Haemophilia (2001), 7, 349–359

Treatment of haemophilia in the United Kingdom 1981–1996

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Organization of haemophilia care in the UK

The history of the development of a network of haemophilia centres in the UK has been described in detail elsewhere [1]. The UK Ministry of Health designated 36 'haemophilia diagnostic and registration centres' in 1968. Three of these Centres (Oxford, Manchester and Sheffield) were designated special treatment centres. The first meeting of the Directors of all the haemophilia centres was held in Oxford in 1968. It was subsequently agreed to establish a national register of patients with bleeding disorders, and this was set up in the Oxford Haemophilia Centre. By 1976, the number of haemophilia centres had grown to 52.

In 1993, two tiers of haemophilia centre were created in accordance with guidelines published by the Department of Health, and 22 centres were designated as comprehensive care centres. These are typically units devoted solely or largely to disorders of haemostasis, and criteria for designation include a recommendation that at least 40 subjects with severe haemophilia be registered with the centre to ensure adequate clinical experience. Comprehensive care centres are obliged to provide a 24-h clinical and laboratory service, as well as specialist support for orthopaedic problems, dental care and patients infected with HIV and/or hepatitis. They are now also subject to triennial review.

A network of some 80 haemophilia centres was also created as a second tier. These are largely general haematology departments with facilities for the diagnosis and treatment of haemophilia. In 1991, the United Kingdom Haemophilia Centre Directors' Organisation (UKHCDO) was established, and the title underwent a subtle change in 1999 to the United

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Accepted 28 February 2001

Kingdom Haemophilia Centre Doctors' Organisation to permit broadening of the membership. The UKHCDO national database continues to be maintained at the Oxford Haemophilia Centre, which serves as the Secretariat for UKHCDO. The collaboration between centres has resulted in several important publications, including the epidemiology of hepatitis and HIV amongst people with haemophilia [2–9], the safety of National Health Service (NHS) factor VIII concentrate [10] and the incidence of inhibitors [11,12]. There has also been collaboration between centres to determine the genetic defects in all families with haemophilia, to facilitate carrier detection and antenatal diagnosis [13,14].

This report is a sequel to a publication describing the treatment of haemophilia in the UK for the period 1976–80 [15].

Data collection

The basic details collected for all patients with congenital bleeding disorders include: name, sex, date of birth, diagnosis, factor level, inhibitor status and HIV status. Every year information is collected regarding patients who had received treatment during the year, including the type of blood products used and inhibitor status. Data are also collected on date and cause of death. In addition, cards are sent out from Oxford to every haemophilia centre every 3 months requesting details of any adverse events, including viral transmission, development of an inhibitor, thrombotic event, or allergic reactions to a concentrate. For the period covered by this report, patient consent for data collection was not sought and was not required by law.

Number of people with haemophilia in the UK

The number of people with haemophilia A registered at UK Haemophilia Centres who are usually resident in the UK has increased steadily from 3943 in 1981 to 4826 in 1996 (Table 1), of whom only 1546 (32%) were severely affected (defined as factor VIII [FVIII] < 2 IU dL^{-1}). However, the proportion of patients with severe haemophilia has been falling since 1981, reflecting the relatively greater impact of HIV on severely affected patients, who were more likely to be exposed to blood products [7]. The demographic details of the haemophilia A patients registered in 1996 are shown in Table 2, which classifies patients according to age and factor level and also indicates the number treated that year and the number on home treatment.

The number of patients with haemophilia B (Christmas disease) rose from 701 in 1981 to 1064 in 1996 (Table 1). Relatively few patients with haemophilia B were exposed to HIV in the UK [4] and thus there was little change in the proportion of severely affected patients in the study period (36% with factor IX [FIX] level of < 2% in 1981, and 32% in 1996). The demographic details of the haemophilia B patients registered with haemophilia B in 1996 are shown in Table 3.

During the period covered by this report, 2262 haemophilia A patients and 509 haemophilia B patients were entered into the register for the first

	Haemophilia A					Haemophilia B				
	Factor VIII level (IU dL^{-1})					Factor IX level (IU dL^{-1})				
Year	< 2	2–10	> 10	N/K	Total	< 2	2–10	> 10	N/K	Total
1981	1718	1194	838	193	3943	255	279	131	36	701
1982	1746	1234	911	197	4088	260	300	140	36	736
1983	1755	1273	980	204	4212	267	318	152	36	773
1984	1791	1299	1060	207	4357	275	332	162	40	809
1985	1803	1322	1110	208	4443	283	341	171	39	834
1986	1793	1344	1149	213	4499	287	353	179	41	860
1987	1793	1378	1201	221	4593	295	359	196	42	892
1988	1790	1397	1247	227	4661	304	363	202	45	914
1989	1775	1420	1286	229	4710	307	367	210	48	932
1990	1749	1431	1329	231	4740	314	373	220	48	955
1991	1717	1451	1368	232	4768	323	383	234	47	987
1992	1697	1466	1410	236	4809	323	390	241	48	1002
1993	1662	1485	1457	240	4844	324	395	251	53	1023
1994	1704	1515	1518	245	4982	330	402	259	55	1046
1995	1639	1493	1549	229	4910	331	407	263	48	1049
1996	1546	1489	1552	239	4826	332	408	274	50	1064

Table 1. Total number of haemophilia A and haemophilia B patients registered with UK haemophilia centres in 1981–96, grouped by severity.

