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Haemophilia care in central Scotland 1980–94. I. Demographic characteristics, hospital admissions and causes of death

C. A. LUDLAM, R. J. LEE, R. J. PRESCOTT, J. ANDREWS, E. KIRKE, A. E. THOMAS, E. CHALMERS and G. D. O. LOWE

Haemophilia Centres at Royal Infirmary, Edinburgh and Royal Infirmary and Yorkhill Children's Hospital, Glasgow, and Medical Statistics Unit, University of Edinburgh, UK

Summary. To estimate the resources required to manage patients with haemophilia in Scotland, we studied the demographic features, hospital admissions and causes of deaths for individuals with haemophilia A and B and von Willebrand disease, treated with blood products, during the period 1980–94 living in central Scotland. Data were obtained from 413 adults and children (93% ascertainment). The age distribution in 1980 revealed a paucity of individuals over 60 years but the number in this age group increased over the study period. Of those with haemophilia A and B, 63 and two respectively, became HIV positive. Hospital admissions rose from 103 to 168 per annum; the number of annual bed days utilized also increased, but there was marked annual fluctuation (790–1832). The rate of admission was greater for those with severe haemophilia A and this increased during the 15-year period mainly due to the clinical consequences of human immunodeficiency virus (HIV) and hepatitis C virus (HCV). The admission rate for haemophilia B was significantly lower than that for haemophilia A, and was similar for all degrees of severity of the disorder. Throughout the 15-year period the incidence of admissions for acute bleeds was constant, as was the average duration in hospital. For those with a factor VIII inhibitor, the rate of admission was about double the rate of those without an inhibitor, although the duration of hospital stay was similar for both groups. There were 61 deaths; the death rate increased during the study period principally due to HIV and HCV, and 12 patients died from haemorrhage. We conclude that: (i) the life expectancy for haemophiliacs in Scotland was generally increasing, although HIV and HCV caused increasing mortality and morbidity (as shown by the increase in hospital admissions); (ii) hospital bed usage for the treatment of acute bleeds continued to be required, but fluctuated greatly; and (iii) the clinical impression that haemophilia B is less clinically severe than haemophilia A is confirmed by objective data. The planning implications for haemophilia care in Scotland and similar countries are discussed.

Keywords: causes of death, demography, haemophilia, hospital admissions.

National planning for haemophilia care requires reliable data on number of patients, life expectancy, clinical severity, time trends and year-to-year fluctuations in hospital bed requirements. To assess these for Scotland, which has a stable population and geographically well defined area, we have performed an epidemiological study of haemophilia focused upon the Haemophilia Comprehensive Care Centres in Edinburgh and Glasgow. These directly serve a population of about 4 million inhabitants, representing about 80% of the Scottish population. In the present paper we report the characteristics of the patient population as well as clinically relevant clinical outcomes. These include hospital admissions, particularly the reasons for these [e.g. bleeding, need for surgery, the consequences of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection], the effects of disease type [haemophilia A, B or von Wille-

Correspondence: Professor C. A. Ludlam, Department of Haematology, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel.: +44 131 536 2122; fax: +44 131 536 2145.

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brand disease (vWD)] and severity, factor VIII inhibitors, and of age. The causes of deaths are also presented. Time trends are analysed over the 15 years of the study. Further reports are being prepared on the use of coagulation factor concentrates in this cohort of patients, and on other clinical outcomes including quality of life and musculoskeletal status.

Methods

Case records were reviewed of 413 adults and children with haemophilia A, haemophilia B or vWD who were resident in central Scotland and were treated with blood products, between 1980 and 1994 inclusive, at Haemophilia Centres in Edinburgh and Glasgow. The records of 29 patients could not be traced, yielding a 93% ascertainment rate. Central Scotland was defined as the area covered by the Health Boards for Borders, Dumfries & Galloway, Fife, Forth Valley, Lothian, Argyll & Clyde, Ayrshire & Arran, Greater Glasgow and Lanarkshire.

Severe haemophilia was defined as a factor VIII/IX level of < 0.02 i.u. mL^{-1}, while moderate and mild severity were 0.02–0.09 i.u. mL^{-1} and > 0.10 i.u. mL^{-1}, respectively. The plasma factor VIII and IX were was measured by one stage assays and von Willebrand factor (vWF) by enzyme-linked immunosorbent assay and ristocetin cofactor activity. Patients were screened at least annually for factor VIII inhibitors and these were quantified using the Bethesda assay [1]. Treatment during the study period was predominantly on-demand therapy, although occasional patients had short periods of prophylaxis. Cryoprecipitate was the mainstay of therapy at the beginning of the study period. This was superseded by Scottish National Blood Transfusion Service intermediate purity factor VIII concentrates (NY and Z8) and in 1989 by high purity ion exchange purified, solvent/detergent treated concentrate (Liberate; Scottish National Blood Transfusion, Edinburgh). For HIV-positive patients, *Pneumocystis carinii* pneumonia prophylaxis was started in 1987, initially with nebulized pentamidine and subsequently, oral cotrimoxazole.

