Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-008 Concizumab

Stand: März 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Concizumab
Hämophilie B mit Faktor-IX-Inhibitoren

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL): - Albutrepenonacog alfa (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 1. Dezember 2016 und Beschluss vom 7. April 2022) - Eftrenonacog alfa (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 15. Dezember 2016 (aufgehoben) und Beschluss vom 1. Februar 2024) - Nonacog beta pegol (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 19. April 2018 und Beschluss vom 15. Februar 2024) - Etranacogen dezaparvovec (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 19. Oktober 2023)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Concizumab	**geplantes Anwendungsgebiet laut Beratungsantrag**: "Concizumab wird angewendet als Prophylaxe von Blutungsereignissen bei Patienten ab 12 Jahren mit • Hämophilie A mit Faktor VIII-Inhibitoren (HAwI) oder • Hämophilie B mit Faktor-IX-Inhibitoren (HBwI)"
Faktor-IX-Präparate	
Rekombinante Präparate	
Albutrepenonacog alfa B02BD33 Idelvion	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitaler Faktor-IX-Mangel). IDELVION kann bei allen Altersgruppen angewendet werden. *[FI 02/2021]*
Eftrenonacog alfa B02BD34 Alprolix	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). ALPROLIX kann bei allen Altersgruppeangewendet werden. *[FI 02/2021]*
Nonacog alfa B02BD09 BeneFix	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitaler Faktor-IX-Mangel). BeneFIX kann bei allen Altersgruppen angewendet werden. *[FI 09/2020]*
Nonacog beta pegol B02BD36 Refixia	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). Refixia kann bei allen Altersgruppen angewendet werden. *[FI 08/2023]*
Nonacog gamma B02BD29 Rixubis	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitalem Faktor-IX-Mangel). RIXUBIS ist für Patienten aller Altersgruppen indiziert. *[FI 11/2019]*
aus menschlichem Plasma gewonnene Präparate	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Faktor IX B02BD04 AlphaNine, Berinin, Mononine, Octanine	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel) *bzw.* Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitaler Faktor-IX-Mangel)
Faktor IX B02BD04 Haemonine	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). Haemonine wird angewendet bei Erwachsenen, Jugendlichen und Kindern im Alter von 6 Jahren und älter. *[FI 05/2022]*
Faktor IX B02BD04 Immunine	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). IMMUNINE ist für die Anwendung in allen Altersgruppen – bei Kindern älter als 6 Jahre bis hin zu Erwachsenen – indiziert. Die Anwendung von IMMUNINE bei Kindern unter 6 Jahren kann nicht empfohlen werden, da hierzu nur unzureichende Daten vorliegen. *[FI 08/2022]*
Kombination verschiedener Gerinnungsfaktoren	
Kombinationspräparate aus den Gerinnungs-faktoren II, VII, IX und X B02BD01 Beriplex, Cofact	- […] - Behandlung und perioperative Prophylaxe von Blutungen bei einem angeborenen Mangel eines Vitamin-K-abhängigen Gerinnungsfaktors, sofern keine Einzelfaktorkonzentrate zur Verfügung stehen *[FI Beriplex, 04/2022]*
Kombinationspräparat aus den Gerinnungs-faktoren II, VII, IX und X B02BD01 Prothromplex	- […] - Behandlung und perioperative Prophylaxe von Blutungen bei angeborenem Mangel von Vitamin K-abhängigen Gerinnungsfaktoren, wenn das gereinigte, spezifische Gerinnungsfaktoren-Konzentrat nicht zur Verfügung steht. - Prothromplex NF 600 ist indiziert für Erwachsene. Da nur unzureichende pädiatrische Daten vorliegen, kann die Anwendung von Prothromplex NF 600 bei Kindern nicht empfohlen werden. *[FI 06/2022]*
Mit Faktor VIII-Inhibitor-Bypassing-Aktivität angereicherte Humanplasmafraktion B02BD03 Feiba	- […] - Behandlung und Prophylaxe von Blutungen bei Hämophilie-B-Patienten mit FIX-Inhibitor - […] *[FI Feiba NF 500 E/1000 E 05/2023]* - […]

II. Zugelassene Arzneimittel im Anwendungsgebiet

	- Behandlung von Blutungen bei Hämophilie-B-Patienten mit Inhibitoren, wenn keine andere spezifische Behandlung verfügbar ist (siehe Abschnitt 5.1). - […] *[FI Feiba 500 E/1000 E/ 2500 E 05/2023]*
Weitere Präparate	
Eptacog alfa B02BD08 NovoSeven	Rekombinanter Faktor VIIa NovoSeven® wird angewendet zur Behandlung von Blutungen und Prophylaxe von Blutungen im Zusammenhang mit chirurgischen oder invasiven Eingriffen bei folgenden Patientengruppen: • bei Patienten mit angeborener Hämophilie mit Hemmkörpern gegen Blutgerinnungsfaktoren VIII oder IX > 5 Bethesda-Einheiten (BE) • bei Patienten mit angeborener Hämophilie, bei denen mit einem starken Anstieg des Hemmkörpers bei Verabreichung von Faktor VIII oder Faktor IX zu rechnen ist […] *[FI 05/2022]*
Etranacogen Dezaparvovec Hemgenix	Hemgenix ist indiziert zur Behandlung von schwerer und mittelschwerer Hämophilie B (angeborener Faktor-IX-Mangel) bei erwachsenen Patienten ohne Faktor-IX-Inhibitoren in ihrer Vorgeschichte. *[FI 02/2023]*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-008 (Concizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	27. Februar 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Prophylaxe von Blutungsereignissen bei Patienten ab 12 Jahren mit Hämophilie B mit Faktor-IX-Inhibitoren (HBwI).

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Hämophilie B durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 23.01.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 296 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 4 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Olasupo O et al., 2021 [2].

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B (Review)

Fragestellung

To determine the eHectiveness of clotting factor concentrate prophylaxis in managing previously-treated individuals with hemophilia A or B.

Methodik

Population:

- individuals with congenital hemophilia A or B, receiving secondary prophylaxis
- adults (aged 18 or over) and those trials with participants under 18 years of age if the participants met one of the three following criteria:
  - proven haemophilic arthropathy;
  - presence of one or more target joint;
  - previous on-demand treatment.

Intervention:

- intravenous clotting factor concentrates administered as prophylactic treatment in any formulation (e.g. fresh frozen plasma, cryoprecipitate, lyophilised plasmaderived clotting factor concentrate, or recombinant clotting factor concentrate), any concentration, any frequency and any dose
  - prophylaxis versus prophylaxis with a diHerent regimen;
  - prophylaxis versus on-demand treatment;
  - prophylaxis versus no treatment;
  - prophylaxis versus placebo.

Komparator:

- no treatment, placebo, on-demand treatment, or with one or more different prophylaxis regimens

Endpunkte:

- Primary outcomes: 1. Number of joint bleeding episodes or joint bleeding frequency, during the trial, 2. Orthopedic joint score or clinical joint function, 3. QoL on validated scales (disease-specific where possible)
- Secondary outcomes: 1. Number of total bleeding episodes or total bleeding frequency during the trial period, 2. Pain scores, 3. Radiologic joint score or radiologic measurements or descriptions of joint damage, 4. Clotting factor concentrate plasma levels, 5. Time loss to school or employment, 6. Integration into society (i.e. absenteeism), 7. Scores on scales recording feeling of well-being and global functioning, 8. Economic data: cost-effectiveness, cost-benefit, cost-utilisation, cost-minimisation, 9. Any reported adverse effects or toxicity of clotting factor concentrates (e.g. inhibitors, reactions, transmission of infection)

Recherche/Suchzeitraum:

- Date of the most recent search of the Group's Coagulopathies Trials Register: 24 February 2021.
- Systematische Recherchen in u.a. Medline OVID (2010 – June 2016) und Embase (1974 to June 2016)
- We also searched the following databases and trial registries: 1. MEDLINE Ovid (1946 to June 2016 – search carried out by authors of a previous version of this review 2. Embase Ovid

Qualitätsbewertung der Studien:

- Cochrane ROB-Tool

Ergebnisse

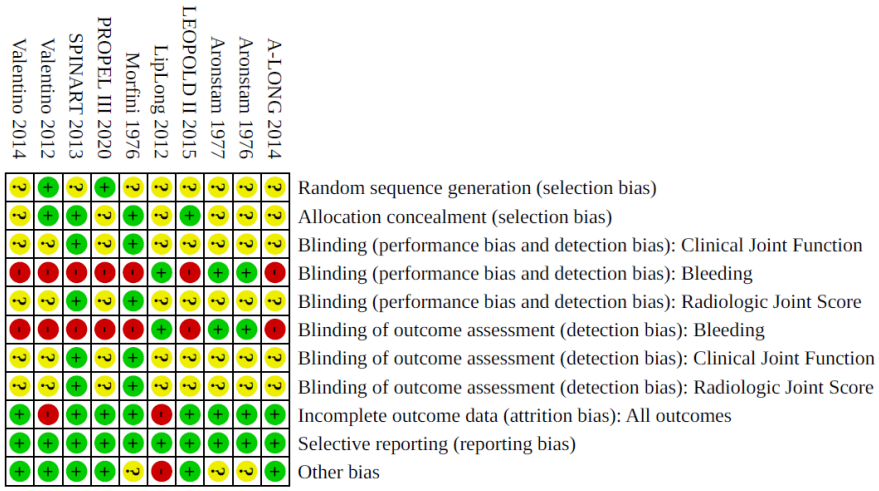
Anzahl eingeschlossener Studien:

- n=10 RCTs (N=608 Patienten)

Charakteristika der Population/Studien:

- All included participants were males and between five years and 65 years of age.
- All trials included participants receiving secondary prophylaxis.
- n=8 RCTs: compared the regular use of clotting factor concentrates to prevent joint bleeds with different dosing schemes to identify regimens that may be better;
- n=4 RCTs: compared the regular use of factor concentrates to prevent bleeds to their 'on demand' use to treat bleeds once they occur (two trials had multiple arms and were included in both comparisons).
- **n=2 RCTs: included individuals with hemophilia B: the Morfini trial included individuals with severe hemophilia B (FIX levels < 1%) (Morfini 1976); and the 2014 Valentino trial included individuals with moderately severe and severe hemophilia B (FIX levels V 2%) (Valentino 2014).**
- n=7 RCTs: included individuals with severe haemophilia A only

Qualität der Studien:



Studienergebnisse (**hier nur für Hämophilie B berichtet**):

- Individuals with hemophilia B were included in two trials (Morfini 1976; Valentino 2014).

- The Morfini trial (n=10 Patienten, [FIX levels < 1%]) showed that a twice-weekly regimen of prophylaxis may be superior to a onceweekly regimen in decreasing total bleeding incidence, but these results should be interpreted cautiously given the small number of participants, the extremely low dose used and the fact that none of the participants were blinded to their treatment allocation (low-certainty evidence).
- The results of the Valentino 2014 (n=50 Patienten, [FIX levels ≤ 2%)]) trial did not establish a superior prophylaxis regimen; however, this trial did show that prophylaxis at any dosing schedule was superior to on-demand treatment to prevent spontaneous bleeds and joint bleeding incidence (Valentino 2014). When considering these data, it must be kept in mind that the bleeding data were aggregated for only 16 weeks, and the annualized bleeding rates were extrapolated from this time period.

Anmerkung/Fazit der Autoren

There is evidence from RCTs that prophylaxis, as compared to on-demand treatment, may reduce bleeding frequency in previously-treated people with hemophilia. Prophylaxis may also improve joint function, pain and quality of life, even though this does not translate into a detectable improvement of articular damage when assessed by MRI.

When comparing two different prophylaxis regimens, no significant differences in terms of protection from bleeding were found. Dose optimization could, however, result in improved efficacy. Given the heterogeneity of the data, pooled estimates were not obtained for most comparisons.

Well-designed RCTs and prospective observational controlled studies with standardized definitions and measurements are needed to establish the optimal and most cost-effective treatment regimens.

Kommentare zum Review

- Nur 2 Studien relevant
- Berichterstattung auf Einzelstudienbasis
- Geringe Patientenzahl in den Studien

3.2 Leitlinien

Hart D.P. et al., 2022 [1].

International consensus recommendations on the management of people with haemophilia B

Zielsetzung/Fragestellung

These recommendations provide a clinical practice framework for the management of PwHB in routine clinical practice based on the published evidence and clinical experience, in conjunction with published guidelines. It is hoped that these recommendations will complement existing haemophilia guidelines and could be adapted and applied across different regions and countries.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zur Behandlung im vorliegenden AWG, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium (keine Patienten integriert); internationales Expertenkomitee
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz (keine Qualitätsbewertung der Evidenz durchgeführt).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt (zum Teil);
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt (Nein);
- Regelmäßige Überprüfung der Aktualität gesichert (unklar).

Recherche/Suchzeitraum:

- Syst. Recherche (PubMed/MedLine, EMBASE and Cochrane Library databases); Suchzeitraum (1990 – 2020)

LoE

- keine

GoR

- keine

Empfehlungen

Recommendations for the management of PwHB in routine clinical practice

Currently, no head-to-head clinical trials in PwHB have directly compared SHL-FIX and EHL-FIX using clinically relevant endpoints such as annualized bleeding rate (ABR), annualized joint bleed rates and progression of arthropathy. However, several indirect comparisons have been carried out and indicate favourable efficacy and reduced factor consumption for EHL products compared with SHL products.[21–23] A number of factors differ between randomized controlled trials, real world and other study types, including participants and adherence to treatment; therefore comparison of data across these data sources should be interpreted with caution. Treatment choice should be a shared decision between the PwHB and physician/nurse prescriber after multidisciplinary discussion, considering the preference of the PwHB (including convenience) and the impact on their QoL. In this respect, PwHB should be informed on differences between different FIX replacement products and how these may affect clinical and patient-relevant outcomes. Several studies that evaluated disease burden, patient perspectives, patient values and resource utilization have revealed that reduced treatment/administrative burden associated with EHL was important to patients and carers,[33–35] offering an opportunity to improve adherence.[34,35] While treatment choices may impact adherence to treatment for PwHB, adherence is a multifactorial construct that is determined by a number of other features (e.g. socio-economic, patient-related, conditionrelated, health care system, treatment-related aspects), and factors that still remain to be elucidated.[36]

Topic 1: Factor product choice, switching and clinical indications	
1	Prophylaxis with FIX should be considered in all people with severe haemophilia B (including those classified as non-severe according to their basal FIX levels but with a severe bleeding phenotype); in these PwHB, prophylaxis should be initiated as early as possible (i.e. prior to the onset of joint bleeding), and thereafter, treatment should not be interrupted
2	Both SHL-FIX and EHL-rFIX are effective treatment options for prophylaxis in PwHB
3	Either SHL-FIX or EHL-FIX products can be used to offer adequate haemostatic cover for bleeds, surgery and invasive procedures; when using EHLs, laboratory requirements for product-specific monitoring should be considered
4	When choosing a product or considering switching to alternative products, venous access, adherence, bleeding phenotype, lifestyle, patient preference and PK should be considered in the context of local licensing and approval status
5	Dose and frequency of prophylactic FIX treatment should be adapted to the clinical phenotype (e.g. bleed rates) and lifestyle considerations, and not based exclusively on plasma trough levels

EHL-rFIX, extended half-life–recombinant factor IX; FIX, factor IX; PK, pharmacokinetic; PwHB, people with haemophilia B; SHL, standard half-life.

Topic 4: Inhibitor management and preparing for novel agents	
1	In people with severe haemophilia B, the causative *F9* genetic defect should be determined as soon as possible after diagnosis to identify those at increased risk of inhibitor development and/or severe allergic reaction
2	Inhibitor screening should be routinely performed in all people with severe haemophilia B and scrutiny intensified if developing allergic reactions towards FIX and/or in those patients with inadequate response to FIX replacement therapy
3	FIX infusion and close clinical observation for allergic reaction should occur in the hospital setting during the first 20 EDs in people with severe haemophilia B
4	Recombinant activated factor VII should be the first choice for bleeding control and/or surgical cover in people with severe haemophilia B and high-responding inhibitors, as well as in those who have developed allergic reactions; aPCC is an option, but the content of FIX and associated risk of anamnesis and/or worsening of allergic reaction(s) needs to be considered
5	ITI to eradicate persistent inhibitors should be considered in people with severe haemophilia B; however, the relative benefits and risks need to be taken into account; ITI should only be initiated in a haemophilia treatment centre with an experienced team
6	Patients should be closely monitored during ITI for the development of nephrotic syndrome and/or severe allergic reactions
7	For those patients who have an allergic reaction, desensitization should be considered; importantly, further serious allergic reaction(s) should be anticipated in these patients, and subsequent infusions should occur in the hospital setting with appropriate resuscitation expertise and equipment
8	For FIX inhibitor eradication, ITI protocols with a combination of FIX and immunosuppressive agents may be considered as a first-line treatment

aPCC, activated prothrombin complex concentrate; EDs, exposure days; FIX, factor IX; ITI, immune tolerance induction.