Table 2. Haemophilia A patients known at haemophilia centres in 1996, showing the number of patients treated during 1996 and the number of treated patients who were on home treatment, with the severity of the coagulation defect and age.

	Number of patients per factor VIII level														
	< 2 IU dL^{-1}			2–10 IU dL^{-1}			> 10 IU dL^{-1}			Not known			Total		
Age (years)	Regist.	Trtd 1996	On HT 1996	Regist.	Trtd 1996	On HT 1996	Regist.	Trtd 1996	On HT 1996	Regist.	Trtd 1996	On HT 1996	Regist.	Trtd 1996	On HT 1996
< 5	134	124	63	84	52	11	60	16	1	4	3	0	282	195	75
5–9	180	167	141	121	75	35	99	32	4	0	0	0	400	274	180
10–14	172	156	139	92	59	28	102	26	2	0	0	0	366	241	169
15–19	140	125	111	98	58	30	101	20	5	4	1	0	343	204	146
20–29	250	230	192	233	99	41	245	49	3	14	1	1	742	379	237
30–39	294	240	203	288	103	32	291	44	2	12	0	0	885	387	237
40–49	186	150	115	211	63	23	209	33	4	23	2	0	629	248	142
50–59	103	81	60	157	46	8	153	32	3	14	3	1	427	162	72
60–69	47	40	25	116	38	6	154	26	0	11	0	0	328	104	31
70 +	33	19	11	80	20	1	132	25	0	10	1	0	255	65	12
N/K	7	0	0	9	0	0	6	0	0	147	2	0	169	2	0
Total	1546	1332	1060	1489	613	215	1552	303	24	239	13	2	4826	2261	1301

Regist., registered; Trtd, treated; HT, home treatment.

Table 3. Haemophilia B patients known at haemophilia centres in 1996, showing the number of patients treated during 1996 and the number of treated patients who were on home treatment, with the severity of the coagulation defect and age.

	Number of patients per factor IX level														
	< 2 IU dL^{-1}			2–10 IU dL^{-1}			> 10 IU dL^{-1}			Not known			Total		
Age (years)	Regist.	Trtd 1996	On HT 1996	Regist.	Trtd 1996	On HT 1996	Regist.	Trtd 1996	On HT 1996	Regist.	Trtd 1996	On HT 1996	Regist.	Trtd 1996	On HT 1996
< 5	20	21	5	21	12	2	7	1	0	1	0	0	49	34	7
5–9	37	32	22	25	18	3	16	3	0	0	0	0	78	53	25
10–14	31	24	18	37	17	4	25	6	1	1	0	0	94	47	23
15–19	31	23	21	33	21	6	35	5	2	0	0	0	99	49	29
20–29	54	49	38	82	40	15	43	1	0	0	0	0	179	90	53
30–39	61	41	31	72	20	10	40	4	0	8	0	0	181	65	41
40–49	42	31	23	60	17	3	44	8	0	1	0	0	147	56	26
50–59	30	24	19	21	6	2	33	4	0	5	1	0	89	35	21
60–69	17	10	6	29	16	5	16	5	0	2	1	0	64	32	11
70 +	7	6	2	27	8	1	12	2	0	1	0	0	47	16	3
N/K	2	0	0	1	0	0	3	0	0	31	1	0	37	1	0
Total	332	261	185	408	175	51	274	39	3	50	3	0	1064	478	239

Regist., registered; Trtd, treated; HT, home treatment.

time. Of the haemophilia A patients, 621 (27%) were severely affected; for the haemophilia B patients, the figure was 122 (24%). As expected, most of the severely affected patients were aged < 5 years when first registered but many of the mildly affected patients with FVIII or FIX levels > 10 IU dL^{-1} were aged > 20 years when first registered. In the period 1981–1996, 2094 boys with haemophilia A (of whom 916 were severely affected) and 463 with haemophilia B (of whom 163 were severely affected), were born. It is interesting to note that the introduction of methods for carrier detection and prenatal diagnosis of haemophilia do not appear to have resulted in a substantial reduction in the number of haemophilia A and haemophilia B patients born (Fig. 1). The general experience in the UK is in line with the published experience of one centre that only a minority of pregnant carriers request antenatal diagnosis [16].

