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ILLUSTRATED REVIEW

Haemophilia B: an illustrative review of current challenges and opportunities

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Abstract

Background: Hemophilia B is a genetic bleeding disorder caused by a deficiency of clotting factor IX, which presents unique challenges in clinical management. Advances in therapeutic strategies for hemophilia B have significantly improved patient outcomes but have also necessitated ongoing education for healthcare professionals. This illustrated review provides an overview of the challenges and opportunities in hemophilia B care, including best practice management, emerging therapies, and remaining research needs.

Objectives: To provide a comprehensive visual summary of contemporary perspectives on hemophilia B pathophysiology and management through an illustrated review.

Methods: The authors, leveraging their clinical experience and expertise in hemophilia B management, conducted a review of relevant articles in PubMed (Supplementary Methods).

Results: The review is divided into illustrated sections that provide an overview of hemophilia B, detailing its clinical manifestations, hemostatic agents, and treatment challenges. It also examines the pharmacokinetic properties of hemophilia B and the importance of individualized treatment approaches.

Conclusion: This illustrated review educates healthcare professionals on hemophilia B management in the current treatment landscape, empowering them to further disseminate knowledge to both their colleagues and patients.

KEYWORDS
antibodies, inhibitory, blood coagulation disorders, inherited, factor IX, hemophilia B, hemophilia treatment, hemostatic agents, illustrated review, prophylaxis

Essentials

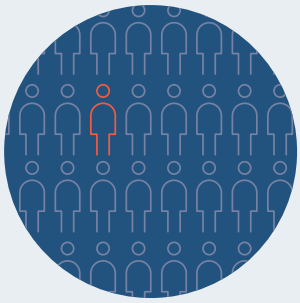
- Hemophilia B is a genetic bleeding disorder that presents unique challenges in clinical management.
- This review provides a visual summary of contemporary perspectives on hemophilia B care.
- Nonfactor therapy and gene therapy are novel therapies that will aid treatment individualization.
- Healthcare professionals and patients require ongoing education on the evolving treatment landscape.

CAPSULE 1A

INTRODUCTION TO HAEMOPHILIA B

HB is an X-linked bleeding disorder caused by an absence or defect of FIX[1]

INCIDENCE OF CONGENITAL HB

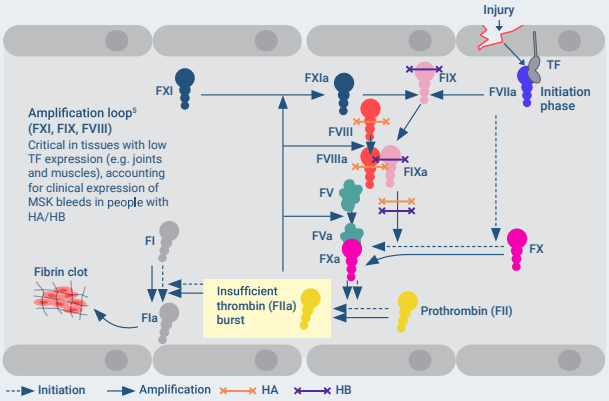


~1 in 30,000

male live births[2]

BLOOD COAGULATION CASCADE[3,4]

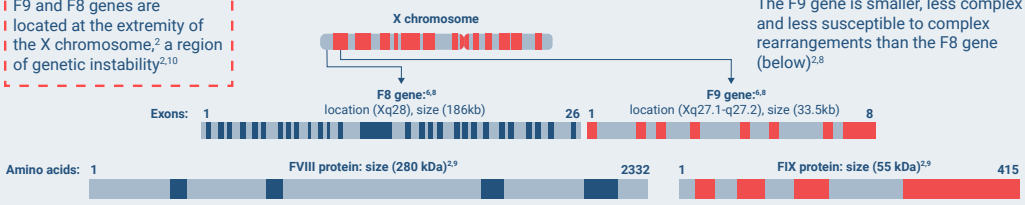
In people with HB, FIX deficiency results in defective thrombin generation on the activated platelet surface during the amplification phase of coagulation[3,4]



