Changes in Hemophilia Treatment in the Eastern Part of Germany between 2015 and 2021—Data from the Kompetenznetz Hämorrhagische Diathese Ost (KHDO)

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Hamostaseologie

Abstract

Introduction Treatment options for patients with hemophilia (PWH) have changed substantially in the last years. This study aimed to compare hemophilia treatment in the eastern part of Germany in 2021 with data from 2015.

Methods Substitution diaries and patient records of PWH from 2021 were collected in 13 hemophilia centers from the "Kompetenznetz Hämorrhagische Diathese Ost" (KHDO) and compared with 2015.

Results A total of 130 children and 357 adults, 411 hemophilia A (HA) and 76 hemophilia B (HB), were included in 2021, and 359 were already analyzed in 2015. In 2021, 97.8% of children and 95.7% of adults with severe hemophilia had prophylaxis compared with 98.8 and 80.2% in 2015. Plasma-derived concentrates were used in 25.6%, recombinant in 30.2%, extended half-life (EHL) factor concentrates in 24.4%, and emicizumab in 19.8% of the children with severe HA (sHA). In adults with sHA, plasma-derived, recombinant concentrates, EHL, and emicizumab were used in 21.0, 33.2, 31.2, and 14.2%, respectively. All children and 93.3% of the adults with severe HB (sHB)

Keywords
- hemophilia
- prophylaxis
- bleeding
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- factor consumption

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were on EHL. Median annual factor consumption per body weight increased in adults with sHA, remained stable in children with sHA and adults with sHB, and decreased in children with sHB between 2015 and 2021. Annualized bleeding rate (ABR) decreased in children with sHB and sHA.

Conclusion The use of EHL and emicizumab has changed hemophilia treatment. About 50% of the sHA patients switched to EHL or emicizumab and almost all sHB patients to EHL. More adults with sHA received prophylaxis and ABR decreased in children.

Zusammenfassung

Einleitung Die Behandlungsmöglichkeiten für Patienten mit Hämophilie (PMH) haben sich in den letzten Jahren erheblich verändert. Ziel dieser Studie war der Vergleich der Hämophiliebehandlung im Osten Deutschlands im Jahr 2021 mit dem Jahr 2015.

Methoden Substitutionstagebücher und Patientenakten von PMH aus dem Jahr 2021 wurden in 13 Hämophiliezentren des Kompetenznetzes Hämorrhagische Diathese Ost (KHDO) erhoben und mit Daten von 2015 verglichen.

Ergebnisse 130 Kinder und 357 Erwachsene, 411 mit Hämophilie A (HA), 76 mit Hämophilie B (HB), wurden eingeschlossen, von denen 359 bereits 2015 analysiert wurden. Im Jahr 2021 erhielten 97,8% der Kinder und 95,7% der Erwachsenen mit schwerer Hämophilie eine Prophylaxe, verglichen mit 98,8% und 80,2% im Jahr 2015. Plasmatische Faktorenkonzentrate wurden bei 25,6%, rekombinante Konzentrate bei 30,2%, Faktorenkonzentrate mit verlängerter Halbwertszeit (EHL) bei 24,4% und Emicizumab bei 19,8% der Kinder mit schwerer HA (sHA) eingesetzt. Bei Erwachsenen mit sHA wurden plasmatische Konzentrate in 21,0%, rekombinante Konzentrate in 33,2%, EHL in 31,2% und Emicizumab in 14,2% verwendet. Alle Kinder und 93,3% der Erwachsenen mit schwerer HB (sHB) erhielten EHL. Der jährliche Faktorverbrauch pro Körpergewicht stieg bei Erwachsenen mit sHA, blieb bei Kindern mit sHA und Erwachsenen mit sHB stabil und nahm bei Kindern mit sHB zwischen 2015 und 2021 ab. Die jährliche Blutungsrate (ABR) nahm bei Kindern mit sHA und sHB ab.

Schlussfolgerung Der Einsatz von EHL und Emicizumab hat die Hämophiliebehandlung verändert. Etwa 50% der sHA-Patienten wechselten zu EHL oder Emicizumab und fast alle sHB-Patienten zu EHL. Mehr Erwachsene mit sHA erhielten eine Prophylaxe und die ABR bei Kindern ist gesunken.

Schlüsselwörter
- Hämophilie
- Prophylaxe
- Blutungen
- Epidemiologie
- Faktorkonsum

Introduction

Hemophilia is a rare hereditary bleeding disorder caused by the deficiency or absence of coagulation factor (F) VIII in hemophilia A (HA) or FIX in hemophilia B (HB). Over many decades, the treatment of patients with hemophilia (PWH) consisted of the substitution of plasma-derived (pd) coagulation factors. In 1991, the first recombinant coagulation factor was licensed to avoid transmission of infections like HIV or hepatitis C. The next milestone in the treatment of PWH was the approval of the first extended half-life (EHL) product for the treatment of HA in 2014[1] and HB in 2016.[2,3] Only 1 year later, the FDA approved emicizumab, a bispecific antibody that mimics FVIII activity, for patients with HA and inhibitors[4] and in 2018 for patients with severe HA (PWSHA) without inhibitors.[5] Those treatment options have changed the landscape of hemophilia treatment tremendously, because higher factor levels and longer substitution intervals can be achieved[6–10] and the subcutaneous administration of emicizumab is beneficial, especially for patients with poor venous access.[11,12] Since that time, gene therapy has been approved for HA in 2022[13] and for HB in 2023[14] and newer treatment options like efanesoctocog alfa, a FVIII product that overcomes the von Willebrand factor-imposed half-life ceiling[15] and rebalancing treatments like anti-TFPI[16] and the mRNA-interfering agent fitusiran,[17,18] have passed phase 3 studies.