The incidence of inhibitory antibodies

The proportion of patients with haemophilia A who are known to have developed inhibitory antibodies to factor concentrates has remained constant at around 6% ever since information was first collected in 1969 [17] (Fig. 4). By 1996, a cumulative total of 249 of 4826 (5%) patients with haemophilia A who

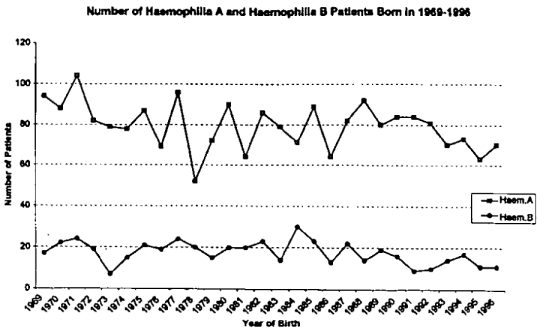

Fig. 1. The number of babies with haemophilia A and B born in the UK in 1969–96. These figures include both severe and mild forms.

were alive were known to have developed inhibitory antibodies at some stage. However, the proportion of severely affected patients with inhibitory antibodies is significantly higher (196/1546 = 12.7%). Of these, 29% developed antibodies before they were aged 5 years and it is also interesting to note that 21% of the patients who developed antibodies had measurable levels of factor VIII before the antibodies were detected (Table 4).

Inhibitor development in haemophilia B is unusual. The proportion of haemophilia B patients with FIX antibodies did not change during the period, and remains less than 1%. Five new cases were detected in 1981–96 and a total of 12 patients with haemophilia B and inhibitors were alive and registered in 1996. All new cases identified during the study period had a baseline FIX level of < 2 IU dL^{-1} and four were aged < 5 years when the inhibitors were first detected (Table 4).

Table 4. Original baseline FVIII/IX level (IU dL^{-1}) of patients who developed inhibitors in 1981–96 and age when detected.

Age when inhibitor Detected (years)	Number on register per baseline factor level				
	< 2	2–10	> 10	N/K	Total
Haemophilia A					
< 1	2	–	–	–	2
1–4	52	7	–	–	59
5–9	22	9	–	–	31
10–14	2	–	–	–	2
15–19	8	2	–	–	10
20–29	5	2	2	–	9
30–39	11	4	–	–	15
40–49	9	4	2	–	15
50–59	10	3	–	–	13
60–69	5	4	2	–	11
70–79	1	2	–	1	4
Total	127	37	6	1	171
Haemophilia B					
1–4	4	–	–	–	4
20–29	1	–	–	–	1
Total	5	–	–	–	5

von Willebrand disease

Information regarding patients with von Willebrand disease has been included in the UKHCDO National Register since 1976 Unfortunately, there was no common method of assaying von Willebrand factor levels for much of the early part of the study period. Some laboratories reported the results of 'vWF Ag' immunoassays and others reported the results of 'functional' assays, using a variety of methods, including some which only yielded semiquantitative results. It was therefore decided for the purpose of this report to classify patients with von Willebrand disease according to the FVIII:C level. Over the period 1981–96 the number of registered patients with von Willebrand disease rose from 709 in 1981 to 4417 in 1996. Forty-five (1%) are known to have an FVIII:C level of < 2 IU dL^{-1} and 367 (8%) have an FVIII:C level between 2 and 14 IU dL^{-1}. The increase in the number of patients registered is likely to be the result of greater awareness of the condition and improved laboratory tests. National guidelines on the diagnosis and management of von Willebrand disease have been published by UKHCDO and it is hoped that these will further increase awareness of the condition and also improve laboratory diagnosis [18]. A cumulative total of only eight registered patients with von Willebrand disease were recorded as having developed inhibitory antibodies by the end of 1996.

Acquired haemophilia

Information on cases of acquired haemophilia has been collected by UKHCDO since 1984. Although it is accepted that a significant number of cases are not registered with haemophilia centres, some general conclusions may be drawn. Between 1985 and 1996, 240 patients with acquired haemophilia A were registered and treated at UK haemophilia centres, of whom 151 are known to have died. The number of new patients registered rose from nine in 1984 to 32 in 1996, and probably reflects increased awareness of the problem. The age of the patients at diagnosis ranged from 20 to 99 years and 125 (52%) of the 240 cases reported were female.

Only 24 (10%) patients were aged < 50 years of age at diagnosis. Possible predisposing conditions prior to the detection of the antibodies were reported

for 98 patients. Twenty-four (10%) had malignant disease, 16 had rheumatological conditions and 11 were females who developed the inhibitor during pregnancy or within 12 months of delivery. A total of five cases of acquired haemophilia B were reported up to 1996. Four of the patients were aged 70 or over and none died during the survey period. One patient was known to have systemic lupus erythematosus (SLE) and one had rheumatoid arthritis.