GENETICS

F9 and F8 genes are located at the extremity of the X chromosome,[2] a region of genetic instability[2,10]

F9 and F8 gene[6,7]



The F9 gene is smaller, less complex and less susceptible to complex rearrangements than the F8 gene (below)[2,8]

FEATURES OF THE FIX PROTEIN AND HAEMOPHILIA B

- FIX is produced in hepatocytes and FVIII in sinusoidal endothelial cells[8,11,12]
- Missense or nonsense variants in HB are more common than inversion events[2,6,8]
- FIX protein has a longer physiological half-life than FVIII[13]
- FIX protein is smaller than FVIII, resulting in extravascular distribution and haemostatic function[13,14]
- ~24–32% of people with HB have severe disease vs ~30–40% with HA, due to differences in gene structure and the founder effect[2,3]
- **FIX protein: vitamin K-dependent and undergoes -carboxylation for binding to lipid membranes to express procoagulant activity[7]**
- The immunogenic properties of FIX seem to differ from FVIII, with a lower incidence of inhibitor development[1,15,16]
- Gene therapy facilitated by hepatocyte production and small F9 gene size[12,17,18]
- FIX Leyden phenotype: FIX levels and reduced disease severity during puberty and pregnancy owing to a unique FIX variant that is susceptible to androgens[6,8,9]
- Smaller gene and protein for FIX versus FVIII[2,8]
- FIX is a factor (enzyme), not a co-factor like FVIII[2,9]
- Half-life prolongation easier to achieve with FIX than FVIII[13]
- FIX does not bind to chaperone protein as with vWF for FVIII[2,9]

FI, fibrinogen; **FIa**, activated fibrinogen; **FIX**, factor IX; **FIXa**, activated factor IX; **FV**, factor V; **FVa**, activated factor V; **FVIIa**, activated factor VII; **FVIII**, factor VIII; **FVIIIa**, activated factor VIII; **FX**, factor X; **FXa**, activated factor X; **FXI**, factor XI; **FXIa**, activated factor XI; **HA**, haemophilia A; **HB**, haemophilia B; **MSK**, musculoskeletal; **TF**, tissue factor; **vWF**, von Willebrand factor.

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CAPSULE 1B

INTRODUCTION TO HAEMOPHILIA B

INHERITANCE

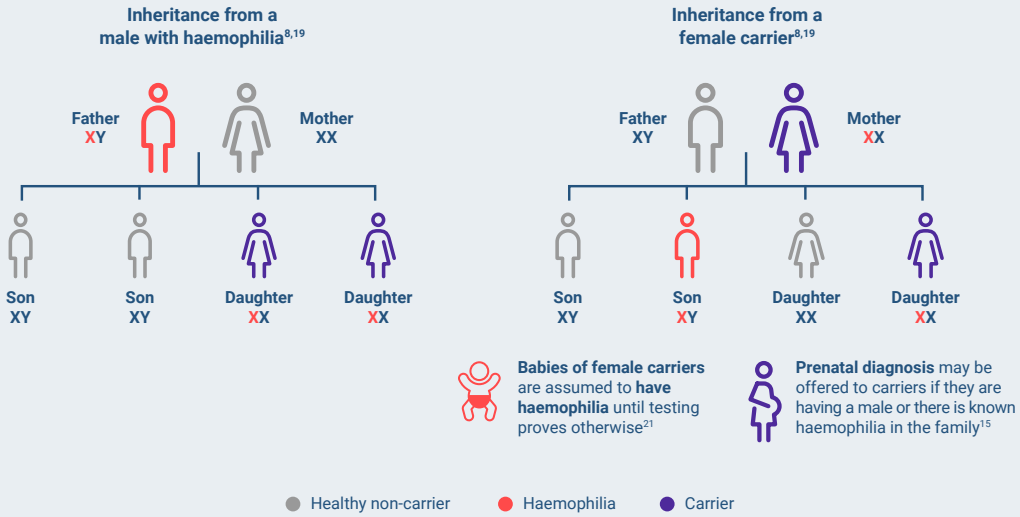
Congenital HB is X-linked,

predominantly affecting males, while females typically act as obligate carriers[8,19]

