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Epidemiological data and treatment strategies in children with severe haemophilia in Italy

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Abstract

Objectives. In a period of important therapeutic changes in the field of haemophilia care, we provide updated statistics on children with severe haemophilia (0-12 years of age) in Italy.

Methods. Data presented are from the Italian National Registry of Congenital Coagulopathies (NRCC) – survey 2017.

Results. Children with severe Haemophilia A (HA) were 242, those with severe haemophilia B (HB) 48. Prophylaxis was adopted in 92.1% of individuals with severe HA and 88.6% with severe HB. Thirty-nine children (14.8%) were on treatment for inhibitors. FVIII prescribed to children with severe HA represented 11.1% of the total consumption, of which 4.6% was extended half-life (EHL). FIX given to children with HB accounted for 7.2% of the total FIX, of which 19.1% was EHL-FIX.

Conclusion. The paediatric population analysed is characterized by a great adherence to therapy, so this data may constitute a benchmark for use of new, alternative therapies in the coming years.

Key words

- paediatric individuals
- haemophilia A
- haemophilia B
- treatment strategies

INTRODUCTION

Haemophilias and von Willebrand's Disease are the most frequent congenital bleeding disorders. Haemophilia A (HA) and haemophilia B (HB) are characterized by the deficiency of one of the proteins involved in blood clotting: factor VIII (FVIII) in HA and factor IX (FIX) in HB. Clinical picture in haemophilia is classified in three main groups based on residual FVIII or FIX coagulant activity: severe (<1% of normal activity levels), moderate (<5%) and mild (5-40%) [1]. Patients with severe haemophilia often have spontaneous bleeds, above all haemarthrosis, chronic pain and impaired joint function [2], and are at risk of life-threatening bleedings, most commonly in young children [3]. Patients with moderate or mild haemophilia usually suffer from abnormal bleeding after trauma or surgery.

Rapid and reliable identification of these diseases is important to allow the adoption of appropriate replacement therapies based on plasma-derived or recombinant FVIII and FIX concentrates that can be administered for the treatment of a bleeding event (on demand) or on a regular basis to prevent bleeding episodes (prophylaxis). Although haemophilia is an inherited bleeding disorder, about a third of cases of mild and moderate HA and HB, almost half of cases of severe HB and more than half of cases of severe HA are sporadic, being the first occurrence in the family [4].

Children diagnosed with haemophilia need regular follow-up that, in Italy, is provided by the national health system through the 54 Haemophilia Treatment Centres (HTCs). In children with severe haemophilia, prophylaxis today is considered the first-choice therapy for reducing bleedings and preserving joint health [5-7]. Patients with haemophilia on prophylaxis require frequent intravenous injections owing to the short half-life of FVIII and FIX. In this light, over the last years a new generation of coagulation factors characterised by extended half life (EHL) has been developed for treatment of patients with haemophilia. By reducing the frequency of administrations, these products may, in the

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future, improve adherence to treatment and the quality of life, especially in young patients [8].

Nowadays, an important issue in haemophilia treatment remains the risk, especially in children, of the development of neutralizing antibodies, or inhibitors, to FVIII and FIX. In the literature, inhibitor development is reported in about 30% of previously untreated individuals with severe HA [9] and in up to 10% of those with severe HB [10].

Currently, the only known intervention to successfully eradicate inhibitors is immune tolerance induction (ITI) that consists in the infusion of high doses of FVIII, regularly administered for months or years [11, 12]. Patients with high-titre inhibitors also require treatment with bypassing agents – activated prothrombin complex concentrates (aPCC, FEIBA®) and recombinant activated factor VII (rFVIIa, NovoSeven®) – which bypass the role of the FVIIIa-FIXa complex within the clotting cascade. Both, rFVIIa and aPCCs, are effective for the treatment of acute bleeds in haemophilia with inhibitors [13]. Since the second half of 2018, another treatment for HA subjects with inhibitors, emicizumab, an antibody that bridges FIXa and FX mimicking the function of FVIII has become available in Italy [14].