Rare congenital disorders of coagulation

Since 1984, the UK Haemophilia Centre Directors have collected information regarding the patients under their care who have rare inherited blood coagulation disorders. The number of patients registered in 1996 with congenital deficiencies are as follows: fibrinogen, 79; prothrombin, 11; factor V, 50; factor VII, 164; factor X, 84; factor XI, 610; factor XII, 543; factor XIII, 26; combined factor V + factor VIII deficiency, 19. As has been noted in a previous survey of patients from the UK and other countries with rare congenital disorders of coagulation, parental consanguinity is often a factor in the inheritance of these autosomal recessive conditions [19]. Concentrates of factors VII, XI, and XIII are available on a named-patient basis from Bio Products Laboratory (BPL; Elstree, Herts, UK). In the UK, an intermediate-purity FIX concentrate manufactured by BPL named 9A, was widely used for the treatment of congenital deficiencies of prothrombin (FII) and FX during the study period of 1981–96. Table 5 shows by diagnosis the number of registered patients and the number treated in 1996. It is only a small proportion of the patients that required treatment.

The treatment of haemophilia

Concentrates of both FVIII and IX, derived from UK volunteer donors, have been available ever since the early 1960s. These are manufactured by BPL and by the Protein Fractionation Centre (PFC; Edinburgh, UK) which also supplies Northern Ireland. Both agencies are an integral part of the National Health Service, and are thus enterprises supported by the State. Commercial FVIII concentrates became available in the UK from the early 1970s. At first, these products were supplied free of charge to haemophilia centres but budgets were devolved to individual centres in England and Wales in 1993, which offered freedom of choice of products. All centres in the UK now have devolved budgets that permit selection from a wider range of products. In the UK, in contrast to many other countries, the choice of product ultimately rests with individual physicians, who are also responsible for purchasing concentrates for use at home as well as in hospital.

There has been a consistent rise each year of approximately 10% in the usage of both FVIII and FIX. A total of 63.2 million units of FVIII were used in 1981 to treat haemophilia A patients but consumption had risen to 149.7 million units by 1996 (Fig. 2). Factor IX consumption rose from 9.9 million to 23.2 million units over the same period (Fig. 3). Perhaps contrary to expectation, concentrate usage did not fall between 1981 and 1985, despite concerns about HIV infection.

Table 5. Number of patients with rare congenital blood coagulation defects known to UK haemophilia centres, with the number treated with blood products during 1996 and the number on home treatment.

	Number of patients		
Coagulation defect	On register in 1996	Treated in 1996	On HT in 1996
Fibrinogen deficiency	79	6	–
Prothrombin deficiency	11	1	–
Factor V deficiency	50	6	–
Factor VII deficiency	164	17	2
Factor X deficiency	84	17	7
Factor XI deficiency	610	29	–
Factor XII deficiency	543	3	–
Factor XIII deficiency	26	11	2
Combined XI + XII deficiency	11	–	–
Combined II + VII + X deficiency	5	–	–
Combined V + VIII deficiency	19	5	–
Combined XI + VIII deficiency	7	1	–
Combined VIII + IX deficiency	1	–	–
Other combined defects	43	2	1
Platelet defects	559	26	5
Total	2212	124	17

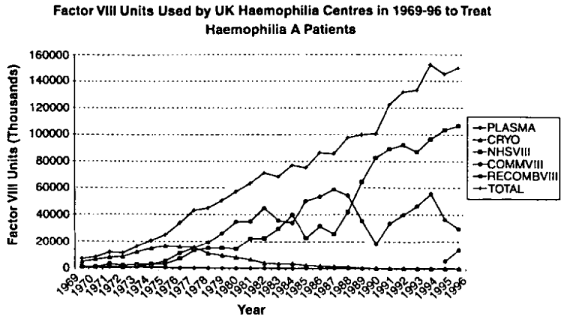

Fig. 2. The consumption of factor VIII in the UK 1969–96. Total consumption is illustrated, as well as the separate amounts of NHS (BPL or PFC) and commercial products.

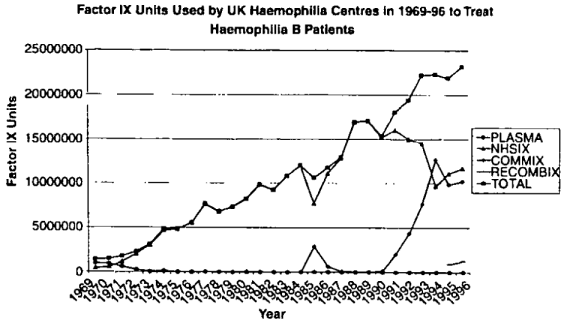

Fig. 3. The consumption of factor IX in the UK 1969–96. Total consumption is illustrated, as well as the separate amounts of NHS (BPL or PFC) and commercial products.