Topic 5: Preparing for GT	
1	Based on current AAV haemophilia B GT trial data, this therapy should be considered as a future treatment option in adults with severe haemophilia B
2	As part of the informed consent process, patients should be made aware of the unpredictability of achieved FIX level and duration of expression
3	With liver-directed AAV GT for haemophilia B, patients should be aware that pre-existing liver pathology may be an exclusion criterion; for those proceeding to GT, patients should be counselled about other potential sources of hepatotoxicity that may interfere with FIX expression (e.g. medication use, alcohol)
4	Clinicians should be aware that a rise in transaminase levels during the acute phase of GT may indicate an immune response that can potentially threaten the expression of FIX; close monitoring of transaminase levels is needed to ensure that timely immunosuppression can be implemented
5	Clinicians should consider that the specific geographic pattern of AAV seropositivity may help direct which GT is chosen
6	When establishing a programme for haemophilia B GT, it is important to set up a network of care directed by experienced haemophilia treaters to include comprehensive education programmes for patients, haemophilia centre staff, extended multidisciplinary team and allied services
7	Patients and HCPs should be well informed of the potential need for either prophylactic or interventional immune suppression following GT administration, including duration and potential side effect profiles
8	Patients and HCPs should be aware of the need for long-term safety and efficacy follow-up, including assessment of liver health and levels of FIX expression, coordinated by the haemophilia centre
9	Centres and stakeholders, including regulators, payers and patients, should recognize the importance of participating in a post-authorization registry to gather real-world data on safety and efficacy of haemophilia B GT

AAV, adeno-associated virus; FIX, factor IX; GT, gene therapy; HCP, healthcare provider.

Referenzen aus Leitlinien

21. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med 2013; 369: 2313–2323.
22. Iorio A, Krishnan S, Myrén KJ, et al. Continuous prophylaxis with recombinant factor IX Fc fusion protein and conventional recombinant factor IX products: comparisons of efficacy and weekly factor consumption. J Med Econ 2017; 20: 337–344.
23. Powell J, Shapiro A, Ragni M, et al. Switching to recombinant factor IX Fc fusion protein prophylaxis results in fewer infusions, decreased factor IX consumption and lower bleeding rates. Br J Haematol 2015; 168: 113–123.
33. Sun HLYM, Poon M-C, Lee A, et al. Observational study of real-world factor utilization and health outcomes in patients with hemophilia in Canada. Blood 2018; 132: 4813.
34. Furlan R, Krishnan S and Vietri J. Patient and parent preferences for characteristics of prophylactic treatment in hemophilia. Pat Pref Adher 2015; 9: 1687–1694.
35. Shapiro A, Chaudhury A, Jain N, et al. Realworld data on the use of rFIXFc in subjects with hemophilia B for up to 3.7 years demonstrates improved bleed control and adherence with reduced treatment burden. Blood 2018; 132: 2493.
36. Strike K, Chan A, Iorio A, et al. Predictors of treatment adherence in patients with chronic disease using the multidimensional adherence model: unique considerations for patients with haemophilia. The Journal of Haemophilia Practice 2020; 7: 92–101.

Srivastava A et al., 2020 [4].

World Federation of Hemophilia (WFH)

WFH guidelines for the management of hemophilia, 3rd edition

Zielsetzung/Fragestellung

Guideline for the management of haemophilia.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zur Behandlung im vorliegenden AWG, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt (Nein).
- Systematische Suche, Auswahl und Bewertung der Evidenz (keine Qualitätsbewertung der Evidenz durchgeführt).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt (NEIN)
- Regelmäßige Überprüfung der Aktualität nicht spezifiziert.

Recherche/Suchzeitraum:

- Searches were run in PubMed, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE, covering the period from January 1, 2000, to the date of the search between May and November 2019.

LoE / GoR

- No LoE and SoR caused by low level of evidence in this field. In the interest of transparency the WFH guideline recommendations were not graded but were clearly marked “CB” for consensus-based.
- Following the drafting of the recommendations by the assigned healthcare professionals, each set of recommendations went through the modified Delphi consensus process.

Empfehlungen

Chapter 5: Hemostatic Agents

Recommendation 5.1.1:

For patients with hemophilia, the WFH does not express a preference for recombinant over plasma-derived clotting factor concentrates.

REMARK: The choice between these classes of product must be made according to local criteria including availability, cost, and patient preferences. CB

Recommendation 5.2.1:

For people with hemophilia, the WFH recommends the use of products that have been accepted by the official regulatory agencies responsible for protecting and promoting public health with consideration given to the plasma quality (i.e., purity of the product) and the manufacturing process (i.e., viral inactivation/elimination).

• REMARK: A plasma-derived product created by a process that incorporates two viral reduction steps should not automatically be considered better than one that only has one

specific viral inactivation step. If only one step is used, this step should preferably inactivate viruses with and without lipid envelopes. Most recently, licensed products use two orthogonal viral inactivation/ elimination steps.

• REMARK: Current prothrombin complex concentrates should be considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z. CB

5.3. Clotting factor concentrates (CFCs)

FIX CFCs

- All currently marketed plasma-derived and recombinant FIX products are listed in the WFH Online Registry of Clotting Factor Concentrates. 3 Consult the individual product inserts for details.
- FIX CFCs are categorized into two classes:
  - Pure FIX CFCs, which may be plasma-derived or recombinant (see below for information on EHL FIX CFCs);
  - FIX CFCs that also contain factors II, VII, IX, and X, known as prothrombin complex concentrates (PCCs), which are nowadays only rarely used. Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B 8,9 as they are associated with a reduced risk of thrombosis and disseminated intravascular coagulation compared to PCCs, particularly in the following instances:
    - surgery;
    - liver disease;
    - intensive exposure, i.e., prolonged therapy at high doses;
    - previous thrombosis or known thrombotic tendency;
    - concomitant use of drugs known to have thrombogenic potential, including antifibrinolytic agents.

Recommendation 5.3.3:

- For treatment of FIX deficiency in patients with hemophilia B, the WFH recommends a product containing only FIX rather than prothrombin complex concentrates (PCCs), which also contain other clotting factors, such as factors II, VII, and X, some of which may become activated during manufacture and may predispose the patient to thromboembolism.

  REMARK: Pure FIX products have reduced risk of thrombosis or disseminated intravascular coagulation, compared to what was observed with large doses of older-generation PCCs.

  REMARK: Current PCCs are considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z. Nevertheless, in cases of intensive treatment (e.g., perioperative management), prothrombotic clotting factors may accumulate in plasma and may increase the risk for thromboembolic complications. When PCCs are used in high doses in order to normalize FIX levels, thromboprophylaxis should be considered. CB

Recommendation 5.3.4:

- For hemophilia B patients requiring prolonged therapy at high doses, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Recommendation 5.3.5:

- For hemophilia B patients undergoing surgery, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Recommendation 5.3.6:

- For hemophilia B patients with liver disease, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Recommendation 5.3.7:

- For hemophilia B patients with previous thrombosis or known thrombotic tendency, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Recommendation 5.3.8:

- For hemophilia B patients concomitantly using drugs known to have thrombogenic potential, including antifibrinolytic agents, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Dosage/administration

- FIX CFCs are available in vials labelled with the product potency, ranging from approximately 250-4000 IU per vial.
- In the absence of an inhibitor, each IU of plasma-derived or recombinant SHL FIX per kilogram of body weight infused intravenously will raise the plasma FIX level by approximately 1 IU/dL.
- The half-life of SHL FIX is approximately 18-24 hours. Guidelines for PK studies on FIX CFCs include at least 8 blood samplings taken over a period of 72 hours (additional samplings over up to 2 weeks for EHL FIX). However, for dose tailoring in routine practice, useful PK parameters can be estimated from population PK models which enable Bayesian estimation of individual PK from limited samples. 15

Recommendation 5.3.9:

- For patients with hemophilia B receiving FIX concentrates who would benefit from optimization of prophylaxis, the WFH recommends pharmacokinetic monitoring.

  REMARK: Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 1-2 weeks), or with limited sampling in combination with population PK estimates. CB
- Unmodified recombinant FIX (rFIX) CFCs have a lower recovery than plasma-derived FIX CFCs, such that each unit of FIX infused per kilogram of body weight will raise FIX activity by approximately 0.8 IU/dL in adults and 0.7 IU/dL in children under 15 years of age. 22
- To calculate dosage, multiply the patient ' s weight in kilograms by the FIX level in IU/dL desired.
  - Example: 50 kg body weight × 40 (IU/dL level desired) = 2000 IU of plasma-derived FIX.
  - For rFIX, the dose is calculated as 2000 IU ÷ 0.8 (or 2000 IU × 1.25) = 2500 IU for adults, and 2000 IU ÷ 0.7 (or 2000 IU × 1.43) = 2860 IU for children.
- FIX CFCs should be infused slowly over several minutes as specified in the product insert. 14 The patient ' s peak FIX level should be measured approximately 15-30 minutes after infusion to verify the expected FIX activity of the dose given. 12
- For patients undergoing surgery or those with severe bleeds that require frequent infusions, laboratory monitoring of FIX levels is required including measurement of FIX trough level to aid in the calculation of subsequent doses. (See Chapter 3: Laboratory Diagnosis and Monitoring – Factor assays, and Chapter 9: Specific Management Issues – Surgery and invasive procedures.)
- Purified FIX CFCs may also be administered by continuous infusion (as with FVIII CFCs).
- Allergic reactions may occur with infusions of both recombinant and plasma-derived FIX CFCs (in approximately 2%-4% of cases). These are often associated with anti-FIX inhibitors.