The "Kompetenznetz Hämorrhagische Diathese Ost" (KHDO), an association of clinicians who treat PWH and other bleeding disorders in the eastern part of Germany, published data on treatment strategies and factor consumption in the years 2005 and 2015.[19,20] Those studies have shown an increasing proportion of patients with severe hemophilia (PWSH) on prophylaxis leading to an increased factor consumption and lower bleeding rates. In addition,

more patients were treated with recombinant factor concentrates in 2015.

The aim of the current study was to describe hemophilia treatment in the eastern part of Germany in 2021, to compare the new data with those from 2015 prior to the approval of EHL and emicizumab and before the introduction of gene therapy and the new treatment options into clinical practice.

Methods

Data Extraction

Data for the year 2021 from PWH from 13 hemophilia care centers in eastern Germany from the KHDO located in the federal states Mecklenburg-Western Pomerania, Brandenburg, Berlin, Saxony-Anhalt, Saxony, and Thuringia were retrospectively analyzed. Patient diaries (paper and digital) and medical records were reviewed regarding age, height, body weight (BW), blood group, dosing regimen, factor consumption, documented bleeds, and inhibitory antibodies. Severity of hemophilia, bleeding events and inhibitor status were recorded corresponding to the International Society on Thrombosis and Haemostasis (ISTH) guideline.[21] All patients with HA or HB with a complete patient diary with documented bleeds and factor application for 2021 were eligible.

Definition of Bleeding, Prophylaxis, and Factor Concentrates

Bleeds were counted as documented by the patients. In cases of doubt, the treating physicians were asked for clarification. All documented bleeds were counted as annualized bleeding rate (ABR), documented joint bleeds as annualized joint bleeding rate (AJBR). Factor administration for bleeding on consecutive days outside the specified prophylaxis regime was counted as one bleeding event. Major bleedings were defined as life-threatening, requiring hospitalization or red blood cell transfusion, as in the previous study[20] for the purpose of comparability. Minor bleeds were all other hemorrhages with documented bleeding sites.

In this study, in contrast to the previous study from 2015, only the bleeding events reported by the patient and/or verified by the doctor were counted and are summarized as the total ABR. In 2015, all additional substitutions were counted as unclear substitutions and summarized in the ABR. For the comparison of bleeding events between 2015 and 2021, all unclear substitutions in 2015 were excluded and only the number of documented bleeding events in 2015 and 2021 were taken into account and referred to as ABR. All other methods of data extraction and analysis were comparable to those used in 2015.

Eight patients (two children, six adults) who switched from on-demand treatment to prophylaxis within 2021 were excluded from the calculation of the bleeding rates for patients on prophylaxis. Patients with immune tolerance induction (ITI) were counted as patients on prophylaxis. For the calculation of the annual factor consumption, 10 patients (3 children, 7 adults) with active inhibitors in 2021 were excluded.

In this study, recombinant factor concentrates with standard half-life (SHL) are referred to as recombinant factor concentrates, while recombinant factor concentrates with EHL are called EHL products. Efmoroctocog alfa, damoctocog alfa pegol, rurioctocog alfa pegol and turoctocog alfa pegol for HA and eftrenonacog alfa, albutrepenonacog alfa, and nonacog beta pegol for the treatment of HB were counted as EHL products.

Statistical Analysis

Normal distribution was calculated using the Kolmogorov-Smirnov test. As data were not normally distributed, comparison between groups was performed with the Mann–Whitney *U*-test and values are given as median with interquartile range (IQR; 25th and 75th percentiles). Bleeding rates are given as mean with standard deviation (SD) and median (IQR) for the better comparison with data from other studies.

Mann–Whitney *U*-test was also for the comparison of bleeding rates between the entire 2015 and the entire 2021 cohorts. For the intraindividual comparison of bleeding rates in patients with available data from both 2015 and 2021, the Wilcoxon test was applied. The statistical analysis was performed using IBM SPSS Statistics version 27.

Results

Data were collected from 487 patients with hemophilia A or B, including 130 children and 357 adults. Of the 413 patients already included in 2015, data from 359 patients (67 children and 292 adults) were available in 2021. In addition, 128 patients have been newly included in 2021. The median age of the entire cohort was 34 years (range: 0–87, IQR: 16–54 years), 10 years (IQR: 6–13 years) in children, and 44 years (IQR: 30–57 years) in adults.

The majority of patients had hemophilia A ($n = 411$, 112 children and 299 adults), while 76 patients (18 children and 58 adults) had HB. Most patients suffer from severe hemophilia: 93 children (71.5%) and 235 adults (65.8%). The characteristics of the patients are summarized in ►**Table 1**.