Data were extracted from the case records onto standardized forms and entered into Dbase IV databases on a PC. After validity and consistency checks the data were transferred into SAS version 6.12 for analysis and into S-Plus for graphical presentation; these packages were run under a Unix operating system on a Sun workstation. Only descriptive methods of analysis are presented in this report.

Results

Number of patients by diagnosis and severity

The total number of individuals with haemophilia A, B and vWD by disease severity and age treated with blood products in 1980 and 1994 is given in Table 1. The number of patients increased throughout the study period with the main rise occurring during the period 1980–85 due to a small increase in the number of patients in each diagnostic group (Fig. 1). After 1985 there was only a minimal 2.5% increase in the total number of treated patients. The prevalences of blood product treated haemophilia A, haemophilia B and vWD patients in 1980 were 0.040, 0.013 and 0.008, and in 1994 were 0.052, 0.019 and 0.012 per 1000 persons, respectively.

The number of individuals with factor VIII inhibitors detected in any year, i.e. prevalence, was relatively constant (range between 12 and 17) with a cumulative total of 30 patients seen with inhibitors at some stage of the study period; of this total 83% had severe haemophilia A. No patient was recorded as having factor IX or vWF inhibitors.

Age distribution of patients

The age distribution of haemophilia A and B patients in 1980 and 1994 was compared with that of the male population of central Scotland. In 1980 the age distribution of patients was similar to the normal population apart from the paucity of patients with haemophilia over 60 years (3.7% vs. 15.6%) while by 1994 there had been an increase in the percentage in this older age group (9.9% vs. 17.1%). This increase was due to a rise in the number with haemophilia A from 7 to 19 and with haemophilia B from 1 to 9 (Table 1).

HIV status

No patient was HIV positive in 1980 and all who became HIV positive had haemophilia A, except two who had haemophilia B. None with vWD was HIV positive. The HIV status of the patients by age in 1985 and 1994 is given in Table 2.

Hospital admissions

The number of admissions for each year by diagnosis and severity of disorder are shown in Fig. 2. There was an increase in total admissions from 131 in 1980 to 207 in 1994. There was a general upward trend

Table 1. Age distribution in 1980 and 1994 of patients with haemophilia A and B and von Willebrand disease treated with blood products.

	Severity							
	Mild		Moderate		Severe		Total	
Age	1980	1994	1980	1994	1980	1994	1980	1994
Haemophilia A								
0–12	5	6	8	13	19	22	32	41
13–20	2	5	9	7	14	13	25	25
21–39	10	12	17	27	41	39	68	78
40–59	4	8	11	17	15	18	30	43
60+	3	7	3	5	1	7	7	19
Total	24	38	48	69	90	99	162	206
Haemophilia B								
0–12	4	2	9	3	2	4	15	9
13–20	0	2	4	7	6	2	10	11
21–39	2	5	6	12	9	10	17	27
40–59	2	5	6	7	1	8	9	20
60+	1	5	0	4	0	0	1	9
Total	9	19	25	33	18	24	52	76

Age	1980	1994
von Willebrand disease		
0–12	4	6
13–20	2	6
21–39	13	16
40–59	8	13
60+	5	6
Total	32	47

throughout the period except for a large fall in 1989 which is unexplained and occurred independently in both Edinburgh and Glasgow. Admissions of patients with haemophilia A were most common (77%) while those for haemophilia B (11%) and vWD (12%) were similar. Although there was considerable variation in the number of admissions each year by diagnosis and severity, the largest increase over the 15-year period was seen in those with haemophilia A, which rose from 103 to 168.

The rate of hospital admissions (per 100 patients by severity of haemophilia A, B or vWD per annum) is shown in Fig. 3(a,b). The admission rate was highest for those with severe haemophilia A and progressively less for those with moderate and mild disease. Those with vWD were admitted at a frequency between that of moderate and mild haemophilia A. Overall admission rates for haemophilia B were lower than those for haemophilia A at all levels of severity with little difference in rates between grades of severity. The admission rate increased appreciably after 1985 for individuals with severe haemophilia A, while for other groups any trends over time were slight.