HB is also known as the 'royal disease'

owing to sequencing of samples from the Romanov family, within which Alexei Romanov had severe HB and his mother was a carrier[20]

Genetic inheritance of haemophilia



Babies of female carriers are assumed to **have haemophilia** until testing proves otherwise[21]

Prenatal diagnosis may be offered to carriers if they are having a male or there is known haemophilia in the family[15]

Healthy non-carrier · Haemophilia · Carrier

DIAGNOSIS

HB can be diagnosed before or after birth:[6,15,21,22]

Before birth: chorionic villus biopsy, amniocentesis or preimplantation genetic diagnosis

After birth: using an umbilical cord blood sample

FIX activity is low in newborns both with or without haemophilia:[15]

Thus, HB may require additional screening to be confirmed

Diagnosis is also made after symptom onset:[15]

Patients with severe HB often present at a young age with excessive bleeding following trauma/surgery, easy bruising, or spontaneous bleeds

HB can be identified through:[6]

- **Clinical diagnosis**
  Anamnesis, bleeding symptoms, physical examination, family history
- **Laboratory diagnosis**
  Normal TT and PT, abnormal aPTT, FIX:C, FIX:ag
- **Genetic diagnosis**
  Next Generation / Sanger Sequencing

aPTT, activated partial thromboplastin time; **FIX**, factor IX; **FIX:Ag**, factor IX antigen; **FIX:C**, factor IX coagulant activity; **HB**, haemophilia B; **PT**, prothrombin time; **TT**, thrombin time.

CAPSULE 2

CLINICAL MANIFESTATIONS

People with HB experience bleeding episodes that are not able to clot properly due to a deficiency in FIX[15]

BLEEDING PHENOTYPE IS DEPENDENT ON THE LEVEL OF FIX ACTIVITY[7,8,15,23]

Plasma concentrations of FIX[15]		Anticipated* bleeding phenotype (ABR)[7,22]
>150%		0
>40–<150%		0
	Haemophilia B: FIX ≤40%[15]	
>5–<40%	**Mild haemophilia**[7,8,15] symptoms include bruising, severe bleeding with major surgery/trauma, rare spontaneous bleeds	0–1
1–<5%	**Moderate haemophilia**[7,8,15] occasional spontaneous bleeds, prolonged bleeding with minor surgery/trauma, joint bleeds	1–5
<1%	**Severe haemophilia**[7,8,15] spontaneous joint, muscle and mucous membrane bleeds (mostly in the absence of an identifiable cause)	>5

Less clotting factor ↓ More clinical bleeds ↑

*Plasma concentrations of FIX and ABR outcomes may vary; some people with mild or moderate HB may have a severe bleeding phenotype[7,15,23]

BLEEDING EVENTS

Age at first bleed for HB

~10.6

months of age[24]

Joint bleeds

are one of the most common types of bleeds, which can lead to joint damage, haemophilic arthropathy, pain, reduced range of motion and need for surgery[3,15]

Muscle, soft tissue and life-threatening bleeds

(e.g. CNS bleeds, intracranial haemorrhages) can also occur[15]

The clinical presentation of HB and HA is generally similar,[1]

including ABR and number of patients undergoing joint arthroplasty[2,15,24]

Some evidence suggests that the clinical phenotype of HB is less severe than HA; however, data are inconclusive[21]

QUALITY OF LIFE IMPACT[2,22-24]

HB is a **lifelong** bleeding disorder that can **impair QoL**, especially in those with severe disease[2,15,25]

Areas of QoL that are impacted by HB[2,15,25–28]

- Joint and muscle bleeds
- Life-threatening bleeds
- Chronic arthropathy and disability
- Functional impairment
- Need for orthopaedic surgery
- School attendance
- Work productivity
- Career choices
- Financial burden
- Pain
- Limitations in physical activities / sports
- Psychosocial, family and mental health impacts

ABR, annualised bleed rate; **CNS**, central nervous system; **FIX**, factor IX; **HA**, haemophilia A; **HB**, haemophilia B; **QoL**, quality of life.