Therapeutic Regimen

Ninety-one of 93 (97.8%) children with severe hemophilia were treated prophylactically at the end of 2021. Two patients with sHA had on-demand therapy due to their young age of 5 and 9 months at the end of the year. At the end of 2021, 225 of 235 adults (95.7%) with severe hemophilia also received prophylactic therapy. This is an absolute increase of 15.5% compared with 2015. At the end of 2021, 14 of 16 (87.5%) children (HA 88.9%, HB 85.7%) and 17 of 50 (34.0%) adults (HA: 40.0%, HB: 20.0%) with moderate hemophilia were treated prophylactically. This is an increase compared with 2015, when 54.5% of the children and 18.4% of the adults with moderate hemophilia had prophylaxis.

Distribution of Factor Concentrates and Emicizumab

Among all noninhibitor patients with HA and HB of all severities, treated with prophylaxis or on-demand therapy, the distribution of the different factor concentrates and emicizumab in all PWH was almost balanced. In children,

Table 1 Characteristics of 487 patients included in the study

			Children	Adults
Age (y)		*n*; median (range)	130; 10 (0–17)	357; 44 (18–87)
Body weight (kg)		*n*; median (range)	128; 36.6 (5.8–94.3)	336; 83.0 (56.0–142.5)
BMI (kg/m^2)		*n*; median (range)	119; 18.3 (13.0–31.6)	324; 26.0 (17.3–48.3)
Hemophilia A	Severe	*n* (%)	86 (66.1%)	205 (57.4%)
	Moderate	*n* (%)	9 (6.9%)	35 (9.8%)
	Mild	*n* (%)	17 (13.1%)	59 (16.5%)
Hemophilia B	Severe	*n* (%)	7 (5.4%)	30 (8.4%)
	Moderate	*n* (%)	7 (5.4%)	15 (4.2%)
	Mild	*n* (%)	4 (3.1%)	13 (3.6%)
Therapeutic regimen	Prophylaxis	*n* (%)	104 (80.0%)	241 (67.5%)
	On demand	*n* (%)	24 (18.5%)	110 (30.8%)
	Switched to prophylaxis in 2021	*n* (%)	2 (1.5%)	6 (1.7%)
Inhibitor status	Active inhibitor	*n* (%)	3 (2.3%)	6 (1.7%)
	History of an inhibitor	*n* (%)	7 (5.4%)	7 (2.0%)

28.0% received a plasma-derived, 28.0% a recombinant, 28.8% an EHL product, and 12.8% were on emicizumab. In adults, 31.1% received a plasma-derived, 26.2% a recombinant, 33.7% an EHL concentrate, and 7.8% emicizumab. Three children (2.4%) and four adults (1.2%) were treated with nonfactor agents only (►**Supplementary Fig. S1** [available in the online version only).

Among the 86 children and the 205 adults with sHA, 25.6 and 21.0% were on plasma-derived, 30.2 and 33.2% on recombinant factor concentrates, 24.4 and 31.2% on EHL, and 19.8 and 14.2% on emicizumab, respectively. One adult with HA and inhibitor had prophylaxis with a bypassing agent. All children with severe HB and 93.3% of the adults with severe HB were on EHL. In contrast, 55.4% of the children and 47.5% of the adults with severe hemophilia were using plasma-derived concentrates in 2015.[20] The distribution of factor concentrates and emicizumab among PWSHA in 2015 and 2021 is shown in ►**Fig. 1**.

Prophylaxis in Severe Hemophilia A

Around 50.9% of all children and 71.1% of all adults with sHA without inhibitors on factor concentrates received prophylaxis with a dosage between 20 and 39 IU/kg BW (BW). Among HA patients, 32.4% of children and 38.9% of the adults used an EHL. Prophylaxis with plasma-derived or recombinant factor concentrates was most commonly administered