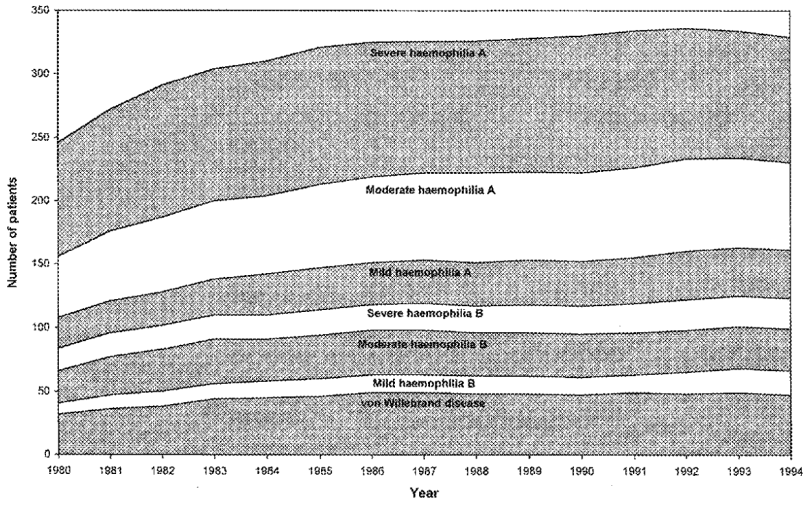

Fig. 1. Number of patients at Edinburgh and Glasgow haemophilia centres each year by diagnosis and severity of haemophilia and von Willebrand disease treated with blood products.

Table 2. HIV status in 1985 and 1994 by age and severity in patients with haemophilia A (number HIV positive/number of patients).

	Mild		Moderate		Severe	
Age	1985	1994	1985	1994	1985	1994
0–12	0/7	0/6	2/10	0/13	6/22	0/22
13–20	0/4	0/5	5/13	3/7	9/16	5/13
21–39	0/10	0/12	2/25	2/27	17/44	14/39
40–59	0/8	0/8	2/12	2/17	10/22	9/18
60+	0/4	0/7	0/6	0/5	0/4	3/7
Total	0/33	0/38	11/66	7/69	42/108	31/99

As with hospital admissions, there was a marked fluctuation in the number of bed-days per year for each degree of severity of haemophilia; the annual total number of bed-days for all patients varied over twofold ranging from 790 to 1832. The greatest demand for beds was for patients with haemophilia A (78% total). The bed occupancy was highest for those with severe, but similar for moderate and mild haemophilia A being 7.3, 3.5 and 3.6 bed-days per patient per year, respectively. For haemophilia B the equivalent bed usage for severe, moderate and mild disease were 3.1, 2.1 and 1.7 bed-days per patient per year. The number of bed-days per patient for those with vWD was 4.1 per annum; this being equivalent to non-severe haemophilia A. (Detailed data are available by writing to the authors.)

Hospital admission rate and number of bed days per patient for haemophilia A patients with an inhibitor

Whereas the admission rate for individuals with moderate and severe haemophilia A without inhibitors was relatively constant, for those in whom an inhibitor had been detected during the year of admission, there was a marked annual variation. For most years it was approximately twice that for those without an inhibitor. The average duration of admission for inhibitor patients was the same as