Extended half- life products

Rationale for development of EHL CFCs

- The frequency of infusions using SHL CFCs is associated with an increased burden of treatment and often leads to poor adherence to prophylaxis regimens. 23 Annualized bleeding rates (ABRs) are not always zero with prophylaxis with SHL CFCs, and joint disease can still appear in young adults. 24,25 EHL products were developed to address the need to reduce the treatment burden of prophylaxis and to maintain higher factor trough levels to improve bleed prevention.

Recommendation 5.3.10:

- For patients with hemophilia A or B, there is no evidence for any clinical safety issues in persons with hemophilia to recommend a preference among the various mechanisms of action (e.g., PEGylation, Fc-fusion, albumin-fusion) used to extend the halflife of clotting factor concentrates. CB

Safety and efficacy of EHL products

- All registered EHL products have been shown to be efficacious in the prevention and treatment of bleeds in children, adolescents, and adults. Over 90% of bleeds were successfully treated with a single administration, and the efficacy in bleed prevention resulted in ABRs <4-5 across all EHL products. Hemostatic efficacy was demonstrated in a variety of minor and major surgeries. 32
- In previously treated children, adolescents, and adults, no increased risk of new inhibitor development has been observed in those receiving EHL FVIII/FIX products; all clinical trials in previously treated patients (PTPs) have demonstrated either no inhibitor development or very low incidence rates that were within regulatory safety limits.
- EHL products have been given to previously untreated patients (PUPs), either as part of clinical PUP studies or outside of studies. Although inhibitor development has been reported in such settings, no substantial difference in levels of inhibitor development has been observed with EHL compared to SHL products. However, no completed trial in PUPs has yet been published in full.

Activated prothrombin complex concentrate (aPCC)

- Recommendation 5.4.2: For patients with hemophilia B and an inhibitor with a history of anaphylaxis to FIX-containing clotting factor concentrates, recombinant activated factor VIIa must be administered as activated prothrombin complex concentrate cannot be used. CB
- Recommendation 5.4.3: The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events. CB

Recommendation 5.4.2:

- For patients with hemophilia B and an inhibitor with a history of anaphylaxis to FIX-containing clotting factor concentrates, recombinant activated factor VIIa must be administered as activated prothrombin complex concentrate cannot be used. CB

Recommendation 5.4.3:

- The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events. CB
- In addition to bypassing agents, non-factor replacement therapies (e.g., emicizumab) are becoming available that offer new treatment paradigms including for the treatment of inhibitors.
- See 5.7 Non-factor replacement therapies, below; and Chapter 6: Prophylaxis in Hemophilia – Prophylaxis using non-factor replacement therapies.

5.5 | Other plasma products

Recommendation 5.5.1:

- For patients with hemophilia, the WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant clotting factor concentrates in preference to cryoprecipitate or fresh frozen plasma.

  REMARK: The WFH supports the use of CFCs in preference to cryoprecipitate or FFP due to concerns about quality, safety, and efficacy. However, the WFH recognizes the reality that they are still widely used in countries around the world where they are the only available or affordable treatment options. CB

Recommendation 5.5.2:

For patients with hemophilia, fresh frozen plasma is not recommended due to concerns about the safety and quality.

REMARK: However, the WFH recognizes the as yet unavoidable reality of their continued use in some parts of the world where it is the only available or affordable treatment option. CB

Recommendation 5.5.3:

- For patients with hemophilia, cryoprecipitate is not recommended due to concerns about the safety and quality.

  REMARK: The use of cryoprecipitate can only be justified in situations where clotting factor concentrates are not available as there is no proven advantage for their use over CFCs. It is strongly encouraged that viral-inactivation procedures be used, if available. CB

5.6 | Other pharmacological options

Recommendation 5.6.6:

- For patients with hemophilia, the WFH recommends that antifibrinolytics are a valuable alternative to use alone or as adjuvant treatment, particularly in controlling mucocutaneous bleeding (e.g., epistaxis, oral and gastrointestinal bleeding, and menorrhagia) and for dental surgery and eruption or shedding of teeth.

  REMARK: Antifibrinolytics can be used with standard doses of clotting factor concentrates, including bypassing agents. However, they should not be used with prothrombin complex concentrates due to the increased risk of thromboembolism. CB

Recommendation 5.6.7:

- For patients with hematuria, the WFH recommends against the use of antifibrinolytics, as it is contraindicated in these patients due to increased risk of obstructive uropathy. CB

Recommendation 5.6.8:

- For patients with renal impairment, the WFH recommends reduced dosing of antifibrinolytics and close monitoring. CB

Chapter 6: Prophylaxis in Hemophilia

Recommendation 6.1.1:

- For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly

recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference.

- REMARK: Individualizing prophylaxis means that if patients continue to experience bleeds, their prophylaxis regimen should be escalated (in dose/frequency or both) to prevent bleeding.
- REMARK: In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic therapy but recognizes that less intensive prophylaxis may be used. CB

Standard half- life factor replacement therapy

- Prophylaxis has conventionally been defined as the regular intravenous (IV) infusion of the missing clotting factor VIII (FVIII) in people with hemophilia A and factor IX (FIX) in people with hemophilia B, given in order to increase the FVIII/FIX level with the intent to prevent bleeding. 1 The focus of this conventional definition of prophylaxis has been on preventing joint bleeds and maintaining musculoskeletal health.
- The objective of prophylaxis has been to convert a person with severe hemophilia (baseline FVIII/FIX level <1 IU/dL [1%]) to a bleeding phenotype typical of moderate or mild hemophilia by maintaining factor levels above 1 IU/dL (1%) at all times. 4
- This was based on the observation that people with moderate hemophilia seldom experienced spontaneous bleeding and had much better preservation of joint function.
- However, there has been increasing recognition and evidence that factor trough levels of 1-3 IU/dL (1%-3%) are insufficient to totally prevent bleeds in all people with hemophilia and allow occasional clinical and subclinical bleeds, resulting in gradual progression of joint disease over a lifespan. 5
- In general, the higher the factor levels at all times, the less the bleeding. For every 1% increase in baseline factor levels (in people with hemophilia not on prophylaxis), there is a decrease in bleeding frequency, and when baseline FVIII:C levels are above 15 IU/dL (15%), spontaneous bleeding is uncommon. 6-8 The same is thought to apply with FIX:C levels, although this has been less well studied. Similarly, it has been shown that the more time spent with FVIII levels below 1 IU/dL (1%), the higher the rate of breakthrough bleeds during prophylaxis.

Extended half- life factor replacement therapy

- The use of extended half-life (EHL) CFCs fits within the definition of conventional factor prophylaxis but allows for more ambitious prophylaxis than simply converting an individual from a severe to a moderate phenotype.
- This is particularly the case with some EHL FIX products which allow individuals to have FIX levels in a non-hemophilic range (>40 IU/dL [40%]) for a substantial proportion of time and levels in the mild hemophilia range (5-40 IU/dL [5%-40%]) just prior to the next infusion.
- While prophylaxis with CFCs has been the mainstay of hemophilia treatment for many decades, the treatment landscape is changing with the development of new types of therapies.

Initiation of prophylaxis: timing and approach

- Age at initiation of prophylaxis has been a strong predictor of long-term clinical outcomes.
- People with hemophilia initiated on early prophylaxis (i.e., primary or secondary prophylaxis) have shown the best long-term outcomes. 12 (See Table 6-1 for prophylaxis definitions.) Furthermore, early initiation of prophylaxis also reduces the risk and incidence of intracranial hemorrhage (ICH), which is highest in very young children. 13
- Long-term cohort studies have shown that a small number of joint bleeds occurring early in life prior to the start of prophylaxis may (in some patients) ultimately result in hemophilic arthropathy. 14-16

- Regular prophylaxis begun at a young age and given in appropriate doses should therefore be considered the standard of care to treat hemophilia until an alternate long-term therapy such as gene therapy is available.
- There have been various approaches regarding how to initiate conventional prophylaxis with IV factor replacement therapy. The two main ways (high-dose prophylaxis and low-dose escalating prophylaxis) are mainly differentiated in the frequency of CFC administration and less so in the doses used. 17
- Escalating frequency prophylaxis, which starts with less intense prophylaxis (e.g., once-weekly infusions), followed by an increase in frequency, has enabled young children and their families to gradually adapt to the burdens of prophylaxis (e.g., peripheral venous infusion). 18,19 Young children commenced on low-dose escalating prophylaxis need to be followed closely, and strong consideration should be given to escalating prophylaxis quickly (either all patients or according to bleeding symptoms) in order to prevent bleeding and resulting morbidity.
- Starting with less intense prophylaxis and then gradually escalating may improve family acceptance of starting prophylaxis early and may improve adherence to prophylaxis. This approach also appears to result in less need for placement of central venous access devices (CVADs). However, patients on less intense prophylaxis are at a higher risk of bleeding until escalation of prophylaxis occurs. 20,21
- For people with hemophilia A, starting with small doses of FVIII CFC therapy may have the additional (unproven) benefit of decreasing inhibitor development, as large and frequent doses of FVIII early on have been associated with an increase in the rate of inhibitor development. 22
- People with severe/moderate hemophilia who have had a life-threatening bleed in early childhood should, however, not be placed on escalating dose prophylaxis but instead be started immediately on high-dose prophylaxis.
- How to start and when to start prophylaxis with either standard half-life (SHL) or extended half-life (EHL) CFCs is not significantly different. In both cases, prophylaxis should be commenced early by starting with a high-dose/high-frequency approach or a low-frequency approach, followed by escalation of frequency.
- With EHL CFCs, less frequent infusions (e.g., once weekly) may be sufficient for many individuals, particularly those with severe hemophilia B receiving EHL FIX CFCs. As EHL CFCs must still be given intravenously, they remain difficult to administer in very young children with poor peripheral venous access. 17