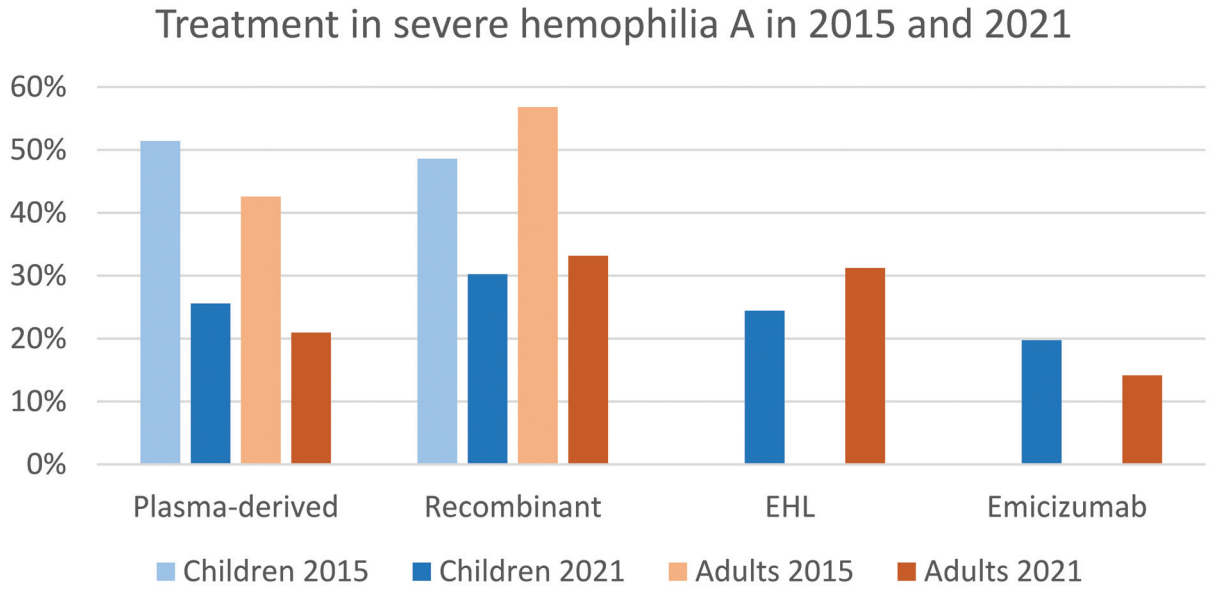

Fig. 1 Types of therapy in severe HA including inhibitors in 2015 (74 children, 176 adults) and 2021 (86 children, 205 adults).

Table 2 Prophylaxis regimens in 217 patients with severe hemophilia A without inhibitors on factor concentrates in 2021

		Plasma-derived (IU/kg)					Recombinant (IU/kg)					EHL (IU/kg)					Total
		≤ 19	20–29	30–39	≥ 40	all	≤ 19	20–29	30–39	≥ 40	All	≤ 19	20–29	30–39	≥ 40	All	
Children, *n* = 65	0.5–1.5 d	0	0	1	0	**1**	0	0	0	0	**0**	0	0	0	0	**0**	**1** 1.5%
	>1.5–2.5 d	1	7	3	4	**15**	1	4	7	12	**24**	0	1	2	3	**6**	**45** 69.2%
	>2.5–4 d	0	1	0	2	**3**	0	0	1	0	**1**	0	1	5	9	**15**	**19** 29.2%
	Total	**1** 1.5%	**8** 12.3%	**4** 6.2%	**6** 9.2%	**19**	**1** 1.5%	**4** 6.2%	**8** 12.3%	**12** 18.5%	**25**	**0** 0%	**2** 3.1%	**7** 10.8%	**12** 18.5%	**21**	**65** 100%
Adults, *n* = 152	0.5–1.5 d	0	0	0	0	**0**	0	1	0	0	**1**	0	0	0	0	**0**	**1** 0.7%
	>1.5–2.5 d	5	11	5	5	**26**	5	15	5	3	**28**	2	7	4	3	**16**	**70** 46.1%
	>2.5–4 d	1	5	1	0	**7**	3	13	3	1	**20**	3	18	7	7	**35**	**62** 40.8%
	>4–7 d	0	1	0	0	**1**	1	4	1	0	**6**	0	2	1	5	**8**	**15** 9.9%
	>7–14 d	0	2	0	0	**2**	0	1	1	0	**2**	0	0	0	0	**0**	**4** 2.6%
	Total	**6** 3.9%	**19** 12.5%	**6** 3.9%	**5** 3.3%	**36**	**9** 5.9%	**34** 22.4%	**10** 6.6%	**4** 2.6%	**57**	**5** 3.3%	**27** 17.8%	**12** 7.9%	**15** 9.9%	**59**	**152** 100%

Abbreviation: EHL, extended half-life concentrate.
Notes: Values are given as absolute numbers of patients. No child was treated less frequently than every 4 days.

Table 3 Prophylaxis regimens in 31 patients with severe hemophilia B without inhibitors with an extended half-life concentrate (EHL) in 2021

		Dosage of EHL (IU/kg)					Total
		≤ 19	20–29	30–39	40–49	≥ 50	
Children, $n = 7$	7 d	1	1	2	1	0	5 (71.4%)
	14 d	0	0	0	1	1	2 (28.6%)
	Total	1 (14.3%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	1 (14.3%)	7 (100%)
Adults, $n = 24$	3–5 d	0	2	0	0	1	3 (12.5%)
	7 d	1	5	3	4	3	16 (66.7%)
	8–10 d	0	0	1	2	0	3 (12.5%)
	14 d	0	0	1	1	0	2 (8.3%)
	Total	1 (4.2%)	7 (29.2%)	5 (20.8%)	7 (29.2%)	4 (16.7%)	24 (100%)

Note: Values are absolute numbers of patients.

every 1.5 to 2.5 days (every other day and three times a week), while EHL products were mainly injected every 2.5 to 4.5 days (every 3 days and twice a week).

Four adults with sHA, two with plasma-derived and two with recombinant factor concentrate, used prophylactic factor injections only every 9, 10, 11, and 14 days due to irregular prophylaxis. The prophylaxis regimens in sHA are shown in ►Table 2.

Prophylaxis in Severe Hemophilia B

Almost all patients with severe HB without inhibitors received prophylaxis with an EHL product (100% of the children and 96% of the adults). One adult (4.0%) with severe HB injected a plasma-derived factor concentrate at intervals of 7 days at a dose of 60.2 IU/kg.

Most children (71.4%) and adults (66.7%) on EHL concentrates injected once weekly. Only three adults (12.5%) but no child with severe HB used their EHL product more frequently. The details of the prophylactic regimens are summarized in ►Table 3.