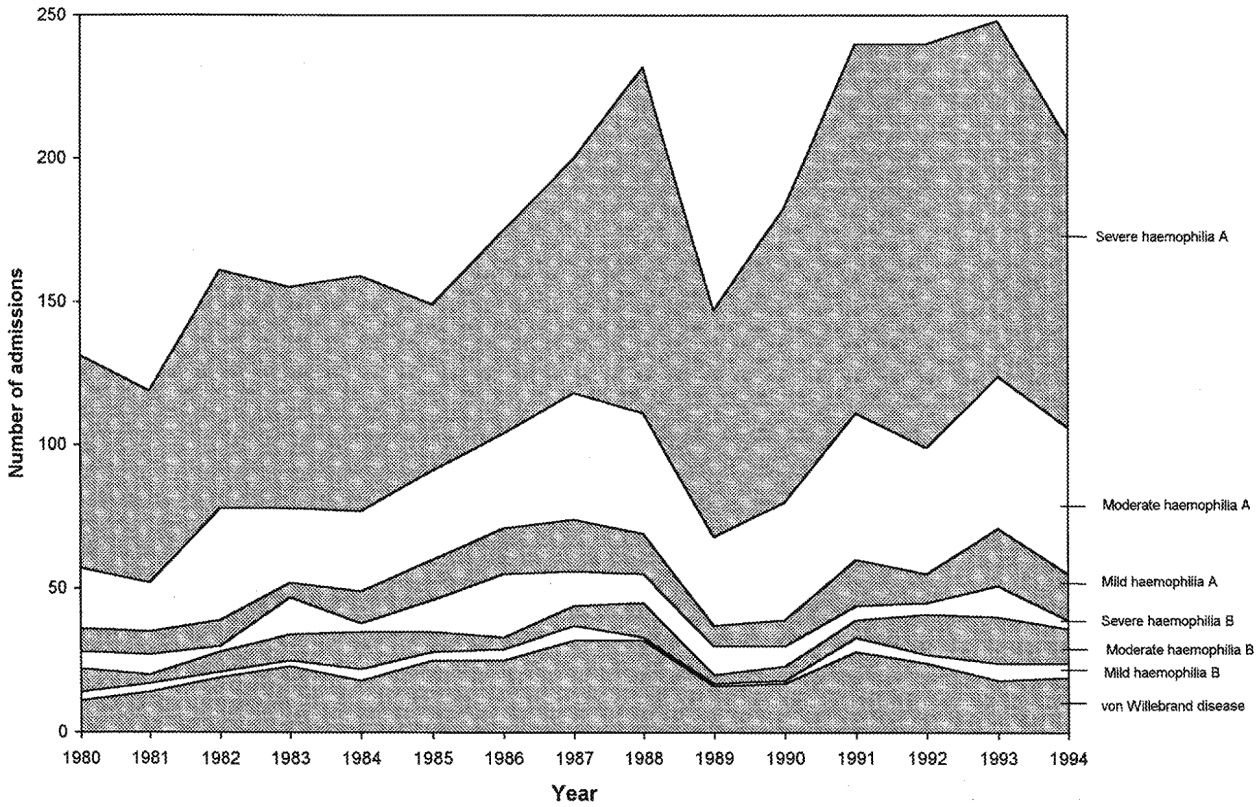

Fig. 2. Number of hospital admissions per annum by diagnosis and severity of condition.

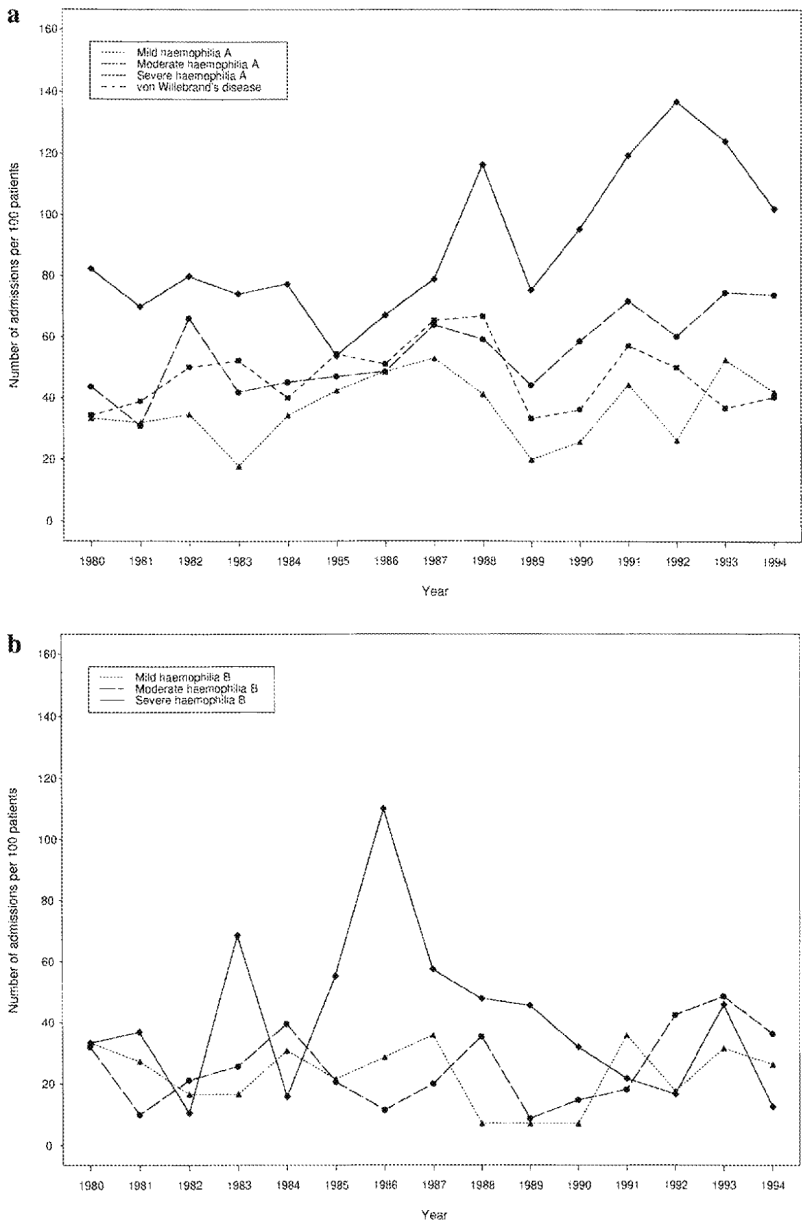

Fig. 3. Admission rate per annum for (a) haemophilia A and von Willebrand disease and (b) haemophilia B.

non-inhibitor patients at 7 days. (Detailed data are available by writing to the authors.)

