 500
<b>Total</b>	<b>22</b>	<b>687 500</b>	<b>416 300</b>

NB: MonoFIX<sup>®</sup> and Prothrombinex<sup>™</sup> (CSL) are plasma-derived products

### (c) Inhibitors

	<b>Patients (n)</b>	<b>Treatment type</b>	<b>Cost (\$)</b>
Adults	1	Prophylaxis – AHF	610 200
	2	Prothrombinex™	41 900
	1	Prothrombinex™ and FEIBA	94 900
Children	2	Prophylaxis – AHF	742 950
	1	Factor VIIa	143 000
	1	Factor VIIa and FEIBA	134 400
<b>Total</b>	<b>8</b>		<b>1 767 300</b>

AHF = antihæmophilic factor; FEIBA = factor eight inhibitor bypassing activity (Baxter)

Twenty four hæmophilia A patients received treatment on demand for acute bleeds; fourteen on plasma-derived product and ten on recombinant product. Five patients on recombinant product were less than 14 years old. Twenty two patients with hæmophilia B received treatment on demand; nine received a plasma-derived, purified factor IX concentrate (MonoFIX<sup>®</sup>, CSL) and thirteen received a plasma-derived product containing factors IX, X and prothrombin (Prothrombinex™, CSL). Only one hæmophilia B patient using treatment on demand was less than 14 years old.

The majority of patients who received treatment had severe hæmophilia, with only 10 cases of moderate and four cases of mild hæmophilia treated during the audit period.

**Product use** The UK Hæmophilia Director's Guidelines recommend that hæmophilia A patients on prophylaxis should receive 15 iu/kg of factor VIII three times each week, rising to 25 iu/kg if breakthrough bleeding is a problem.<sup>6</sup> Therefore, the average patient on prophylaxis would be expected to use around 2500 iu/kg/year. In our audit, 12 patients used the expected dose, with usage ranging between 1500 iu and 3000 iu/kg/year. Two patients on recombinant factor VIII used more than expected for additional breakthrough bleeds, but still used less than 5000 iu/kg/year. Three patients were particularly heavy users. These patients have previously been on the tolerisation programme. All three patients continue to have a detectable factor VIII inhibitor (two cases at 2 BU and one at 3 BU) and require higher doses of factor VIII to maintain adequate plasma levels. All three cases had a number of significant bleeds during 2001. One case required high-dose treatment for removal of a portacath. There was no other surgery performed on the inhibitor patients during 2001. One case with hæmophilia B was on prophylaxis at an appropriate dose (recommended dose is 25 iu/kg twice a week, ie, 2600 iu/kg/year).

The blood products used by patients receiving treatment on demand can be categorised into three groups. A low-usage group of 17 patients used less than 5000 iu each (median 2000 iu) during treatment of one or two bleeds during the audit period. An intermediate-usage group of 12 patients used between 5000 iu and 25 000 iu, and a high-usage group of 17 cases (15 severe and two moderate) used more than 25 000 iu each (range 27 000 iu to 146 000 iu, median 50 000 iu).

A total of eight hæmophilia A patients (12% of the severe cases) had detectable factor VIII inhibitors (Table 1). Three cases had previously completed a tolerisation programme and continued on regular prophylaxis. The other five cases were not suitable for tolerisation either due to a high inhibitor titre or poor compliance. In these

cases small bleeds were managed conservatively, whereas larger bleeds required treatment with recombinant factor VIIa, FEIBA (Baxter) or Prothrombinex<sup>TM</sup> (CSL). Recombinant factor VIIa is now the treatment of choice. Prothrombinex<sup>TM</sup> (CSL) is less effective, but far cheaper. Some adult patients appear to show some response to this agent. It is therefore used as first line for some cases.

In 2001, the two children with inhibitors primarily received treatment with recombinant factor VIIa for acute bleeds, with FEIBA (Baxter) used for one bleeding episode. FEIBA (Baxter) has similar activity to recombinant factor VIIa, but is a plasma-derived product and has largely been replaced by recombinant factor VIIa. In general, the three adult patients received Prothrombinex<sup>TM</sup> (CSL).

**Cost of treatment (Table 2)** The total cost of replacement products used by 69 patients with haemophilia at the Auckland Haemophilia Centre during 2001 was in excess of \$5.2 million. The largest proportion is for patients on regular prophylactic treatment. Fifteen cases on primary prophylaxis used \$2.4 million of products and three inhibitor patients on regular treatment following tolerisation used a further \$1.35 million. The product use in these 18 cases accounted for over 72% of the total expenditure.