Factor Consumption

The median annual factor consumption in PWSH was 193,250 IU in children ($n = 76$) and 249,000 IU in adults ($n = 205$). Children with sHA consumed significantly more factor than children with HB (median factor consumption of 202,500 vs. 68,000 IU; $p < 0.001$). The same was observed in adults (280,000 vs. 167,000 IU, $p < 0.001$). The median annual factor consumption of all patients in 2015 and 2021 is summarized in ►Table 4 and the ►Supplementary Figure S2.

Corresponding to this, the mean annual factor consumption increased by ~70,000 IU in pediatrics and by almost 100,000 IE in adult PWSHA between 2015 and 2021. For better comparison with the publication from 2015, the mean annual factor consumption for all patients without inhibitors for both years is summarized in ►Supplementary Table S1 (available in the online version only).

When factor consumption was adjusted to BW, children and adults with sHA had a significantly higher median factor consumption than children and adults with severe HB (children: 5,335 vs. 1,097 IU/kg, $p < 0.001$; adults: 3,378 IU/kg vs. 1,793 IU/kg, $p < 0.001$).

In contrast to the increased absolute factor consumption in children with sHA, median factor consumption was comparable between 2015 and 2021 when it was calculated according to the BW (2015: 4,700 IU/kg, 2021: 5,335 IU/kg, $p = 0.106$) but increased in adults with sHA (2015: 2,280, 2021: 3,378 IU/kg, $p < 0.001$). The median annual factor consumption calculated per BW was comparable between SHL and EHL in children (5,390 vs. 5,270 IU/kg, $p = 0.743$) and in adults (3,440 vs. 3,430 IU/kg, $p = 0.614$), respectively.

The median consumption per BW in children with severe HB (sHB) decreased significantly between 2015 and 2021 from 2,062 IU/kg in 2015 to 1,097 IU/kg in 2021 ($p = 0.008$) and remained stable in adults with sHB (2015: 1,940 IU/kg, 2021: 1,793 IU/kg, $p = 0.696$). The median annual factor consumption calculated per BW is given in ►Supplementary Tables S2 and S3 (available in the online version only).

Bleeding Rates in Patients on Prophylaxis

In 2021, children with severe hemophilia without inhibitors on prophylaxis ($n = 87$) had a mean ABR of 1.45 (median 1, IQR 0–2) and a mean AJBR of 0.49 (median 0, IQR 0–0). Adults with severe hemophilia on prophylaxis ($n = 212$) had a mean ABR of 2.06 (median 1, IQR 0–2) and a mean AJBR of 1.35 (median 0, IQR 0–2). Forty-two children (48.3%) and 101 adults (47.6%) with severe hemophilia on prophylaxis without inhibitors had zero bleeds in 2021. Major bleeds did not happen in children and only once in adults.

The median ABR in children with severe hemophilia on prophylaxis was significantly lower in 2021 compared with 2015 but did not change significantly in adults. AJBR was not different in children, but there was a trend to a lower AJBR in adults in 2021. Minor bleeding decreased significantly in children.

Bleeding rates in 2015 and 2021 for PWSH on prophylaxis without inhibitor are summarized in ►Table 5.

Intraindividual comparison of the patients on prophylaxis included in both surveys (48 children, 126 adults) showed that the ABR decreased significantly both in children (2015:

Table 4 Median annual factor consumption (IU) in all patients without inhibitors with available data, in 2015 ($n = 401$) and 2021 ($n = 435$)

		Children			Adults		
		2015	2021		2015	2021	
Hemophilia A	Severe	129,000 (90,000–209,000) $n = 71$	202,500 (131,125–310,250) $n = 69$	$p < 0.001$	186,000 (116,750–289,000) $n = 169$	280,000 (197,000–369,000) $n = 175$	$p < 0.001$
	Moderate	144,000 (9,000–195,000) $n = 7$	133,000 (98,000–234,000) $n = 7$	$p = 0.383$	34,500 (6,750–161,250) $n = 22$	41,000 (4,000–198,000) $n = 33$	$p = 0.904$
	Mild	3,000 (0–17,000) $n = 15$	500 (0–2,500) $n = 17$	$p = 0.278$	0 (0–12,000) $n = 51$	0 (0–15,250) $n = 58$	$p = 0.940$
Hemophilia B	Severe	80,400 (68,700–138,300) $n = 9$	68,000 (5,500–108,000) $n = 7$	$p = 0.210$	116,400 (43,200–247,000) $n = 27$	167,000 (104,000–205,500) $n = 30$	$p = 0.565$
	Moderate	7,800 (1,650–41,625) $n = 4$	29,000 (12,500–60,500) $n = 7$	$p = 0.230$	1,200 (0–6,000) $n = 15$	4,000 (0–100,000) $n = 15$	$p = 0.285$
	Mild	0 (0–250) $n = 6$	0 (0–0) $n = 4$	$p = 0.762$	0 (0–23,000) $n = 5$	3,600 (0–25,000) $n = 13$	$p = 0.703$
	Total	$n = 112$	$n = 111$		$n = 289$	$n = 324$	

Note: IQR in parentheses.