Hospital admissions by age

The fluctuation in number of admissions by age of patients is illustrated in Fig. 4. An increase was observed in those over the age of 21 years. The hospital admissions for those aged 21–59 years increased by about 50%, whereas those over 60 years increased sixfold. The contribution of this oldest group of patients to bed occupancy was further enhanced by their duration of stay being about 50% longer than the younger individuals.

Hospital admissions by HIV status

The admission rates for those HIV positive and negative for each year is given in Fig. 5 with those in the former group progressively increasing after 1985, while the rate in those who remained HIV negative was constant.

Reasons for hospital admission

The principal reason for each hospital admission is presented in Fig. 6. The number being admitted primarily because of an acute bleed was reasonably constant during the entire 15-year period. The

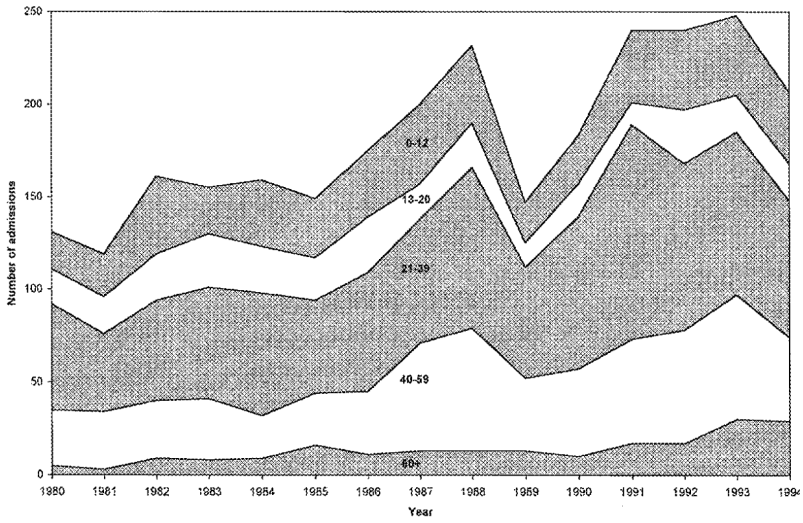

Fig. 4. Number of hospital admissions by age group (years).

increase in total number of hospital admissions after 1985 was largely due to HIV (from the late 1980s) and to HCV (from 1992). There was also an increase in surgical and medical admissions for reasons not related to haemophilia. The medical admission rates for reasons not related to haemophilia were not affected by HIV status, while the surgical admissions were lower in HIV positive patients. Of the 243 admissions for reasons not related to haemophilia, infections (mainly respiratory) accounted for 20%, undiagnosed abdominal pain 10%, alcohol and drug abuse 10%, malignancy 9%, headache and confusion 8%, head injury 5% and cardiac 5%. Over the period 1985–94 the mean number of bed days per patient for surgery not related to haemophilia was 0.16 per annum in HIV positives compared with 0.39 per annum in HIV negatives.

When the duration of hospital admissions was reviewed it was found that the mean duration for those with a bleed was constant at about 7 days throughout the 15 year study period (data not shown). Admissions primarily due to HIV were associated with very variable lengths of stay ranging from a mean of 7.3–20.5 days for the years 1986–94. The number of general surgical admissions was small (4–21 per annum) and those relating to haemophilia (2–9 per annum) were mainly orthopaedic. These were of very variable duration, this being reflected in the marked variability in the annual bed days per admission (range 3.0–61.7). Throughout the 15-year