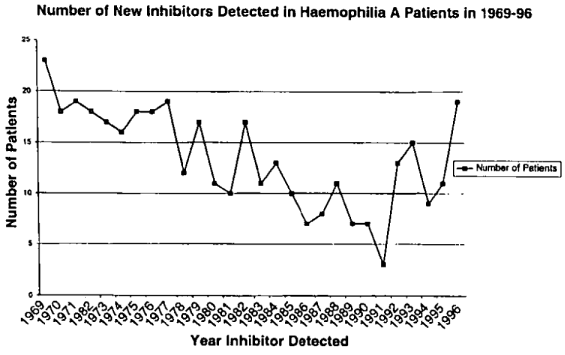

Fig. 4. The number of new inhibitors (factor VIII antibodies) detected in haemophilia A patients in 1969–96.

Commercial (non-UK-sourced) FIX was used for the first time to treat haemophilia B in the UK in 1985, because the NHS fractionation laboratories did not produce heat-treated FIX until the following year. Heat-treated commercial FVIII was introduced for general use in the UK in December 1984, and heat-treated FVIII (8Y; BPL) became available in July 1985. Factor VIII concentrates made from human blood plasma donated in the UK and manufactured by either BPL or PFC were used for the treatment of a total of 4148 patients over the 16-year period. Over the same period, 3219 patients with haemophilia A received one or more of the commercial concentrates. In 1981–96, the total number of people with haemophilia A who received human blood products, from all sources, was 4834.

With the introduction of NHS heat-treated FIX, use of commercial FIX fell dramatically in 1986 but rose again from 1989 onwards, following the recommendation that high-purity FIX concentrates should be used in patients with severe FIX deficiency undergoing surgery, because of a risk of thromboembolism [20]. The NHS manufacturers responded by producing high-purity FIX concentrates for the same cost as the intermediate-purity equivalent, and thus all patients in the UK were transferred to high-purity plasma FIX products by 1993.

During the study period, the use of cryoprecipitate for the treatment of haemophilia A ceased, although this material was used for the treatment of 1583 patients with haemophilia A patients in the survey period. In 1981, 6.1 million units of FVIII in the form of cryoprecipitate were used. The last year in which cryoprecipitate was recorded as being used in the UK for the treatment of haemophilia was 1992, when only 1000 units of FVIII were administered as cryoprecipitate.

An interesting but consistent observation is that approximately 85% of patients with severe haemophilia A require treatment each year. The corollary is that a significant proportion of patients with even severe haemophilia can apparently go a whole year without requiring treatment.

Treatment of patients with inhibitors

Table 6 shows the number of haemophilia A patients with FVIII inhibitors treated each year in 1981–96 and the amount and type of materials they received. In 1996, 10.4 million units of human FVIII concentrate were used to treat these patients. Intermediate-purity FIX was widely used throughout the UK between 1981 and 1996 as an alternative to activated prothombin-complex concentrates. The use of porcine FVIII (Hyate:C) declined steadily over the study period as the use of FEIBA and recombinant FVIIa (NovoSeven) increased. Use of porcine FVIII fell from around 1 million units during the early years of the study period to 420 000 units in 1995. The product was withdrawn from the market in the

Table 6. Total materials used (at hospital and for home treatment) in 1981–96 to treat haemophilia A patients who had FVIII antibodies (inhibitors).

Year	Number of patients treated	Factor VIII units				Other materials (u)				
		Cryoprecipitate	NHS concentrate	Commercial concentrate	Total human FVIII	Porcine FVIII	NHS FIX	FEIBA*	Autoplex	Commercial FIX	rVIIa**
1981	135	133 000	1345 000	4186 000	5664 000	924 000	377 000	1119 000	336 000	–	–
1982	149	87 000	763 000	5001 000	5851 000	1183 000	1388 000	1573 000	501 000	–	–
1983	139	100 000	1299 000	4158 000	5557 000	1513 000	1217 000	1058 000	417 000	–	–
1984	157	62 000	1193 000	4459 000	5714 000	2020 000	2533 000	475 000	132 000	–	–
1985	141	19 000	670 000	5910 000	6599 000	1689 000	1543 000	834 000	169 000	1082 000	–
1986	169	65 000	1519 000	4469 000	6053 000	1078 000	1460 000	1554 000	592 000	447 000	–
1987	145	3 000	1293 000	6499 000	7795 000	1204 000	1806 000	2107 000	23 000	3 000	–
1988	167	91 000	1044 000	5675 000	6810 000	684 000	1929 000	3538 000	207 000	–	–
1989	168	–	4359 000	3597 000	7956 000	429 000	1289 000	2588 000	168 000	–	871.1
1990	172	2 000	3989 000	987 000	4978 000	741 000	1858 000	2625 000	174 000	–	984.9
1991	139	–	3632 000	2634 000	6266 000	884 000	1371 000	3781 000	96 000	–	84.3
1992	109	–	5458 000	2110 000	7568 000	706 000	1397 000	5294 000	65 000	85 000	
1993	113	–	5740 000	910 000	6650 000	429 000	1688 000	6477 000	99 000	10 000	961.6
1994	123	–	4116 000	5049 000	9165 000	329 000	1052 000	9051 000	376 000	42 000	561.7
1995	145	–	5457 000	6498 000	11 955 000	420 000	1633 000	4971 000	–	–	2071.6
1996	106	–	6241 000	4190 000	10 431 000	156 000	2038 000	6043 000	438 000	9 000	1059.2