Table 5 Bleeding rates in 2015 and 2021 in all patients with severe hemophilia on prophylaxis without inhibitor on factor concentrates or emicizumab

		2015			2021			
		Total number, *n*	Mean (SD)	Median (IQR)	Total number, *n*	Mean (SD)	Median (IQR)	*p*
Children	*n*	79			87			
	ABR	249	3.15 (4.62)	1 (0–5)	126	1.45 (2.17)	1 (0–2)	0.031
	AJBR	75	0.95 (1.94)	0 (0–1)	43	0.49 (1.07)	0 (0–0)	0.112
	Major bleeding	0	0.00 (0.00)	0 (0–0)	0	0.00 (0.00)	0 (0–0)	1.000
	Minor bleeding	174	2.20 (3.55)	1 (0–3)	83	0.95 (1.61)	0 (0–1)	0.048
Adults	*n*	148			212			
	ABR	433	2.93 (5.57)	1 (0–4)	437	2.06 (3.70)	1 (0–2)	0.200
	AJBR	289	1.95 (4.43)	0 (0–3)	287	1.35 (2.78)	0 (0–2)	0.087
	Major bleeding	8	0.05 (0.33)	0 (0–0)	1	0.00 (0.07)	0 (0–0)	0.034
	Minor bleeding	136	0.92 (2.38)	0 (0–1)	149	0.70 (1.60)	0 (0–1)	0.300

Abbreviations: ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; IQR, interquartile range; SD, standard deviation.

mean 2.77, median 1 [IQR 0–5] vs. 2021: mean 1.22, median 1 [IQR 0–2], $p = 0.028$) and in adults with severe hemophilia (2015: mean 3.19, median 1 [IQR 0–4] vs. 2021: mean 2.28, median 1 [IQR 0–3]; $p = 0.049$).

The AJBR remained unchanged in children, but there was a trend to lower AJBR in adults with severe hemophilia). In patients who were children in 2015 and adults in 2021 with severe hemophilia and data from both years ($n = 25$), the mean (median; IQR) ABR decreased significantly from 3.44 (2; IQR 0–5) to 1.24 (0; IQR 0–1), $p = 0.024$. Bleeding rates in PWSH with available data from 2015 and 2021 are shown in ►Fig. 2 and ►Supplementary Table S4 (available in the online version only).

Children with sHA without inhibitors treated with emicizumab ($n = 14$) had a trend to a lower ABR but a significantly lower AJBR than patients on prophylaxis with SHL ($n = 45$). Mean (median; IQR) ABR and AJBR were 0.64 (0; 0–1) versus 1.60 (1; 0–2), $p = 0.072$, and 0.00 (0; 0–0) versus 0.64 (0; 0–1), $p = 0.019$, in patients on emicizumab and SHL, respectively. There was no significant difference in bleeding rates between children treated with SHL ($n = 45$) or EHL ($n = 21$) and between children on EHL or emicizumab. Mean (median; IQR) ABR and AJBR in children on prophylaxis with EHL were 1.24 (0; 0–1) and 0.33 (0; 0–0), respectively.

The bleeding rates in adults with sHA without inhibitors did not differ significantly between prophylaxis with SHL ($n = 101$), EHL ($n = 62$), and emicizumab ($n = 22$). The mean (median, IQR) ABRs were 2.41 (1; IQR 0–2), 2.18 (1; 0–3), and 1.09 (0; 0–1.25) and mean AJBRs were 1.58 (0; 0–1), 1.39 (0; 0–2), and 0.64 (0; 0–0.25) on SHL, EHL, and emicizumab, respectively.

Patients with Inhibitors

Among the 130 children in the analysis, 3 (2.3%) had an active inhibitor in 2021. The inhibitor titer was < 5 Bethesda units (BU) in one child and > 5 BU in two children. Another seven children (5.4%) had a history of an inhibitor but were negative in 2021. All children with an active inhibitor received prophylaxis with emicizumab; one child with a high titer inhibitor received ITI with a plasma-derived concentrate in addition to emicizumab.

Among the 357 adults, there were 6 patients (1.7%) with an active inhibitor: 5 were low-titer and 1 was high-titer. Another seven adults (2.0%) had a history of an inhibitor. In the cohort of patients with active inhibitors, one patient was treated with ITI with a plasma-derived concentrate and immunosuppression with rituximab, one patient with low-titer inhibitor, and atrial fibrillation had prophylaxis with activated prothrombin complex concentrate (APCC); the other patients received prophylaxis with emicizumab.

Discussion

This study analyzed a large cohort of PWH and compared historical data from 2015, when only plasma-derived and recombinant SHL concentrates were available, with data