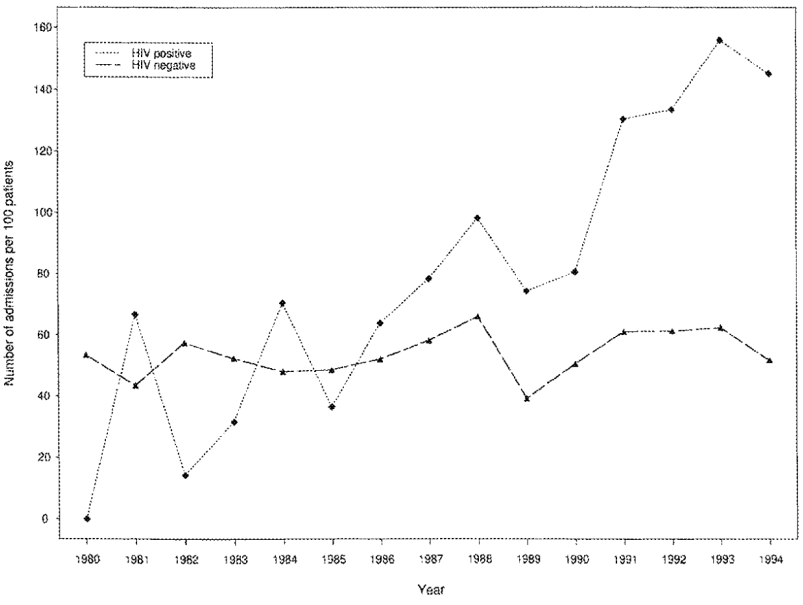

Fig. 5. Admission rate per annum by human immunodeficiency virus status.

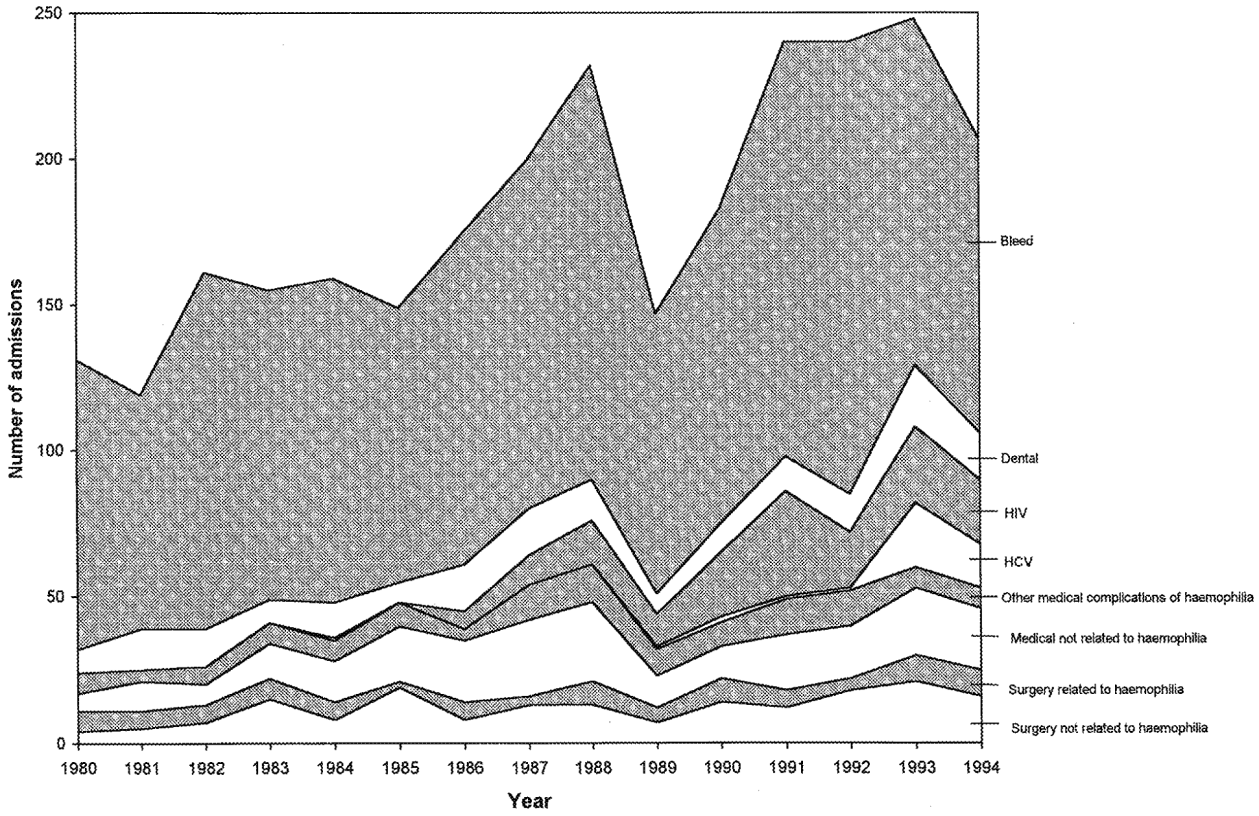

Fig. 6. Number of admissions per annum by reason for hospitalization.

period the number of admissions for dental surgery was constant, but the mean duration of stay fell from 5.8 days in 1980 to 1.7 days in 1994.