*FEIBA, Factor VIII inhibitor by passing activity; **mg.

autumn of 1996 following identification of porcine parvovirus in some batches of the product and in that year only 156 000 units were used in the UK. By contrast, use of FEIBA rose from 1 million units in 1981 to 6 million units in 1996. In 1995, the last full year before temporary withdrawal of the product, 70 000 units (16% of total usage) of porcine FVIII was supplied for home treatment of patients with haemophilia A and inhibitors, while 62% of the FVIII concentrate and 37% of FEIBA was supplied for home treatment. Recombinant VIIa (NovoSeven) was first used on a trial basis in 1990 at a few centres and had increased to 1430.2 mg in 1996 (1059.2 mg for patients with congenital haemophilia A and inhibitors; 322 mg for patients with congenital haemophilia B and inhibitors; and 49 mg for acquired haemophilia A).

Treatment of von Willebrand disease

The amount of FVIII used to treat von Willebrand disease patients rose from 2.2 million units in 1981 to 5.9 million units in 1996. Cryoprecipitate was finally abandoned for the treatment of von Willebrand disease as late as 1994. In addition, 813 patients were treated with DDAVP and 138 received EACA (ε-amino-caproic acid) tranexamic acid. Specific concentrates of von Willebrand factor (vWF) became available in 1990 and a total of 3.8 million vWF units were used to treat a total of 68 individuals in 1990–96.

Causes of death

Patients registered with the UKHCDO database are 'flagged' with the Office for National Statistics (ONS) and the Oxford Haemophilia Centre automatically receives copies of the death certificates of patients previously registered as having a congenital bleeding disorder. This system has greatly improved the accuracy of the data regarding mortality in haemophilic patients. A detailed analysis of mortality has already been published [7].

The cause of death for 1190 patients with haemophilia A, 108 with haemophilia B and 155 with von Willebrand disease who were known by haemophilia centre directors to have died during 1981–96 is shown in Table 7. The principal cause of death in patients with haemophilia A during this period was AIDS, which accounted for 564 (38%) deaths and has been the commonest cause of death for people with haemophilia in the UK since 1987. Cerebral haemorrhage was the second most common cause of death (159–10%), followed by cancer (129–9%),

Table 7. Deaths in 1981–96 of haemophilia A, haemophilia B and von WIllebrand disease patients.

Cause (as reported by haemophilia centre)	Number of patients*				
	Haem. A	Haem. B	von Willebrand	Total	
AIDS	546 (546)	12 (12)	6 (6)	564 (564)	
Cerebral haemorrhage/stroke	132 (32)	16 (1)	11	159 (33)	
Cancer	95 (18)	14 (1)	20	129 (19)	
Ischaemic heart disease	65 (7)	8	15	88 (7)	
Aortic stenosis	3 (1)	–	–	3 (1)	
Respiratory problems					
Pneumonia (not PCP)	53 (20)	5	7	65 (20)	
Chronic obstructive airways disease	5	–	–	5	
Pulmonary tuberculosis	1	–	–	1	
Pulmonary oedema	1 (1)	–	1	2 (1)	
Pulmonary embolism	–	1	4	5	89 (21)
Acute asthma attack	2	–	–	2	
Chest infection	4	–	1	5	
Bronchitis	1	–	–	1	
Respiratory failure	–	1	1	2	
Emphysema	–	–	1	1	
Liver disease	69 (41)	6 (1)	3	78 (42)	
Septicaemia	14 (10)	1	1	16 (10)	
Haemorrhage					
G.I. bleed	11 (3)	2	–	13 (3)	
Retroperitoneal bleed	5 (3)	–	–	5 (3)	
Throat haemorrhage	1	–	–	1	32 (10)
Iliopsoas bleed	1	–	–	1	
Intra-abdominal bleed	3 (1)	–	–	3 (1)	
Haemorrhage (misc.)	8 (2)	1	–	9 (3)	
Renal failure	8 (3)	1	2	11 (3)	
Acute myeloid leukaemia	2	–	–	2	
Hodgkin's disease	5 (1)	–	–	5 (1)	
Non-Hodgkin's lymphoma	2	–	1	3	
Post-operative complications	11 (1)	3	2	16 (1)	
Accident					
RTA	9 (4)	1	2	12 (4)	
Head injury	5 (3)	2	2	9 (3)	
Fractured femur	1	–	–	1	
Inhalation of vomit	1	–	–	1	28 (7)
Fall	–	1	1	2	
Drowning	–	–	1	1	
Smoke inhalation – fire at home	–	–	1	1	
Killed in France – no details	1	–	–	1	
Suicide	10 (4)	3	2	15 (4)	
Overdose (not suicide)	5 (2)	1	1	7 (2)	
Intestinal obstruction	1	–	–	1	
Staphylococcal peritonitis	1	–	–	1	
Cot death	2	1	–	3	
Ruptured spleen	3	–	–	3	
Perforated peptic ulcer	1 (1)	–	–	1 (1)	
Haemophilic pseudotumour	2 (1)	–	–	2 (1)	
Graft v Host disease	–	–	1	1	
Perforated aortic aneurysm	2	–	–	2	
Ruptured oesophagus	–	1	–	1	
Ruptured splenic artery	–	–	1	1	
Abdominal aneurysm	–	–	1	1	
Acute infection	1 (1)	–	–	1	
Legionnaires disease	1	–	–	1	