The last annual survey of the Italian National Registry of Congenital Coagulopathies (NRCC), for the year 2017, indicates that children ≤12 years of age with severe haemophilia are about three-hundred. We have addressed our study to the analysis of this paediatric population because, in an age of important therapeutic changes, it represents the population that can benefit most from the recent innovations in haemophilia therapy and, considering the great adherence to therapy in this cohort of individuals, it can represent the benchmark for further management in the coming years.

In this paper, we provide information on this cohort of paediatric individuals with severe haemophilia, as it emerges from the Italian Annual Survey 2017. The following have been analysed: epidemiological data, treatment regimens, treatment-related complications, and concentrate consumption.

MATERIALS AND METHODS

The 54 Italian HTCs are coordinated by the Italian Association of Haemophilia Centres (AICE) that develops uniform therapeutic and diagnostic strategies and contributes to data monitoring and transmission to the NRCC.

The patients' demographic and clinical data are recorded in a password-secured web-based platform, managed by AICE and shared anonymously with the Italian National Institute of Health for elaboration by NRCC [15, 16]. Individual data are collected in accordance with the current EU standards on privacy and the subjects enrolled in the registry were asked to sign a consent form to allow data collection for epidemiological and clinical research purposes. A specific section of the registry is dedicated to drug prescriptions. Data are collected on the basis of the factor concentrate prescriptions by the HTCs, mandatory for patients with inherited bleeding disorders [16]. Data were analysed by age groups (0-3, 4-6, 7-9 and 10-12 years of age).

The total of FVIII and FIX concentrate prescriptions reflects the voluntary adhesion of each HTC to report on the prescriptions in the registry database. We have considered EHL recombinant products those that meet the classification proposed by Mahlangu [17, 18]. In 2017 novel EHL available in Italy were: recombinant FVIII and FIX fused to the Fc portion of human immunoglobulins (rFVIII-Fc, Elocta®, from the second half of 2016; rFIX-Fc, Alprolix®, from 2017), recombinant FIX fused to albumin (rFIX-FP, Idelvion®, from 2017) and rFVIII-SingleChain (Afstyla®, available from the second half of 2017).

Concentrates and bypassing agents utilized for inpatients were not included in the study because data on prescriptions are not available.

RESULTS

Epidemiology

The NRCC counted 542 paediatric individuals with haemophilia: 435 with HA and 107 with HB, accounting for 10.4% and 11.9% of the total number of registered patients with HA and HB, in 2017. The severe forms accounted for 290 individuals: 55.6% and 44.9% of the total number of registered children with HA and HB, respectively *(Table 1)*.

Since the treatment of these patients started after the introduction of recombinant products and the adoption of robust methods for viral inactivation and highly sensitive assays for testing plasma-derived products, none of the patients, as expected, resulted positive to hepatitis nor Human Immunodeficiency Virus (HIV).

Data on HA and HB child patients were provided from 48/54 HTCs; the six missing centres were non-paediatric HTCs.

Home treatment

The assessment of treatment regimens for home therapy was based on the HTC prescriptions to HA and HB children for home treatment. As shown in *Table 1*, prescriptions provided to the registry database during 2017 covered almost all the patients with the severe forms registered in this cohort, as high as 92.1%

Table 1
Children with haemophilia A and B, registered in the NRCC, as of 2017

Pathology	Children registered	Children with therapeutic prescriptions	Coverage (%)
Severe haemophilia A	**242**	**223**	***92.1***
Moderate haemophilia A	67	46	*68.7*
Mild haemophilia A	126	47	na
Severe haemophilia B	**48**	**40**	***83.3***
Moderate haemophilia B	22	16	*72.7*
Mild haemophilia B	37	13	na

na: not applicable; NRCC: National Registry of Congenital Coagulopathies.