Causes of death

During the study period there were a total of 61 deaths (53 with haemophilia A, eight with vWD). As can be seen in Fig. 7, there was an increasing number of deaths during the 15-year period with the rise being mainly due to HIV and HCV. The number dying of bleeds was almost constant throughout the study period.

Of the 23 deaths due primarily to HIV, the median age of death was 32.0 years (range 12–62); four of these had lymphomas (one Hodgkin's disease, three non-Hodgkin's lymphoma). There were eight deaths attributable to HCV (mean age 51.5 years, range 33–60); two with hepatocellular carcinoma (one with inhibitor died of bleeding varices), two with cirrhosis and four with hepatocellular failure. Haemorrhage was the principal cause of death of 12 patients (median age 46.5 years range 22–68); ten were due to intracerebral (two with inhibitors), and one each subarachnoid (vWD) and intra-abdominal bleed. Deaths of seven factor VIII inhibitor patients were recorded, one from varices and two from intracranial bleeds (see above), three with HIV and one with liver failure. There were eight other patients with haemophilia A who died (two with malignancy, two with myocardial infarct and one each from stroke, road traffic accident, congenital heart defect and asthma). Of the other deaths, seven were patients with vWD (five with malignancy, one each of stroke and myocardial infarction). The cause of death was unknown in three individuals (two with haemophilia A and one with vWD).

Discussion

Effective management of congenital bleeding disorders is achieved by use of prophylactic therapy to prevent bleeds and by the early treatment of haemorrhage. Even within western Europe there is a 10-fold range in the amount of coagulation factor concentrate used per capita [2] yet very little is known about the long-term clinical effectiveness of therapy. The cost of providing care for haemophilia is high and rising partly because of the increasing amount of factor VIII used per patient [3]. The

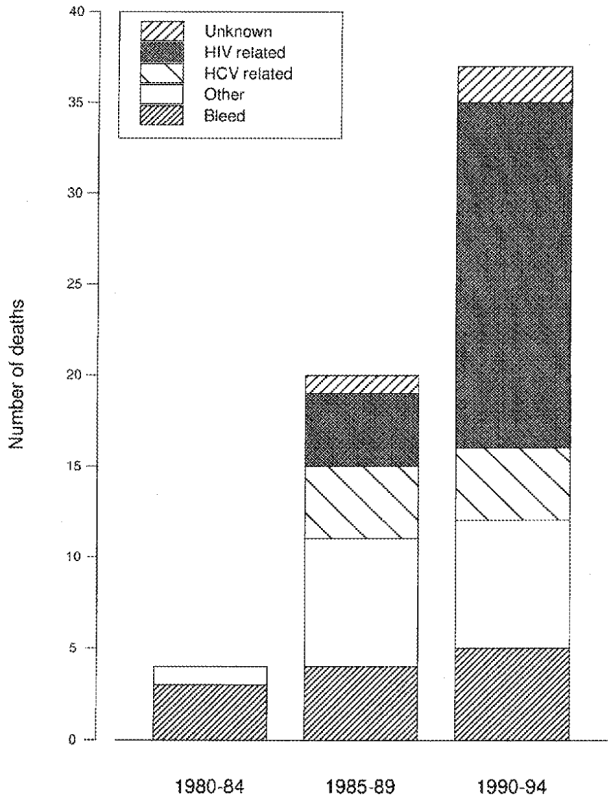

Fig. 7. Number and causes of deaths in 5-year periods 1980–94.

overall cost of haemophilia care also includes the consequences of partially effective therapy resulting in long-term musculoskeletal damage and subsequent orthopaedic surgery (including arthroplasties) and to the cost of treating the consequences of transfusion transmitted viruses, e.g. HIV and HCV [4]. There is also an additional socio-economic cost if people with haemophilia are not fully integrated in the community because of their bleeding disorder [5].

There are few surveys of clinical outcomes in haemophilia populations in a defined geographical area over a long period of time [6,7]. This study, covering the 15-year period 1980–94, was undertaken to assess demographic characteristics, treatment and clinical outcomes of those with haemophilia living in a moderately large stable population. As this study was designed primarily to estimate resources required to manage those with haemophilia, the population investigated only included those who at any time were treated with a blood product. There are a number of patients (principally with mild haemophilia A or vWD) who can be managed with desmopressin [8]: these individuals are unlikely to use significant health care resources compared with those who receive a coagulation factor concentrate and they were therefore excluded from the present study.