Table 7. (Continued).

Cause (as reported by haemophilia centre)	Number of patients*			
	Haem. A	Haem. B	von Willebrand	Total
Gastroenteritis	1	–	–	1
Epileptic fit	1 (1)	–	2	3 (1)
Cerebral palsy	–	–	1	1
Combined immune deficiency	1	–	–	1
Undiagnosed metabolic disorder	–	–	1	1
Senility/Alzheimer's disease	2	–	–	2
Natural causes	1	–	–	1
Unascertainable	2 (2)	1	–	3 (2)
Not known	88 (4)	26	66	180 (4)
Total	1190 (713)	108 (15)	159 (6)	1457 (734)

*( ) = number of HIV+ patients.

myocardial infarction and other forms of heart disease (88–6%), and respiratory problems, including pneumonia (89–6%). Haemorrhage of various types including gastrointestinal bleeding and post-operative bleeding was given as a cause of death in 32 patients. Seventy-eight patients died of liver disease, 28 had fatal accidents and 15 committed suicide. Cerebral haemorrhage was the most common cause of death in haemophilia B patients (14%), followed by cancer (10%), then myocardial infarction and other forms of heart disease (7%). Of the haemophilia B patients who died, only 15 (14%) were HIV positive.

In 1981–96, 159 patients with von Willebrand disease died. Twenty patients (13%) had cancer, 15 (9%) had ischaemic heart disease, 15 (9%) had respiratory problems and 11 (7%) had cerebral haemorrhage/stroke. Seven patients suffered fatal accidents. Only six of the von Willebrand's disease patients who died were seropositive for anti-HIV.

Discussion

This report covers the period from 1981 to 1996. There were many significant events during this period, including the reporting of the first cases of AIDS and the identification of the hepatitis C virus. The gene for FVIII was cloned in 1984. Ten years later, recombinant FVIII was licensed in the UK and the first clinical trials of recombinant FIX started in 1995.

There has been a heavy toll due to HIV infection, which has represented the commonest cause of death among people with haemophilia in the UK since 1987. Patients with severe haemophilia A were most affected by this blood-borne virus, and a significantly smaller proportion of patients with haemophilia B was infected in the UK. Heat-treated commercial FVIII was introduced for general use in the UK in December 1984, and heat-treated NHS FVIII (8Y; BPL) became available in July 1985. This obviously created a dilemma for clinicians and patients at the beginning of 1985 who were forced to choose between imported, heat-treated American concentrates and the equivalent British products that had not been heat-treated. While it is accepted that some people with haemophilia could have been exposed to HIV through the use of British product in preference to heat-treated commercial products during this critical period, it must be remembered that HIV seroconversions with a heat-treated commercial FVIII were reported in 1986, leading to withdrawal of this product in the UK [21]. The virucidal process developed by BPL for the manufacture of 8Y involved heat-treatment at 80 °C for 72 h. A subsequent clinical study co-ordinated by UKHCDO showed that this process was also effective against hepatitis C [10]. This intermediate-purity FVIII concentrate is still widely used in the UK. Although recombinant FVIII was launched in the UK in 1994, funding of these expensive products was initially denied by many local health authorities. Only 4% of all FVIII used in 1994 and 1995 was recombinant, rising to 16% in 1996. Permission to treat all patients under the age of 16 with recombinant products was only granted by the government in February 1998.