Table 2
Children with severe haemophilia A and B registered in the NRCC, as of 2017

Age group	Children registered	Children with therapeutic prescriptions	Coverage (%)
		Severe HA	
0-3	59	58	*98.3*
4-6	48	44	*91.7*
7-9	65	59	*90.1*
10-12	70	62	*88.6*
Total	**242**	**223**	***92.1***
		Severe HB	
0-3	11	10	*90.1*
4-6	16	15	*93.7*
7-9	12	8	*66.7*
10-12	9	7	*77.8*
Total	**48**	**40**	***83.3***

in the severe cases, but lower in the moderate forms (68.7%). For HB the coverage was 83.3% for the severe and 72.7% for the moderate form. Patients with mild HA and HB rarely needed replacement therapy, especially those mild HA patients who can benefit for the desmopressin. For this reason, we did not deem it appropriate the analysis of replacement therapies in the population of mild HA *(Table 1)*. The analysis by age groups showed that therapeutic prescriptions covered more than 88% in all age groups of children, except in the two oldest cohorts (7-9 and 10-12 years of age) of children with severe HB *(Table 2)*. The coverage differences were not statistically significant (Chi-square test, p=0.2304).

Prophylaxis resulted the therapeutic regimen of choice for 92.1% of children with severe HA and for 88.6% with severe HB. Details on therapeutic regimens distinguished by age group are given in *Table 3*. Excluding the individuals with an inhibitor, the on demand treatment was used (25.5% of the patients) only in the 0-3 years of age group with severe HA, while prophylaxis was the most widely used therapeutic regimen in the other age groups of both severe HA and HB subjects (more than 97.1% in HA and more than 83.3% in HB). The mean annual amount of FVIII and FIX prescribed for children with severe haemophilia in prophylaxis, detailed by age group, is reported in *Table 4*. The proportion of children switched to prophylaxis with EHL-FVIII and -FIX was 10.3% and 29.0%, respectively *(Table 4)*. In severe HA children on prophylaxis, plasma-derived FVIII concentrates were employed only in 2.9% of the patients (5/174).

Treatment of inhibitor patients

During 2017, 39 individuals with severe haemophilia were under treatment for inhibitors: 15.2% (n=34) of children with severe HA and 12.5% (n=5) of those with severe HB. The age distribution of these individuals and the treatment regimens used are reported in *Table 3*. Among the 34 children with severe HA, ITI alone was used in 12 children (35.3%), and combined treatment with bypassing agents and ITI was used in 10 children (29.4%). The 5 individuals with severe HB and inhibitors were treated with rFVIIa alone.

Drugs prescribed for home treatment

The total amount of FVIII prescribed to children with severe HA, was about 46,000,000 international units (IU): 85.5% was conventional recombinant FVIII, 4.6% EHL-FVIII and the remaining 9.9% plasma-derived FVIII (*Table 5*). This value (46,000,000 IU) represents 11.1% of the FVIII prescribed to all individuals (adults and children alike) with severe HA [16].

As for FIX, the total amount prescribed to children with severe HB was about 3,400,000 IU, all in recombinant form: 80.9% conventional recombinant FIX and 19.1% EHL-FIX *(Table 5)*. The prescription in the pae-

Table 3
Therapeutic regimens used for children with severe haemophilia A and haemophilia B, as of 2017

	Age group	Children without inhibitor			Children with inhibitor		Total
Severe HA		**Prophylaxis**	**On demand**	**ITI**	**ITI + aPCC and/or rFVIIa**	**aPCC and/or rFVIIa**	
	0-3	38	13	2	3	2	**58**
	4-6	33	1	4	5	1	**44**
	7-9	50	-	5	1	3	**59**
	10-12	53	1	1	1	6	**62**
	Total	**174**	**15**	**12**	**10**	**12**	**223**
Severe HB		**Prophylaxis**	**On demand**	**ITI**	**ITI + rFVIIa**	**rFVIIa**	
	0-3	7	1	-	-	2	**10**
	4-6	10	2	-	-	3	**15**
	7-9	8	-	-	-	-	**8**
	10-12	6	1	-	-	-	**7**
	Total	**31**	**4**	**-**	**-**	**5**	**40**

aPCC: activated prothrombin complex concentrate; HA: haemophilia A; HB: haemophilia B; ITI: immune tolerance induction; rFVIIa: recombinant activated factor VII.