The apparent increase in the number of patients during the period 1980–85 mostly represents the referral of patients previously cared for at outlying hospitals to the Haemophilia Centres. After 1985 the numbers within all diagnoses and severities, apart from severe haemophilia A, increased slightly (Fig. 1). This finding is consistent with other reports and predictions [9]. The number of those with severe haemophilia A during the later 1980s was constant; their slight decline in the early 1990s is mostly due to the effects of HIV. It is thus interesting to note that despite HIV the number of treated patients has risen almost continuously throughout the period. The effect of HIV on the total number of patients, particularly with severe haemophilia A is less in this population than in many others because the prevalence of HIV in 1985 was 39% among those with severe haemophilia A compared with 59% for the UK as a whole [10] and to approximately 90% in some other countries [11]. Fewer patients became infected with HIV in Scotland in the early 1980s, because the virus was not endemic in the general population in Scotland at that time and because the majority of patients were treated with factor VIII containing blood products derived from locally collected plasma [12,13].

In 1980 the most noticeable feature of the haemophilic population was the paucity of individuals over 60 years of age, probably reflecting reduced life expectancy due to bleeds in severe haemophiliacs in the years prior to 1980 [14–16]. By 1994 there were over three times the number of individuals living beyond the age of 60. This had occurred despite the epidemic of HIV which has caused the premature deaths of many older individuals with haemophilia [15]. These older individuals are increasing the demand for surgical resources, not only because of the number of procedures unrelated to haemophilia (Fig. 6), but also because their stay in hospital is longer than that for younger individuals.

The number of hospital admissions rose by nearly 50% over the 15-year period; and the annual admission rate fluctuated markedly, particularly between 1985 and 1991. It is clear that the largest number of admissions were in those with severe haemophilia A, and that the principal causes of the increases in admissions were HIV and HCV. Following HIV infection the number of admissions rose from 1985 onwards, although the duration of each admission varied markedly reflecting the many different clinical consequences of this viral infection (Fig. 6).

Hospital admissions for those with severe haemophilia A were most commonly due to a bleed (Fig. 6). Although those with severe haemophilia A were most likely to occupy a hospital bed, this was because they constitute the largest group of patients in this cohort (Fig. 1). It is of interest to note that the duration of hospital stay was independent of whether or not the patient had an inhibitor. When the number of bed days per 100 patients per annum was examined, the rate for those with severe haemophilia A was approximately 80 per 100 compared with 50 and 35 for moderate and mild severity haemophilia A, respectively (Fig. 3a). It was noteworthy that the number of annual bed days per 100 patients with haemophilia B was approximately 20, this being little influenced by the severity of the condition (Fig. 3b). This lower rate of hospital admissions for those with haemophilia B suggests that these individuals have fewer, or less severe, bleeds than those with haemophilia A, confirming clinical impressions [17].

Apart from admissions due to acute bleeds it is interesting to review the other reasons for admission (Fig. 6). The effect of HIV on bed occupancy rose to a peak in 1991 and thereafter declined. This decline was due to a falling number of survivors, although the duration of admission did not change. The contribution due to HCV was only significant in the last 2 years of the study, and part of this was due to the admission of patients for investigation of liver disease, including liver biopsy. Over the 15-year period, particularly in the period 1985–88, there was a significant increase in admissions due to medical conditions unrelated to haemophilia or viral infection. The duration of admissions was very variable, being shortest for those requiring dental surgery and longest in those following orthopaedic surgery. In this latter, relatively small, group of patients, were those who stayed for very long periods because of a series of complications particularly related to excess postoperative bleeding.

The mortality trends illustrated in Fig. 7 are consistent with those reported for larger populations [15, 18]. The number of deaths from acute bleeds remained constant over the 15-year period while it increased markedly for those with HIV and is beginning to increase due to HCV. It is likely that the number of deaths from HIV will decline partly due to falling numbers but also due to highly active antiretroviral therapy. The number of deaths due to HCV will probably increase, unless effective therapy becomes available for those with advanced liver disease [18]. Over the next few years there are likely to be an increasing number of liver transplants for those who develop hepatomas or end-stage cirrhosis.

We conclude that the present study highlights several important considerations for the planning of haemophilia care in Scotland and in other countries. First, despite HIV and HCV infection, the increasing prevalence of haemophilia and life expectancy may require increasing resources, particularly for elderly patients who stay longer in hospital and require surgery. Second, increasing resources are required at present for managing HIV and HCV infection, although current and future developments in therapy make prediction difficult. Third, hospital bed usage is increasing overall, not only because of the increasing burden of viral disease, but also because hospital bed occupancy for bleeds has not fallen since 1980. The present study highlights the fluctuation in year-to-year bed occupancy, which requires flexible planning. Fourth, hospital admissions reflect the underlying severity of haemophilia A, as expected; the study data also confirm objectively the clinical impression that haemophilia B is overall less clinically severe than haemophilia A.

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