It is of interest that the number of boys born with haemophilia each year has not fallen despite the wide availability of tests for carrier detection and antenatal diagnosis (Fig. 1). Several studies have documented that only a minority of carriers opt for termination of pregnancy if they are found to be carrying an affected child [16,22]. The reasons for this are probably complex and may reflect the unacceptability of termination to individuals, or the recognition by carrier females that prophylactic treatment and the availability of new, safer products offer the

prospect of an essentially normal lifestyle for the new generation of haemophilic boys. The increased longevity of patients with haemophilia, together with the availability of safer products, is likely to lead to a gradual increase in the number of patients with haemophilia in developed countries. A study from the Netherlands, a country in which relatively few people with haemophilia were exposed to HIV, predicted a 20% increase in the number of people with haemophilia over the next generation [23].

Antibodies to FVIII have been reported in approximately 6% of patients with haemophilia A in the UK. This figure has changed little since 1981, or indeed during the past 30 years, notwithstanding the introduction of a variety of therapeutic materials of differing purity. Consistent with other reports, antibodies usually appear within the first few years of treatment and thus the greater percentage develop before the age of 5 years. A previous analysis showed no evidence of an increase in the incidence of inhibitory antibodies following the adoption of high-purity plasma-derived concentrates in the period from 1990 to 1993 [11]. Although recombinant FVIII was available in the UK in late 1994, usage was limited until the government made funding available in early 1998 for children under 16 years and infrequently treated adults, and thus it is not possible in this report to assess the impact of the introduction of recombinant FVIII on the incidence of inhibitors. Almost one-quarter of those who developed antibodies to FVIII had measurable levels of FVIII before the antibody appeared. A study published in 1998 documented the appearance of inhibitory antibodies in 26 subjects with mild or moderate haemophilia A in the UK, the Netherlands and the USA [24]. By contrast, antibodies to FIX are extremely uncommon. All those who developed FIX antibodies did so before the age of 5 years and all had levels of FIX < 2 IU dL^{-1}. A previous analysis of patients in the UK documented a high frequency of large gene deletions in such cases [25].

While the register for people with haemophilia is regarded as complete and accurate, it is accepted that many cases of mild von Willebrand disease remain unrecognized. The number of patients registered with the database as having von Willebrand disease now approaches that for haemophilia A, and it is undoubtedly the commonest hereditary disorder of haemostasis in the UK. By contrast with haemophilia, only a small proportion of the registered patients with von Willebrand disease have a severe phenotype. The increasing numbers of patients with acquired haemophilia probably also simply reflect greater awareness of the condition.

The period under review saw the introduction successively of blood products treated by heating or by other means (monoclonally prepared products and more recently clotting factors prepared using genetic engineering methods) to reduce the risk of transmitting viruses.

Usage of both FVIII and FIX has greatly increased since 1981, reflecting increased availability and more intensive treatment regimens to meet the needs and aspirations of patients. It is interesting to note that in any one year 15% of severely affected patients apparently did not receive replacement therapy.

The total amount of human FVIII used in 1996 to treat the various forms of FVIII deficiency was 192.6 million units. This represents a 193% increase over the amount used in 1981. It is interesting that the advent of AIDS did not cause a noticeable slowing down in this upward trend in usage and might even have contributed to this increased use, as factor cover was required for invasive diagnostic investigations in patients with HIV-related complications.

The total usage of FIX has shown an even greater increase from 1.27 million units in 1981 to 29.5 million units in 1996. It is notable that although the UK NHS has been self-sufficient in FIX since the early 1960s, commercial concentrate began to be used in 1985 and in 1996 more commercial FIX was used than UK-produced FIX prepared from voluntary NHS donors.

The causes of death recorded during the study period in 1190 patients with haemophilia A, 108 with haemophilia B and 159 with von Willebrand's disease to some extent reflect the risks associated with the different treatment and plasma source used for these diagnostic groups. The commonest cause of death in haemophilia A was AIDS, followed by cerebral haemorrhage and cancer. Liver disease accounted for 69 (5.8%) deaths in haemophilia A patients and six (6%) deaths in haemophilia B patients. In contrast, the commonest cause of death in patients with von Willebrand disease was cancer (13%), followed by respiratory disease (9%), ischaemic heart disease (9%) and cerebral haemorrhage (7%). Six patients (4%) with von Willebrand disease died of AIDS. It is interesting that the proportion of von Willebrand's patients dying of ischaemic heart disease is the same as that in haemophilia.

Acknowledgements

This report is published on behalf of the UK Haemophilia Doctors' Organization, and could not have been prepared without the sustained support of colleagues throughout the United Kingdom. The

authors also express their gratitude to Mrs. Patricia Wallace at the Oxford Haemophilia Centre for her assistance with the preparation of the manuscript.

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