Recommendation 6.1.2:

- For pediatric patients with severe hemophilia A or B, the WFH recommends early initiation of prophylaxis with clotting factor concentrates (standard or extended half-life FVIII/FIX) or other hemostatic agent(s) prior to the onset of joint disease and ideally before age 3, in order to prevent spontaneous and breakthrough bleeding including hemarthroses which can lead to joint disease. CB

Recommendation 6.1.3:

- For adolescents and adults with hemophilia who show evidence of joint damage and have not as yet been on prophylaxis, the WFH recommends commencing tertiary prophylaxis in order to reduce the number of hemarthroses, spontaneous and breakthrough bleeding, and slow down the progression of hemophilic arthropathy. CB

Intensity of prophylaxis

- Although intensity of prophylaxis has generally been referred to as high, intermediate, and low dose, it should be appreciated that intensity is a function of both dose and frequency and that high dose usually refers to a combination of both high doses and high frequencies, while low dose usually refers to a combination of lower doses and lower frequencies, although not always.

6.2 | Benefits of prophylaxis

Prophylaxis using clotting factor concentrates

- All forms of prophylaxis (high/intermediate/low dose with CFCs or prophylaxis with non-factor replacement agents, e.g., emicizumab) provide superior benefits over episodic therapy. Conventional high-dose and intermediate-dose prophylaxis, initiated early in life, have been associated with over 90% reduction in joint bleeding rates, annualized joint bleeding rates (AJBRs) below 3 per year, and a significant reduction in joint deterioration and degenerative joint disease.
- Prophylaxis also provides protection from other types of hemorrhages in hemophilia, including preventing or substantially reducing the risk of intracranial hemorrhage.
- Longer-term benefits include reduction of chronic musculoskeletal pain, functional limitations and disability, need for orthopedic surgery, hospitalization, emergency room visits, and reduced length of hospital stays; all of this leads to greater participation (i.e., regular attendance) in educational, recreational, and professional activities, with improved quality of life.
- Because of these benefits, the World Health Organization (WHO), the World Federation of Hemophilia (WFH), and many national and international hemophilia organizations have endorsed early prophylaxis as the standard of care for children with a severe phenotype hemophilia 27 and recommend that prophylaxis be continued lifelong. Additionally, adults with severe phenotype hemophilia (if not already on prophylaxis) should initiate prophylaxis as well.

Recommendation 6.2.1:

- For patients with severe phenotype hemophilia A or B, especially children, the WFH recommends regular long-term prophylaxis as the standard of care to prevent hemarthrosis and other spontaneous and breakthrough bleeding, maintain musculoskeletal health, and promote quality of life. When prophylaxis is not feasible, episodic therapy is essential treatment for acute hemorrhages, but it will not prevent long-term joint damage.

  REMARK: In the long term, early and regular prophylaxis for children reduces hemarthrosis and other hemophilic bleeding, produces better health and joint outcomes, reduces the number of hospital visits and admissions, and may avert the need for orthopedic interventions, including surgery, in the future. CB

6.3 | Standard half- life factor prophylaxis

- All SHL CFCs (i.e., plasma-derived and recombinant) have essentially similar pharmacokinetic properties. The short half-life of SHL CFCs results in the need for frequent venipunctures for prophylaxis (3-4 times per week for FVIII and 2-3 times per week for FIX); this often leads to the need for CVADs in young children and to reduced adherence in older children/adults. 28
- With SHL CFCs, it is difficult to achieve factor trough levels much higher than 1 IU/dL (1%); to do so would require very frequent infusions (possibly daily) that many patients are likely unwilling or unable to do.

Recommendation 6.3.1:

- For patients with severe phenotype hemophilia A or B, prophylaxis with clotting factor concentrates (either standard or extended half-life) is recommended at a dose and dosing interval (dependent on the pharmacokinetic [PK] properties of the clotting factor concentrate) that allow them to at all times have sufficient circulating factor to prevent hemarthrosis, and spontaneous and breakthrough bleeding, based on their individual needs and lifestyles and preserve musculoskeletal function.

  REMARK: In the past, a trough factor level of 1 IU/dL (1%) was deemed an adequate goal. Now recognizing that with a 1% trough level, patients remain at risk of bleeding, most clinicians would prefer to target higher trough levels (>3%-5%, or higher). Recent

studies show that such trough levels achieve less bleeding. However, the trade-off is that higher trough levels may require higher doses or more frequent infusions of clotting factor concentrates. This should therefore be personalized based on the individual ' s activities, lifestyle, and PK handling of factor. CB

Recommendation 6.3.2:

- For patients who are adherent to their prescribed prophylaxis regimen but still experience breakthrough bleeds, the WFH recommends escalation of prophylaxis with measurement of trough levels and, if required, orthopedic interventions as appropriate.

  REMARK: Any patient who fails to respond to adequate factor replacement therapy after past responsiveness should be tested for inhibitor development prior to escalation of therapy. CB

6.4 | Extended half- life factor prophylaxis

- The limitations of prophylaxis with SHL CFCs led to the recent development, introduction, and increasing use of EHL CFCs.

Half- life/clearance

- Current EHL FVIII CFCs show modest improvement (1.4- to 1.6-fold) in half-life/clearance in comparison to SHL FVIII CFCs, with no significant differences in PK properties between these EHL FVIIIs. (Note that there is one EHL FVIII still in clinical trials [BIVV001] that shows a 3- to 4-fold half-life extension.) By contrast, EHL FIX CFCs show greatly improved half-lives (3- to 5-fold longer) in comparison to SHL FIX, but unlike with EHL FVIIIs, there are significant differences in the PK properties between EHL FIX CFCs. 9,30-32

Dose

- It is not as yet determined what constitutes high-, intermediate-, and low-dose prophylaxis with EHL CFCs and whether these definitions should be revised, given that much higher factor trough levels can be obtained with EHL CFCs, particularly with EHL FIXs. For the most part, EHL FVIIIs have similar recoveries as SHL FVIIIs, and hence doses used for prophylaxis will be similar. Certain EHL FIX products show higher recoveries on the basis of less extravascular distribution than SHL FIX; for these products, lower doses might be used for prophylaxis. 9,31 It has been hypothesized that differences in extravascular distribution of FIX between various EHL and SHL FIX CFCs may be important in the protective effect that these CFCs deliver. 33,34 Further research into this is necessary.

Frequency of dosing

- Overall, EHL CFCs allow people with hemophilia to reduce the number of infusions needed to still achieve levels of protection similar to SHL CFCs, or allow them to increase their factor trough levels and achieve higher levels of bleed protection with a similar number of infusions, or a combination of both. Modest reductions in infusion frequency or modest increases in factor trough levels (likely not both) may be accomplished with EHL FVIII concentrates.
- Some (but not all) EHL FIX concentrates permit patients to infuse much less frequently (e.g., once every 7-14 days) and still maintain FIX trough levels of ≥10%-20% 9,31,32,35 or infuse weekly or more frequently and achieve FIX trough levels of 20%, 30%, or potentially higher levels. The only caveat to this is that differences in extravascular distribution of FIX may be important in the protective effect of FIX.

Time of day dosing for EHL CFCs

- The longer the half-life of a product, the less critical the timing of infusions. This is particularly the case with some EHL FIX concentrates.

Recommendation 6.4.1:

- For patients with severe phenotype hemophilia A or B using EHL FVIII or FIX concentrates, the WFH recommends prophylaxis with EHL clotting factor concentrates at sufficient doses and dosing intervals to prevent hemarthroses and spontaneous and breakthrough bleeding and preserve joint function. CB

Chapter 8: Inhibitors to Clotting Factor

Recommendation 8.2.5:

- For patients with newly diagnosed hemophilia B, the WFH recommends regular inhibitor screening at least every 6-12 months, and then annually.

  REMARK: In general, more frequent inhibitor screening should be considered when recurrent bleeds or target joints occur despite adequate factor replacement.

  REMARK: Because inhibitor incidence is much lower in hemophilia B than in hemophilia A, experience and evidence are limited.