**Table 2. Total cost of treatment for adults and children with haemophilia**

	Treatment	Patients (n)	Cost (\$)
<b>Adults</b>			
Haemophilia A	Prophylaxis	5	594 700
	On demand	16	437 700
	Inhibitors	4	747 000
Haemophilia B	Prophylaxis	0	403 800
	On demand	21	
<b>Total</b>		<b>46</b>	<b>2 183 200</b>
<b>Children</b>			
Haemophilia A	Prophylaxis	9	1 619 700
	On demand	8	141 500
	Inhibitors	4	1 020 400
Haemophilia B	Prophylaxis	1	240 800
	On demand	1	12 500
<b>Total</b>		<b>23</b>	<b>3 034 900</b>

Haemophilia A patients receiving on-demand treatment used \$580 000 of product (\$350 000 on plasma products and \$230 000 on recombinant products). The average cost of managing patients with haemophilia B is significantly less than managing those with haemophilia A. The products are cheaper and have a longer half-life; also inhibitor development is rare in haemophilia B. The total cost for all cases of haemophilia B (22 receiving on-demand treatment and one on prophylaxis) was \$657 000 compared with \$4.5 million for haemophilia A. Patients with factor VIII inhibitors are clearly very heavy users of blood products, in particular those patients on prophylaxis. Of note is that three adults with inhibitors used relatively small amounts of product as they were primarily treated with Prothrombinex<sup>TM</sup> (CSL) and pain relief.

The average product use was significantly higher in children than adults largely due to the high number of cases on prophylactic recombinant treatment and the use of recombinant factor VIIa for those with inhibitors. A relatively small number of individuals use a large proportion of the blood products. There were 15 patients who each used more than \$100 000 of treatment. The total for these 15 cases exceeds \$3.6 million (69.2% of the total expenditure).

## Discussion

Our review confirms the high cost of haemophilia care.<sup>7</sup> Blood products alone cost \$5.2 million for the treatment of 69 patients at Auckland Hospital. One aim of the audit was to collect data that could be used to predict how treatment patterns would change in the future and from this to estimate downstream costs. The most significant finding is that more than half (\$3 million) of the total expenditure was used to treat children (Table 2). Invariably, these children will require increased treatment as they grow, placing an escalating financial burden on the District Health Board. This is consistent with contemporary clinical practice,<sup>6</sup> but raises questions about equity of care relative to other health needs of the broader population.

The Auckland Haemophilia Centre provides specialist haemophilia care for the whole of the Auckland region. The standard of care provided is equal to recommended international standards for a comprehensive care centre. There are 165 people with haemophilia registered at the Auckland Centre. Only 69 patients received treatment in the year 2001, of whom the majority had severe haemophilia and only fourteen had mild or moderate disease. These less-severe cases all used relatively small amounts of replacement products for one or two bleeding episodes.

These results confirm that children receive significantly more intensive treatment than adults. This is in line with accepted international practice and is largely due to the introduction of prophylaxis for most children with severe disease. There is clear evidence that regular prophylaxis reduces the incidence of chronic joint disease if commenced before significant joint damage has occurred.<sup>8,9,10</sup> There has also been a move in many developed countries to use recombinant blood products in previously untreated patients and all children in order to minimise the risk of viral transmission. The use of prophylaxis with recombinant blood products has been standard practice in New Zealand for several years. Although this treatment has potential clinical advantages, it costs significantly more than treating individual bleeding episodes. Our figures show that 15 patients, without inhibitors, were on regular prophylaxis during 2001 and used \$2.45 million of replacement products (Table 1). Although the adults and older children used large quantities of product, more than half (\$1.8 million) were used by the ten children under 12 years old. The concern for long-term planning is that these children will require increasing amounts of factor VIII as they grow. A conservative estimate would be an increase of around 5% per annum with additional product use for newly diagnosed cases.<sup>11</sup> In practice, it has proved easy to start patients on prophylaxis, but there are no international guidelines recommending when prophylactic treatment should stop. Many people with haemophilia have significantly fewer bleeds as adults than during their childhood. Therefore, the benefit of continued prophylaxis beyond the age of 18 is not clear. It is, however, difficult to stop regular treatment in a young adult who has received prophylaxis for many years and possibly

never experienced a significant joint bleed. Continuing prophylaxis in these cases leads to a constant rise in costs.

The cost of treating the current cohort of adults will probably remain fairly constant. In general, they use on-demand therapy with plasma-derived products. During the audit period, 46 patients received treatment on demand at a cost of just under \$1 million; 37 of these were adults and only three used recombinant blood products.