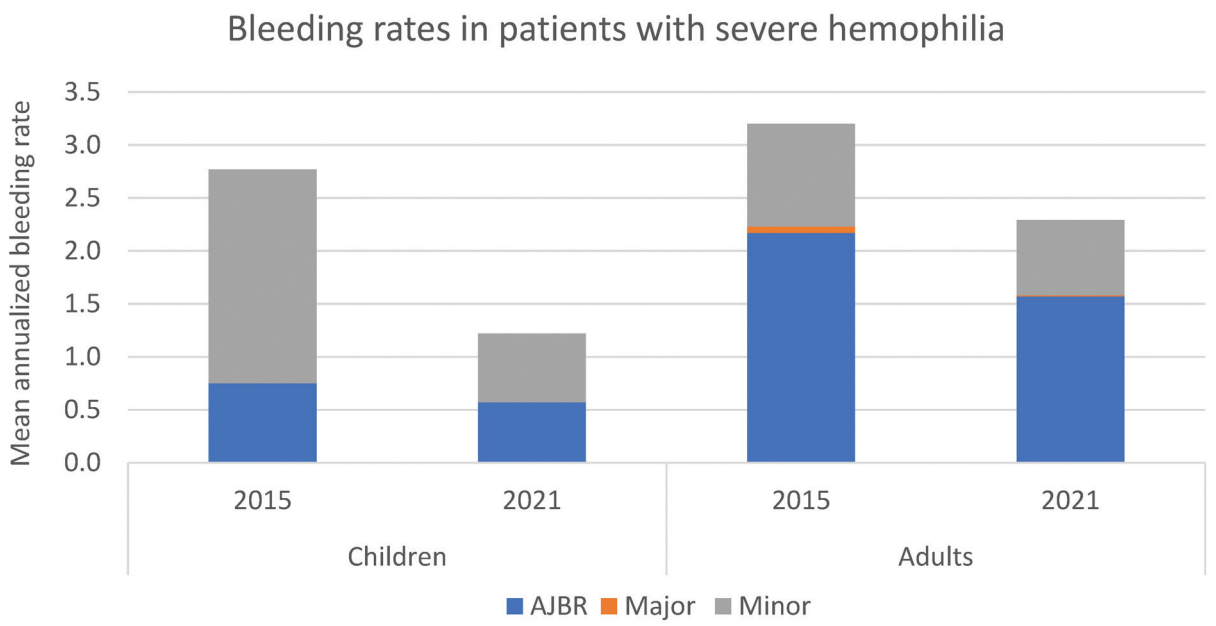

Fig. 2 Bleeding rates in patients with severe hemophilia with available data in 2015 and 2021. AJBR, annualized joint bleeding rate.

from 2021 after the introduction of EHL and emicizumab. We have shown that during this time, the use of prophylaxis increased in adult PWSH by 15.5 to 95.7% and remained almost 100% in children. This shows that the guidelines recommending prophylaxis in PWSH are consistently followed. The WFH Guidelines for the Management of Hemophilia,[22] European consensus proposals,[10] and the German Cross Sectional guideline on hemotherapy[23] recommend prophylaxis in all PWSH.

In addition, guidelines recommend that prophylaxis should not only be based on dosage per BW but rather be individually adapted to the corresponding needs and goals of the patients, taking into account pharmacokinetic aspects and personal activity. For joint protection, a trough factor level of 3 to 5 IU/dL is recommended in recent European and German guidelines.[10,23] The WFH 2020 guidelines state that trough levels of 1 to 3 IU/dL are insufficient to totally prevent bleeds resulting in a gradual progression of joint disease over lifespan.[22] Although higher trough levels were not recommended by the WFH in 2020, the former 2013 guideline still suggested factor trough levels greater than 1 IU/dL.[24] An international Delphi consensus statement from 2017 still recommends trough levels of 1 to 3 IU/dL in most patients especially with a low bleeding phenotype and trough levels of 3 to 5 IU/dL for active patients and patients with arthropathy or target joints.[25] It is noteworthy that the German guideline in 2014 suggested prophylaxis as the standard of care for children and that prophylaxis may be extended in adults on an individual basis for the prevention of late arthropathy.[26] A dosage of 20 to 30 IU/kg BW at least three times weekly was recommended but no trough levels to prevent arthropathy. In line with the recommendations for higher trough levels and individualization of prophylaxis, we observed an increased median annual factor consumption in children with sHA by ~70,000 IU and in adults with sHA of almost 100,000 IU between 2015 and 2021. However, factor consumption per BW increased only in adults but not in children with sHA.

Apart from the increasing factor consumption in HA patients, we found that in 2021 EHL and emicizumab have replaced SHL in almost half of the pediatric and adult PWSHA and were used in almost all PWSHB. This distribution of factor products in PWSHA is in line with findings from the first cross-sectional analysis of data from the pediatric GEPHARD study in Germany.[27] In contrast, less than 60% of PWSHB were reported to be on EHL in GEPHARD. The authors speculated that the rather high proportion of SHL reflected the initial treatment since no longitudinal data and thus no information about treatment and preparation changes were included. In accordance with that the median age of children in GEPHARD was 40 months compared with 10 years in our study, which suggests that children may be switched to EHL after the initial factor substitutions. In addition, a much higher proportion of children with moderate hemophilia was treated prophylactically in our cohort (HA: 88.9%, HB: 85.7%) compared with GEPHARD (HA: 20.8%, HB: 37.5%).

A survey of the European Association for Haemophilia and Allied Disorders (EAHAD) conducted in 33 European hemophilia centers showed that in 2018 72% of the hemophilia centers had switched only up to 10% of their HA patients, but 43% of the hemophilia centers had switched more than 40% of their HB patients to EHL products.[28] However, at the beginning of 2018, only one FVIII-EHL and two FIX-EHL were licensed and available in Europe. In our cohort, documented 3 years later, almost 50% of the patients with sHA were switched to EHL or emicizumab and almost all sHB patients received EHL. This illustrates the rapidly changing landscape of hemophilia care, with more

and more centers switching to new and innovative treatment options.