  REMARK: This recommendation places greater value on early inhibitor diagnosis to avoid uncontrolled bleeds and bleeding complications. The requirement for frequent blood draws was considered in relationship to the potential morbidity of uncontrolled or life-threatening bleeds. CB

  Recommendation 8.2.6:

- For patients with hemophilia B who are treated with clotting factor concentrate for more than 5 consecutive days, the WFH suggests inhibitor screening within 4 weeks of the last infusion. CB

Recommendation 8.2.7:

- For patients with hemophilia B who fail to respond to adequate clotting factor replacement therapy or who have lower than expected factor recovery or half-life, the WFH suggests inhibitor screening. CB

Recommendation 8.2.8:

- For patients with hemophilia B who develop an allergic reaction to FIX therapy, including anaphylaxis or nephrotic syndrome, the WFH suggests inhibitor screening to determine if an inhibitor is present. CB

Recommendation 8.2.9:

- For patients with severe hemophilia B who undergo major surgery, the WFH suggests preoperative inhibitor screening. CB

8.4 | Hemophilia B and FIX inhibitors

Genetic and environmental risk factors

- FIX inhibitors are almost exclusively seen in patients with severe hemophilia B and very rarely in the milder forms. 67
- Inhibitors in patients with severe hemophilia B are rare and occur most commonly in those with null variants, in which no endogenous clotting factor is produced, in most cases due to large deletion, frame-shift, and nonsense variants. 67,68 There is no known ancestral predilection to inhibitor development in hemophilia B.
- Inhibitor formation in hemophilia B is not thought to be related to type of FIX CFC, and it has been reported in those receiving plasma-derived and recombinant FIX CFCs alike.

Inhibitor incidence

- Inhibitor formation in patients with hemophilia B occurs infrequently, with a cumulative incidence of up to 5%. 69,70
- The development of an FIX inhibitor is considered the most serious complication in patients with hemophilia B, 9 due not only to loss of response to FIX replacement, but also to the associated risks of anaphylaxis and nephrotic syndrome. 67
- Inhibitor detection in hemophilia B is similar to that in hemophilia A, with most inhibitors occurring after a median of 9-11 exposures, and before 20 exposures, typically before 2 years of age. 18
- Treatment strategies for FIX inhibitors are similar to those for FVIII inhibitors; specifically, they focus on controlling hemostasis and eradicating the inhibitor.
- It is recommended that because of the severity of complications, patients with hemophilia B should be followed closely and screened for inhibitors every 6-12 months after initiating CFC replacement therapy, and annually thereafter.

Disease burden

Anaphylaxis to FIX

- Inhibitor formation in patients with hemophilia B is overall associated with a similar disease burden as in hemophilia A but may also be associated with allergic reaction to FIX CFCs. Anaphylaxis occurs in 50% of hemophilia B patients with inhibitors, 20 and more frequently in those with null mutations. Such reactions may be the first symptom of FIX inhibitor development. 67
- Newly diagnosed severe hemophilia B patients, particularly those with a family history of severe hemophilia B with inhibitors and/ or with genetic variants predisposing to inhibitor development, should be treated in a clinic or hospital setting capable of managing severe allergic reactions for the initial 10-20 exposures to FIX CFCs, with emergency equipment available to treat anaphylaxis. 67 Reactions may also occur later but may be less severe. 20,71

Recommendation 8.4.1:

- For patients with hemophilia B who develop anaphylaxis to FIX therapy, the WFH recommends screening for an inhibitor to FIX, as an allergic reaction may be the first sign of inhibitor development. CB

Recommendation 8.4.2:

- For patients with hemophilia B and a family history of inhibitors or risk factors for inhibitor development, the WFH recommends monitoring initial infusions in a clinic or hospital setting capable of managing severe allergic reactions. CB

Recommendation 8.4.3:

- For patients with hemophilia B who develop anaphylaxis to FIX therapy, the WFH recommends screening for nephrotic syndrome, as it is more common in FIX inhibitor patients with allergic reactions to FIX. CB

Recommendation 8.4.4:

- For patients with hemophilia B and inhibitors and an allergic reaction/ anaphylaxis to FIX therapy, the WFH recommends rFVIIa to treat acute bleeds but is against use of aPCC as it contains FIX and may cause or worsen an allergic reaction.

  REMARK: For patients with hemophilia B and inhibitors and allergic reaction to FIX therapy, the WFH indicates there are insufficient data to recommend desensitization by

small, repeated doses of FIX, intravenously or subcutaneously, and recognizes that in some, this approach may worsen an allergic reaction or cause anaphylaxis. If undertaken, FIX desensitization should be performed with caution and under close supervision by experts only. CB

Recommendation 8.4.5:

- For patients with hemophilia B and inhibitors who develop anaphylaxis to FIX therapy, the WFH recommends bypass therapy with rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction. CB

Recommendation 8.4.6:

- For patients with hemophilia B and inhibitors who develop an acute bleed, the WFH recommends treatment based on whether the inhibitor is low-responding or high-responding and whether there is a history of allergic reactions. CB

Recommendation 8.4.7:

- For patients with hemophilia B and low-responding FIX inhibitors, the WFH recommends use of a FIX-containing product to treat acute bleeds, as long as there is no allergic reaction to FIX. CB

Recommendation 8.4.8:

- For patients with hemophilia B and high-responding FIX inhibitors, the WFH prefers rFVIIa over aPCC to treat acute bleeds, as aPCC contains FIX and may cause or worsen an allergic reaction. CB

Conventional hemostatic bypassing agents

- Alternative hemostatic agents for prevention of spontaneous or traumatic bleeds (prophylaxis) in hemophilia B inhibitor patients include rFVIIa, or, in the absence of an allergic/anaphylactic reaction to FIX, aPCC. 34,47,60,72,73
- Bypass agent prophylaxis in inhibitor patients is not as effective nor as convenient as standard factor prophylaxis is in patients without inhibitors. 72
- For hemostasis, bypass agent therapy with rFVIIa constitutes the standard approach. In general, aPCC may increase risk of anaphylaxis because of FIX content and should be avoided in those with hemophilia B inhibitors (see above). Both agents are effective in treating 90% of musculoskeletal bleeds and can be used in major and minor prophylaxis. 34,72 (See Table 8-5 .)
- As there are no reliable laboratory assays to monitor bypass agent therapy, careful monitoring of hemoglobin levels, blood loss, wound healing, and clinical response to treatment is advised, including patient-reported outcomes and subjective patient feedback.

Recommendation 8.4.9:

- For patients with hemophilia B and inhibitors who use bypass agent therapy, the WFH recommends clinical monitoring and consideration for laboratory monitoring with thrombin generation and other coagulation tests, although more data are needed to recommend the latter. CB

Recommendation 8.4.10:

- For patients with hemophilia B and inhibitors, the WFH is unable to make a recommendation on the use of immune tolerance induction, as experience with ITI in hemophilia B is limited.

  REMARK : In patients with hemophilia B and inhibitors in whom ITI is attempted, high-dose factor replacement protocols should be followed similar to what is recommended for hemophilia A, with strong consideration for the use of immunosuppression. It should be noted the risk of nephrotic syndrome may increase with high-dose ITI. CB

Recommendation 8.4.11:

- For patients with hemophilia B and low-responding FIX inhibitors who undergo surgery, the WFH has no preference for type of FIX products, but recommends more frequent dosing due to the short FIX half-life. CB

Recommendation 8.4.12:

- For patients with hemophilia B and FIX inhibitors who undergo surgery, the WFH recommends rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction. CB

Recommendation 8.4.13:

- For patients with hemophilia B and inhibitors and an allergic reaction to FIX who undergo surgery, the WFH prefers rFVIIa over aPCC as aPCC contains FIX and may cause or worsen an allergic reaction. CB

Recommendation 8.4.14:

For patients with hemophilia B and inhibitors who undergo surgery or an invasive procedure, the WFH recommends close clinical monitoring for thrombosis or consumptive coagulopathy. CB

Rayment R et al., 2020 [3].

British Society for Haematology (BSH)

Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B.

Zielsetzung/Fragestellung

Guidelines for prophylactic treatment of children and adults with severe haemophilia A (SHA) were produced by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) in 2010, summarising the high-level, evidence-based studies of prophylaxis in boys and advising on the role of prophylaxis in adults with SHA.1 This guideline builds on the former, accepting the clear evidence of benefit of prophylaxis in children with SHA. It addresses the optimum use of prophylaxis in children and adults with haemophilia A and B and gives evidence-based recommendations where appropriate.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zur Behandlung im vorliegenden AWG, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Keine Angaben über das Gremium über die Angabe der Autorenschaft hinaus.
- Interessenkonflikte und finanzielle Unabhängigkeit wurden erfasst, die Informationen sind auf Nachfrage verfügbar. Es liegt keine Angaben vor, wie mit Interessenkonflikten umgegangen wurden.
- Systematische Suche und Bewertung der Evidenz.
- Form der Konsensusprozesse nicht dargelegt.
- Externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist im Hintergrundtext dargestellt.

- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- The following databases were searched on 10.9.18 from 2009 onwards: MEDLINE (OvidSP, 1946 to present), Embase (OvidSP, 1974 to present), The Cochrane Library (CDSR Reviews & Protocols, CENTRAL, 2018, Issue 9 & 8 respectively), PubMed (epublications ahead of print only), Transfusion Evidence Library

LoE und GoR

- Entsprechend GRADE

Empfehlungen

Primary prophylaxis

The bleeding phenotype and clinical outcomes can mostly be predicted from the level of factor VIII (FVII) or factor IX (FIX). Without prophylaxis, nearly all men with SHA (<1 iu/ dl) and most of those with moderate haemophilia A (MHA) who have levels between 1 and 3 iu/dl will have at least one target joint and some degree of disability due to joint bleeds.8,9 For those with MHA, a measured FVIII of 1–2 iu/ dl has been associated with the highest risk of bleeding: median (interquartile range [IQR]) 2.9 (1.4–7.2) joint bleeds per year, despite prophylaxis in 40% compared to 1.4 (0. 5–3.4) for those with a level of 3–5 iu/dl.10 In the UK, adults with MHA (with a level <3 iu/dl) have very similar Haemophilia Joint Health Score (HJHS) to those with SH of the same age.11 However, children with MHA have a worse HJHS than those with SHA, irrespective of whether they are taking prophylaxis, suggesting a discrepancy in the approach to the care of these two groups.11 As detailed previously, there is clear evidence for the use of primary, secondary and tertiary prophylaxis in SHA but little for MHA, although one randomised controlled trial (RCT) did include boys with both SHA and a level of 0– 2 iu/dl.3 However, current evidence suggests that those with a level <4 iu/dl develop significant joint damage and should be considered for primary prophylaxis. Clinically, SHA and severe haemophilia B (SHB) are considered indistinguishable although some studies suggest that SHB might be associated with less severe outcomes.12 Nonetheless, there are insufficient data to be able to treat this cohort differently to those with SHA and a similar approach to initiation and monitoring of prophylaxis is recommended.

- All children with SHA or SHB should receive primary prophylaxis. Grade 1A
- Primary prophylaxis should be considered for all children with baseline factor levels of 1–3 iu/dl. Grade 2CProphylaxis should be offered to any PWH who has sustained one or more spontaneous joint bleeds. Grade 2C
- Prophylaxis should be offered to a PWH who has established joint damage due to haemarthroses who experiences ongoing bleeding. Grade 1B
- Prophylaxis should be offered to a PWH who has established joint damage due to haemarthroses who experiences ongoing bleeding. Grade 1B

Choice of product

- The choice of factor replacement product must involve shared decision-making with the person with haemophilia and/or their parent/legal guardian. Grade 1C
- Switching between factor replacement products may be performed in patients with more than 150 exposure days and no prior inhibitor. Grade 1C
- Recombinant FVIII and FIX EHL products should be used according to published UKHCDO guidance and used only when they provide clear clinical benefit over standard half-life products. Grade 1C

Emicizumab

- Emicizumab may be offered to a PWSHA aged >2 years without an inhibitor as an alternative to prophylaxis with FVIII
- Due to the limited data available for children aged <2 years, both for SHA with and without inhibitors, caution is advised when considering emicizumab in this age-group

- Counselling should be provided before changing treatment and consideration given to individual lifestyle, particularly with regard to high impact activity.
- In PWSHA and a past history of an inhibitor consideration should be given to continuing intermittent exposure to FVIII to maintain tolerance.
- National Guidance should be followed in the prescribing and monitoring of PWSHA using emicizumab prophylaxis and all adverse events should be reported to a national registry.

How to start prophylaxis in children

There are different approaches to commencing prophylaxis in young children. It may be started at the standard full dose, that is, 20–40 u/kg on alternate days and tailored to prevent bleeding. Alternatively, it may be introduced at a reduced frequency, building up to the full dose as soon as possible or based on bleeding phenotype. The latter approach may avoid the need for a CVAD, but there is likely to be suboptimal protection against bleeding, which could have consequences in terms of long-term joint health.45 Indeed, allowing joint bleeds to occur whilst using an incremental approach to primary prophylaxis, permitting up to two bleeds per joint in a 3-month period before intensification, has been shown to result in osteochondral changes on MRI at a median age of 88 years, demonstrating inadequate protection against joint damage.6 The multidisciplinary team (MDT) should support the introduction of prophylaxis in a CWH. Play therapy can be used to prepare, teach and distract the child, reducing difficulties around venous access.46 Psychologists should support the families to address emotional and behavioural issues and anxieties, which might affect both delivery of prophylaxis and the family's quality of life.47 Whether prophylaxis is administered through peripheral or central veins is dependent on the ease of venous access, the child and family. However, before inserting a CVAD, the risk of infection and thrombosis should be weighed against the relative ease of venous access.48 Younger age and use of external CVAD are associated with higher rates of infections.49

<u>Recommendations</u>

- Prophylaxis that is commenced at a reduced frequency should be escalated to full prophylaxis as soon as possible and immediately in the presence of any breakthrough haemarthrosis. Grade 1C
- When introducing a child to prophylaxis the psychosocial needs and social circumstances of the child and his family/carers should be addressed and supported by the haemophilia MDT. Grade 2C
- The route of administration should be agreed with the parent/guardian, according to ease of venous access, the child's compliance, technical abilities and social circumstances. Grade 2C

Choosing the most appropriate regimen for prophylaxis – pharmacokinetics

The prophylaxis regimen should not be based on target peak and trough levels but should be tailored to prevent bleeding for an individual within his usual daily activity schedule. A trough of >1 iu/dl or even >3 iu/dl may be required in many cases to achieve this. Grade 2C

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 01 of 12, January 2024) am 22.01.2024

#	Suchfrage
1	MeSH descriptor: [Hemophilia B] explode all trees
2	h*mophili*:ti,ab,kw
3	((factor NEXT (IX OR 9)) OR F9 OR (F-IX)):ti,ab,kw AND (deficien*):ti,ab,kw
4	(christmas NEXT disease*):ti,ab,kw
5	(plasma NEXT thromboplastin NEXT component NEXT deficien*):ti,ab,kw
6	#1 OR #2 OR #3 OR #4 OR #5
7	#6 with Cochrane Library publication date from Jan 2019 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 22.01.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	Hemophilia B[mh]
2	hemophili*[tiab] OR haemophili*[tiab]
3	(factor IX[tiab] OR factor 9[tiab] OR F9[tiab] OR F-IX[tiab]) AND deficien*[tiab]
4	christmas disease*[tiab]
5	plasma thromboplastin component deficien*[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND

#	Suchfrage
	(literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
8	(#7) AND ("2019/01/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]
10	(#9) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 22.01.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	Hemophilia B[mh]
2	hemophili*[tiab] OR haemophili*[tiab]
3	(factor IX[tiab] OR factor 9[tiab] OR F9[tiab] OR F-IX[tiab]) AND deficien*[tiab]
4	christmas disease*[tiab]
5	plasma thromboplastin component deficien*[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2019/01/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 23.01.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-008

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Bundesärztekammer, Dezernat 6 – Wissenschaft, Forschung und Ethik, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Namen aller beteiligten Sachverständigen	Prof. Dr. med. Bernd Pötzsch
Datum der Erstellung	26. Februar 2024

Indikation
„… wird angewendet als Prophylaxe von Blutungsereignissen bei Patienten ab 12 Jahren mit Hämophilie B mit Faktor-IX-Inhibitoren (HBwI).“
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Die Hämophilie B gehört zu den seltenen angeborenen hämorrhagische Diathesen und ist durch eine Synthesestörung des Gerinnungsfaktors IX (FIX) charakterisiert. Durch die verminderte FIX-Aktivität ist nach einer Verletzung die Thrombinbildung und die nachfolgende Gerinnselbildung eingeschränkt. Dabei ist das Blutungsrisiko abhängig von der FIX-Restaktivität. Eine schwere Verlaufsform mit einem hohen Blutungsrisiko besteht bei einer FIX-Restaktivität von < 1 %. Ein mittelschwerer Verlauf besteht bei einer Restaktivität zwischen 1 und 5 %. Behandlungsziele sind die Blutungsprophylaxe und die Therapie von Blutungen. Dies wird durch die Gabe von FIX-Konzentraten erreicht. Eine mögliche Nebenwirkung der FIX-Therapie besteht in der Induktion einer adaptiven Immunantwort gegen den substituierten FIX. Die gebildeten FIX-Antikörper können die Aktivität des FIX inhibieren und/oder dessen Elimination signifikant erhöhen. In Abhängigkeit von der Konzentration des FIX-Antikörpers führt dies zu einer Unwirksamkeit der FIX-Substitution. Therapieziele sind die Behandlung und Prophylaxe von Blutungen sowie eine stabile Eradikation der FIX-Antikörperproduktion. Zur Behandlung von Blutungen stehen die Bypasspräparate rekombinanter aktivierter Faktor VII (rFVIIa) und das aktivierte Prothrombinkomplexpräparat FEIBA zur Verfügung. Zur Inhibitoreradikation werden verschiedene immunmodulatorische Therapien eingesetzt.
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*

Für die Wahl der Behandlungsoption der Hämophilie B mit Faktor-IX-Inhibitoren ist die in Bethesda-Einheiten gemessene Inhibitorstärke ein wesentliches Entscheidungskriterium. Dieses Vorgehen ist angelehnt an die Erfahrungen in der Behandlung von Hämophilie-A-Patienten mit Inhibitoren.