The audit also highlights the recognised high cost of treating patients with factor VIII inhibitors. International studies have shown that inhibitor patients can account for up to 40% of total treatment costs in haemophilia centres. In our Centre, eight patients with inhibitors were treated during 2001. The total cost of products used was \$1.7 million. Three patients have undergone tolerisation with some degree of success, but still require high-dose prophylaxis. The remaining five cases receive treatment on demand. In this group of patients there is again a clear difference in the management of adults compared with children. The difference is accounted for almost exclusively by the cost of recombinant factor VIIa. Our four children with inhibitors receive recombinant factor VIIa as required. The annual cost of treating these children is just over \$1 million. We have been reluctant to use recombinant factor VIIa in adults, as a single treatment dose for a 70 kg male exceeds \$6000. The adults have historically been treated with Prothrombinex<sup>TM</sup> (CSL), which is significantly less effective than recombinant factor VIIa and as a result they have suffered prolonged bleeding episodes and risk long-term joint damage.

When assessing costs it should be recognised that factor replacement products are only part of the cost of haemophilia care. The expenses associated with staffing and maintaining a dedicated haemophilia centre have not been included in this study. In addition, haemophilia is associated with a high incidence of joint disease, which places an additional demand on orthopaedic services. Many older patients require synovectomy, joint arthrodesis or joint replacement. In addition, hepatitis C remains a considerable problem in this population. Figures from a haemophilia survey in 2000 showed that 22% of people with haemophilia are hepatitis-C positive. Several will require treatment with interferon and ribavirin over the next few years. At this stage it is difficult to predict the long-term outcome for many of these cases, but some may develop cirrhosis with liver failure and may require transplantation.

Overall, the cost of treatment appears extremely high, but the volume of products used in 2001 was less than for an average year. Towards the end of 2000 there was a worldwide shortage of recombinant factor VIII. Patients were asked to ration product use as far as practicable and virtually no elective haemophilia surgery was performed for approximately 18 months. Surgery consumes high volumes of replacement products adding significantly to the cost of treatment.

It is clear that costs will rise as our paediatric population grows, but there are other external pressures that could also have an impact in the future. In Europe and Canada there is concern about the potential risk of variant CJD in blood products. This has led to Canada switching entirely to the use of recombinant products and several European countries are considering following suit. If the same change was made in New Zealand, it would add a further 40% to our replacement product costs.

For clinicians there is a real conflict. Our primary role is to provide the most appropriate treatment for our patients. In the field of haemophilia, the standard of care

in New Zealand has been equal to that provided in most developed countries. At the same time there is pressure to reduce costs as the Auckland District Health Board faces deficit funding. Haemophilia care is demonstrably extremely expensive. This audit has shown that to maintain the same level of care in the future, our costs will inevitably increase. Cost considerations are already influencing treatment as we have shown by the use of Prothrombinex<sup>TM</sup> (CSL) rather than recombinant factor VIIa for adults with inhibitors. It is difficult to resolve the dilemma that this issue is beginning to pose. Like a number of areas of contemporary medicine where the cost of therapies are extremely high, the debate must be held openly and publicly with input from our wider society. Haemophilia treatment is, however, relatively unique in that the extremely high costs are incurred primarily by a relatively small patient pool for the prevention of pain and joint destruction rather than for disease cure. They are, therefore, uncapped and lifelong for the individual.

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#### References:

1. Jones P. The early history of haemophilia treatment: a personal perspective. *Br J Haematol* 2000;111:719–25.
2. Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992;232:25–32.
3. Scharrer I, Bray GL, Neutzling O. Incidence of inhibitors in haemophilia A patients – a review of recent studies of recombinant and plasma-derived factor VIII concentrates. *Haemophilia* 1999;5:145–54.
4. Briet E, Peters M. The incidence of inhibitors in hemophilia A and the induction of immune tolerance. *Adv Exp Med Biol* 2001;489:89–97.
5. O'Connell N, Mc Mahon C, Smith J, et al. Recombinant factor VIIa in the management of surgery and acute bleeding episodes in children with haemophilia and high responding inhibitors. *Br J Haematol* 2002;116:632–5.
6. Aledort LM, Miners A, Bohn R, et al. Economic aspects of haemophilia care. *Haemophilia* 1999;5:216–9.
7. United Kingdom Haemophilia Centre Directors' Organisation Executive Committee. Guidelines on therapeutic products to treat Haemophilia and other hereditary coagulation disorders. *Haemophilia* 1997;3:63–77
8. Fischer K, van der Bom JG, Mauser-Bunschoten EP, et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia* 2001;7:446–52.
9. 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.
10. Miners AH, Sabin CA, Tolley KH, Lee CA. 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.

11. Giangrande P. Distribution and treatment of haemophiliacs. *Haemophilia* 1998;4 (suppl 1):1–2.