Table 4
Mean annual dose used by children with severe HA and HB in prophylaxis, as of 2017

		Conventional FVIII				EHL – FVIII			
	Age group	n	Mean in prophylaxis (IU per pt)	CI (95%)		n	Mean in prophylaxis (IU per pt)	CI (95%)	
Severe HA	0-3	32	133,500	86,300	180,800	6	64,300	21,000	107,600
	4-6	30	125,400	102,800	148,000	3	105,300	46,400	164,200
	7-9	46	182,100	150,800	213,500	4	164,000	70,600	257,400
	10-12	48	213,000	189,700	236,200	5	204,000	162,300	245,700
	Total	**156**	**170,800**	**154,400**	**187,300**	**18**	**132,100**	**94,000**	**170,300**
		Conventional FIX				**EHL – FIX**			
Severe HB	0-3	7	47,300	24,300	70,300	-	-	-	-
	4-6	8	110,700	83,100	138,300	2	53,000	51,000	55,000
	7-9	3	117,000	73,900	160,100	5	93,400	72,300	114,500
	10-12	4	168,000	84,700	251,400	2	100,000	92,160	107,800
	Total	**22**	**107,800**	**80,329**	**135,325**	**9**	**85,900**	**69,300**	**102,500**

CI: confidence interval; FVIII: factor VIII; FIX: factor IX; HA: haemophilia A; HB: haemophilia B; IU: international units; n: number; pt: patient.

diatric population accounts for 7.2% of the total FIX prescribed to severe HB subjects [16].

The amount of bypassing agents prescribed to children with inhibitors was ~3,500,000 IU of aPCC and ~7,700 milligrams of rFVIIa.

DISCUSSION

In this article, we have described the epidemiological data of the Italian children (≤12 years of age) with severe HA and HB and analysed the prescriptions of FVIII and FIX concentrates in this age group as well as the therapeutic regimens adopted.

A meta-analytic approach using national registries from Canada, France and the United Kingdom reported an overall prevalence of 6.0/100,000 males for severe HA and 1.1/100,000 males for severe HB [19], similar to that reported by the NRCC: severe HA=6.3/100,000 males and severe HB=1.1/100,000 males [16].

The prescriptions for home therapy in the 0-12 year cohort, covered about 90% of children with severe HA and severe HB registered in the demographic of the same registry. This percentage, higher than that observed in the total haemophilic population [16], indicates a special attention to disease management and an accurate involvement of parents for the management and monitoring of children with severe haemophilia.

The coverage of the treatment prescriptions for the moderate and mild cases was lower than that of severe cases: this reflects the reduced demand for replacement therapies in these paediatric subgroups as these individuals, particularly those with the mild forms, do not require frequent treatment, namely because most of those with mild HA respond to desmopressin [6].

Prophylaxis has gradually become the standard of care in the developed world and, as expected, is largely adopted in the children analysed in this study. Prophylaxis was less frequently adopted only in the 0-3 years age group; this is probably due to the difficulty of venous access or because bleeds are relatively infrequent, especially in the first year of age. The amount of FVIII

Table 5
Factor VIII and factor IX usage in severe HA and HB children, by age group, regimen and concentrates, as of 2017

	0-3	4-6	7-9	10-12	Total
FVIII for prophylaxis and on demand (IU)	4,728,250	4,041,750	9,299,250	11,405,000	29,474,250
FVIII for ITI (IU)	2,668,000	7,510,000	4,326,000	1,880,000	16,384,000
Total FVIII (IU)	**7,396,250**	**11,551,750**	**13,625,250**	**13,285,000**	**45,858,250**
Plasma-derived FVIII	*4.9%*	*17.4%*	*11.1%*	*4.8%*	*9.9%*
Recombinant FVIII	*89.8%*	*80.7%*	*84.1%*	*88.9%*	*85.5%*
Extended Half-Life FVIII	*5.3%*	*1.9%*	*4.8%*	*6.3%*	*4.6%*
Total FIX (IU)	**340,000**	**1,192,750**	**833,000**	**1,006,500**	**3,372,250**
Plasma-derived FIX	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Recombinant FIX	*100.0%*	*91.1%*	*47.5%*	*90.1%*	*80.9%*
Extended Half-Life FIX	*0.0%*	*8.9%*	*52.5%*	*9.9%*	*19.1%*

FVIII: factor VIII; FIX: factor IX; ITI: immune tolerance induction; IU: international units.

and FIX concentrates prescribed in children with severe haemophilia in prophylaxis, was similar to that reported in France, Germany, Spain, the United Kingdom [20] and Australia [21].