In addition, we have shown that prophylaxis intervals in PWSHA on EHL were longer (59% every 2.5–4.5 days and 14% > 4.5 days) compared with plasma-derived (72.2% every 1.5–2.5 days) and recombinant concentrates (49% every 1.5–2.5 days and 35% every 2.5–4.5 days), with dosages mainly between 20 and 39 IU/kg in all three cohorts. The reduction in injection frequency has been reported in several studies.[7,28,29] However, in addition to the lower injection frequency, those studies have shown at least numerically lower factor consumption with EHL.[7,29] We found no difference in factor use in our cohort, which may be due to the aim of switching patients to achieve higher trough levels to reduce bleeding events.

The total annual factor consumption in PWHA was higher than in PWHB. For pediatric PWHB, factor consumption reduced slightly between 2015 and 2021, while it increased slightly for adult PWHB. When consumption was normalized to BW, the median consumption in children with sHA and adults with sHB was comparable between 2015 and 2021, but decreased in children with sHB and increased in adults with sHA. Because almost all children with sHB already were on prophylaxis in 2015 (and still are in 2021), this trend is mainly caused by the use of EHL products in HB patients, which may lead to a lower factor consumption due to the longer half-life of the product.[8,9]

We observed a significant reduction in the mean ABR in pediatric PWSH under prophylaxis between 2015 and 2021 (3.15–1.45), which is due to a nonsignificant reduction in AJBR and a significant reduction in minor bleeding. This may be explained with the higher use of factor concentrates in pediatric PWSHA and use of EHL in pediatric PWSHB. Another explanation for the lower bleeding rates could be the fact that the current analysis was performed during the corona pandemic and lockdown restrictions were imposed. This may have led to fewer accidents and injuries during outdoor activities like sports and games resulting in lower bleeding rates.[30] Comparing the patients intraindividually between 2015 and 2021, the total number of documented bleeds also decreased significantly in adult PWSH on prophylaxis.

Bleeding rates observed in our study in 2021 are comparable or even lower than those in the trials performed with EHL.[1,2,31–35] Median annual bleeding rates in those studies ranged between 0.0 (IQR: 0–1.87) for a once-weekly regimen of a FIX-EHL[2] and 3.6 (IQR: 1.9–8.4) for a once-weekly regimen of a FVIII-EHL,[31] but in most studies a median ABR between 1 and 2 with an IQR between 0 and up to 5.2 was achieved.[36] Median ABR in our children and adults was 1 (IQR: 0–2). In our study, there were only very few patients with sHA who had a once-weekly prophylaxis, while most of the sHB patients had a once-weekly prophylaxis and about one-third were treated even less frequently.

In addition, in 2021, AJBR was lower in children with sHA treated with emicizumab compared with children on SHL but not compared with children on EHL. There were no differences between SHL and EHL or between emicizumab and SHL or EHL in adults with sHA. Lower bleeding rates in emicizumab-treated patients compared with prior factor prophylaxis have been described already in the HAVEN 3 trial[5] and in observational studies in patients with and without inhibitors.[37,38] The reason why in our cohort no significant difference was seen may be the fact that most patients on factor concentrates had a comparably intense prophylaxis leading to low bleeding rates. Data on children treated with emicizumab are still scarce,[39] but there is some evidence that bleeding rates may be reduced after switching to emicizumab[39,40] in children as well. Interestingly, a longitudinal cohort study on patients aged between 1 month and 74 years has shown that the odds of bleeding while on emicizumab increases by a factor of 1.02 per year of life. This may be another explanation why we had no significant difference in bleeding rates between prophylaxis with emicizumab and factor concentrates in adults.

Limitations

This study has several limitations, which are mainly due to its retrospective design. Bleeding events were patient-reported and we cannot exclude that some bleeding events were not reported by the patients and that the real ABR may be higher. For a better comparison with the data from 2015 and to reduce effects due to different interpretation of possible bleeding events, only documented bleeding events were taken into account in both years.

Another limitation is that we included only patients with complete diaries in the analysis. Therefore, we cannot exclude a selection bias to a more compliant patient cohort which may have influenced factor consumption and bleeding rates.

Conclusion

The use of new treatment options has changed hemophilia treatment. The proportion of adult patients with sHA receiving prophylaxis has increased and was more than 95% in 2021. About 50% of the PWSHA received EHL or emicizumab and almost all sHB patients were on EHL in 2021. Factor consumption calculated per BW increased in adults but not in pediatric PWSHA between 2015 and 2021, and was stable in adult and decreased in pediatric PWSHB. Meanwhile, ABR significantly decreased in children, and AJBR remained at a low level in children and decreased in adults. The lower bleeding rates are an effect of the wider use of more effective prophylaxis. It will be interesting to see how the introduction of gene therapy, rebalancing strategies, and efanesoctocog alfa will change hemophilia treatment in the future.

Ethical Considerations

The study was approved by the Ethics Committee of the University of Leipzig (reference 393/22-ek) and conducted according to the Declaration of Helsinki.

Conflict of Interest

The authors declare that they have no conflict of interest.

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