Liegt die Inhibitoraktivität unter fünf Bethesda-Einheiten, kann meist durch die Gabe eines FIX-Konzentrats in erhöhter Konzentration eine ausreichende Hämostaseantwort aufgebaut werden. Gleichzeitig kann wieder in Analogie zur Behandlung der Hämophilie-A-Patienten eine Immuntoleranztherapie aufgenommen werden. Das Ziel der Immuntoleranztherapie ist die langfristige Eradikation des FIX-Antikörpers.

Übersteigt die Inhibitorkonzentration eine Aktivität von fünf Bethesda-Einheiten, kann durch eine Gabe von FIX-Konzentrat keine ausreichende Gerinnungsaktivität erzielt werden. In diesen Fällen ist die Gabe von Bypasspräparaten, zu denen der rekombinante aktivierte Faktor VII (rFVIIa) und das aktivierte Prothrombinkomplexpräparat (FEIBA) gehört, indiziert. Parallel zur Therapie mit den Bypasspräparaten erfolgt eine immunsuppresive Therapie, beispielsweise mit dem Anti-CD20-Antikörper Rituximab. Die Gabe von rFVIIa oder FEIBA ist auch indiziert, wenn bei Patienten mit einem FIX-Inhibitoraktivität von unter fünf Bethesda-Einheiten die FIX-Substitution nicht zu einer effektiven Blutstillung führt. Relevante Endpunkte zur Beurteilung einer Therapie von Hämophilie-B-Patienten mit einem Hemmkörper sind die Häufigkeit und der Schweregrad von Blutungskomplikationen, die kumulative Konzentration der zur Behandlung erforderlichen Menge an FIX-Konzentrat und der Bypasspräparate FVIIa und FEIBA sowie die Inhibitorkonzentrationen im Therapieverlauf.

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-008

Verfasser	
Institution	DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie GTH Gesellschaft für Thrombose- und Hämostaseforschung
Sachverständige	PD Dr. Robert Klamroth, Berlin (GTH) Prof. Dr. Johannes Oldenburg, Bonn (GTH) Prof. Dr. Bernhard Wörmann, Berlin (DGHO)
Datum	19. März 2024

Indikation
„… wird angewendet als Prophylaxe von Blutungsereignissen bei Patienten ab 12 Jahren mit Hämophilie B mit Faktor-IX-Inhibitoren (HBwI).“
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Die Blutungsprophylaxe bei Patienten mit Hämophilie B hat sich in den letzten 10 Jahren grundlegend verändert und entwickelt sich ständig weiter. Die Prophylaxe bei Hämophilie B-Patienten mit Faktor-IX-Inhibitoren ist nicht etabliert, da etwa die Hälfte der Patienten eine allergische Reaktion bis zur Anaphylaxie gegen Faktor IX entwickelt und daher nicht mit Faktor IX-Konzentraten behandelt werden kann. Bei Hämophilie B Patienten mit Faktor IX-Inhibitoren ohne anaphylaktische Reaktion richtet sich die Prophylaxe nach der Höhe der Antikörper-Titer.

Versucht werden können diese Strategien:

Niedriger Inhibitor-Titer (<5 Bethesda-Einheiten, BE)

- Regelmäßige Prophylaxe mit erhöhter Dosierung
    - halbwertzeitverlängerten Faktor IX-Präparate (aktueller Versorgungsstandard)
    - Standard-Halbwertzeit-Faktor IX-Präparate

Hoher Inhibitor-Titer (≥5 BE)

- Immuntoleranztherapie mit begleitender Immunsuppression
- Aktivierter Prothrombinkomplex oder rekombinanter Faktor VIIa, als Prophylaxe vor geplanten chirurgischen/invasiven Eingriffen oder interventionell beim Auftreten von Blutungen

Die Gentherapie ist keine Option bei Patienten mit Faktor-IX-Inhibitoren und ist für Hämophilie B-Patienten mit Faktor IX-Inhibitoren nicht zugelassen.

Stand des Wissens

Hämophilie B ist eine seltene, X-chromosomal rezessiv vererbte Erkrankung des Gerinnungssystems mit verminderter oder fehlender Synthese von Faktor IX. Klinisch werden die Schweregrade leicht, mittelschwer und schwer unterschieden. Sie korrelieren mit dem Ausmaß des Faktor-IX-Mangels [1-3]. Die Betreuung von Patienten mit Hämophilie B hat in den letzten Jahrzehnten erhebliche Fortschritte gemacht. Die Lebenserwartung von Patienten mit Hämophilie B, die nicht mit HIV infiziert sind, ist heute mit der Lebenserwartung der männlichen Bevölkerung vergleichbar [4].

Ein Problem bei regelmäßig substitutionspflichtigen Patienten mit Hämophilie B ist die Entwicklung von Antikörpern ("Hemmkörper") gegen FIX. Die kumulative Inzidenz liegt mit 3-10% deutlich niedriger als bei der Hämophilie A [5]. Gründe sind das gegenüber der Hämophilie A unterschiedliche Mutationsspektrum. Bei der Hämophilie B ist in 70% aller Patienten eine Missense-Mutation für die Erkrankung ursächlich, die mit der Bildung eines endogenen, wenn auch weitgehend funktionslosem FIX-Protein einhergehen. Innerhalb der schwerwiegenden Mutation ohne endogene FIX-Proteinbildung, wie große Deletionen und Stopmutationen, ist das Hemmkörperrisiko mit der Hämophilie A vergleichbar.

Relevant für die Prophylaxe-Strategie ist das Ausmaß der Inhibitorbildung, gemessen in Bethesda-Einheiten. Bei Patienten mit niedrigem Inhibitortiter (< 5 BE) werden traditionell höhere Dosen von Ersatzfaktoren verwendet. Bei Patienten mit hohem Inhibitortiter (≥5 BE) sind Ersatzfaktoren physiologisch unwirksam. Die einzige Möglichkeit, persistierende Inhibitoren zu beseitigen und eine Toleranz gegenüber den Ersatzfaktoren zu induzieren, ist die Immuntoleranzinduktion (ITI). Der Erfolg ist jedoch unbeständig, und Patienten mit Hämophilie B müssen die Behandlung häufig aufgrund schwerer allergischer Reaktionen auf FIX oder der Entwicklung eines nephrotischen Syndroms abbrechen. Darüber hinaus können die Inhibitoren auch nach erfolgreicher ITI rezidivieren [6].

Standard für Prophylaxe und Therapie von Patienten mit hohem Inhibitortiter sind sog. Bypass-Medikamente wie rekombinanter Faktor VIIa (rFVIIa) oder aktiviertes Prothrombinkomplexkonzentrat [7-9]. Der erste zugelassene, rekombinante FVIIa ist Eptacog alfa. In der EU ist Eptacog beta zugelassen zur Prophylaxe von Blutungen bei Erwachsenen und Jugendlichen (≥12 Jahre) mit angeborener Hämophilie A oder B mit hohem Inhibitortiter (≥5 BE), die sich einem chirurgischen oder invasiven Eingriff unterziehen, und bei denen ein hohes anamnestisches Ansprechen auf FVIII oder FIX zu erwarten ist oder die refraktär gegenüber einer höheren Dosierung von FVIII oder FIX sind.

Ein neuer Ansatz ist die langfristige Steigerung der endogenen FIX-Produktion durch gentherapeutische Ansätze. Zugelassen für die EU und in Deutschland eingeführt ist Etranacogen Dezaparvovec, ein vektorbasiertes Gentherapeutikum [10]. Es basiert auf einem rekombinanten AAV5-(Adeno-assoziiertes Virus Serotyp 5)-Vektor und enthält die FIX-Padua-Variante. Die Expression in diesem Vektorkonstrukt erfolgt unter Kontrolle eines leberspezifischen Promoters. Erwartet wird die EU Zulassung von Fidanacogen Elaparvovec [11].

Aktuell besteht ein ungedeckter, medizinischer Bedarf bei Patienten mit Hämophilie B und hohem Antikörpertiter. Eine effektive Prophylaxe von Blutungen ist im Alltag mit den zugelassenen Präparaten nicht möglich. Neue Konzepte mit Einsatz von monoklonalen Antikörpern gegen Tissue

Factor Pathway Inhibitor (TFPI) wie Concizumab [12] oder Marstacimab können diese Versorgungslücke füllen.
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
Ja, diese sind oben dargestellt.

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