All Italian patients with severe haemophilia are regularly monitored for the occurrence of inhibitor development, as management of bleeding episodes in individuals with inhibitors is particularly difficult. Analysing the therapeutic prescriptions, 15.2% of children with severe HA and 12.5% of those with severe HB were under treatment for inhibitors during the year 2017 and the highest percentage of individuals treated for an inhibitor was in the 4-6 years of age group of severe HA patients (22.7%).

The therapies offered to inhibitor children were ITI and bypassing agents, according to the evidence provided by the medical literature that ITI is effective for the inhibitor eradication and the proven efficacy of recombinant factor VIIa and aPCC for the treatment of bleeding episodes in haemophilia patients with inhibitors [11-13].

The high prevalence of children with severe HA and inhibitors on ITI (64.7%) indicates the popularity of ITI in our country derived from the longstanding experience in this field and the overall success rate of 60-80% [22, 23]. Since the second half of 2018, the Italian national health system provides another treatment for HA patients with inhibitors, emicizumab, an antibody that mimics the function of FVIII [14]. This product has been shown to be safe and efficacious in reducing the incidence of bleeding episodes in patients with inhibitor to FVIII [24]. The benefits of inhibitor eradication include the possibility to restore prophylaxis and to reduce the costs of the long-term inhibitor therapies. This situation could be significantly affected by the availability of emicizumab. Children with HB complicated by an inhibitor respond less frequently to ITI and HB in itself is a poor prognostic indicator of ITI success [25]. As a consequence, no one child with severe HB and an inhibitor was treated with an ITI regimen during the year 2017.

Recombinant factors were the most prescribed products in children with haemophilia: 90% in patients with HA and 100% in those with HB. In over 20 years of clinical trials and worldwide experience with recombinant products, the transmission of infectious pathogens was virtually eliminated and no increase in the inhibitor occurrence in the treated haemophilia population was observed. Recently, the introduction of EHL concentrates that facilitate prophylaxis and improve the quality of life, namely in children, has represented a major breakthrough in haemophilia treatment [8]; especially the EHL-FIX products reduce the frequency of intravenous infusions and are very effective, both in the treatment and in prevention of bleeds [18]. For the first time in 2017, the prescription of the EHL products was reported in the NRCC as they were licenced in Italy at the end of 2016.

The European Medicine Agency has recently licensed emicizumab for severe HA patients without inhibitors and the drug is presently undergoing evaluation by the Italian Drug Agency (AIFA, Agenzia Italiana del Farmaco) to make it available through the national health system. Emicizumab requires dosing frequencies significantly reduced in comparison to EHL-FVIII and the advantage of the subcutaneous infusion makes the drug substantially easier usage, especially in children.

CONCLUSIONS

We have analysed the data reported to the NRCC with reference to the paediatric cohort of children with severe haemophilia (0-12 years of age). This paediatric population is characterized by a great adherence to therapy so it may represent a benchmark for use of new therapies, in the future.

In the time of important therapeutic changes in the field of haemophilia care, the NRCC can represent a powerful tool for the comparative evaluation of the efficacy of new drugs and for the assessment of their side effects.

Authors' contributions

FA, HJH, ES, RA, MB and AG made substantial contributions to conception, design, acquisition of data, analysis and interpretation of data. All Authors and co-authors have been involved in drafting the manuscript and revising it critically for important intellectual content. All Authors gave final approval of the version to be published.

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Conflict of interest statement

The Authors declare that they have no competing interests.

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