Requires further research

CAPSULE 3A

HAEMOSTATIC AGENTS

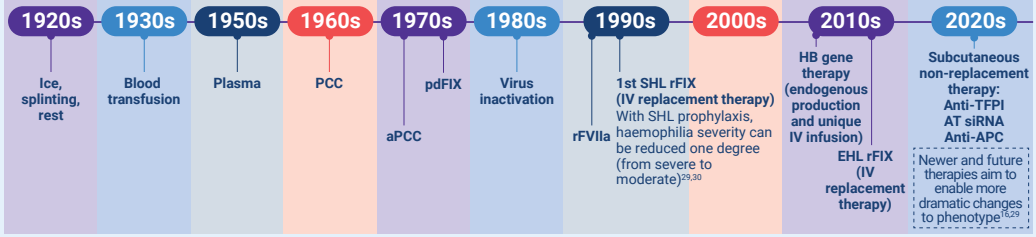
The aims of haemophilia care have evolved with increasing availability and innovation of treatments to reduce the severity of disease to target normal haemostasis[15,18,29]

FACTOR CONCENTRATES, BYPASSING AGENTS AND OTHER PHARMACEUTICAL OPTIONS FOR HB[4,15,18]

Patient survival
Bleed reduction

Goals of treatment:[2,3,16,28]

Patient-centric outcomes (HRQoL, daily activities, burden)



CFC prophylaxis

to replace deficient FIX has been the mainstay to treat and prevent bleeds in people with HB[15]

SHL rFIX
infusion of FIX for on-demand treatment of bleeds or as prophylaxis to prevent bleeds and maintain joint/MSK health[15]

EHL rFIX
Developed with long half-lives to target less frequent injections, reduced treatment burden, higher trough levels, fewer bleeds and better adherence vs SHLs[15,31]

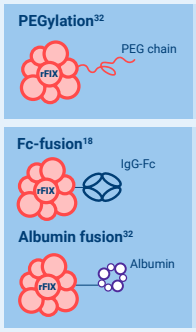
Bypassing agents

(including rFVIIa and aPCC): approved for HBwI[15]

Other pharmaceutical options:

tranexamic acid and epsilon aminocaproic acid[15]

EHL rFIX technology[15,18,32]



GlycoPEGylation
Half-life extension achieved by increasing molecule density, which is conferred by the 40 kDa polythene glycol moiety attached within the activation peptide of FIX[32]

Fc or albumin fusion
Half-life extension involves the natural recycling of the Fc or albumin moiety, which is bound to rFIX through the neonatal Fc receptor[32]

TREATMENT INITIATION IN PUPS WITH HB COMPARED WITH HA

Overview of treatment in people with severe HB[24]

Age at first treatment	Age at first bleed	Age at start of prophylaxis	Number (%) on prophylactic treatment	Number of EDs at start of prophylaxis
HB: 0.88 years (range 0.60–1.18)	**HB:** 0.88 years (range 0.60-1.19)	**HB:** 1.39 years (range 0.96–2.57)	**HB:** 86% (n=67/78)	**HB:** 9 (range 5–16)
HA: 0.81 years (range 0.43–1.11) p=0.20	**HA:** 0.82 years (range 0.50-1.12) p=0.36	**HA:** 1.39 years (range 0.99–2.08) p=0.85	**HA:** 74% (n=442/601)	**HA:** 12 (range 4–21) p=0.44

This observational cohort study consisted of PUPs with severe or moderate HA/HB (born in 2010–2000; n=658) in the PedNet Haemophilia Registry database and the RODIN Study database from 29 haemophilia centres across Europe, Israel and Canada[24]

APC, activated protein C; **aPCC**, activated prothrombin complex concentrate; **AT**, anti-thrombin; **CFC**, clotting factor concentrate; **ED**, exposure days; **EHL**, extended half-life; **Fc**, fragment C; **FIX**, factor IX; **HA,** haemophilia A; **HB**, haemophilia; **HBwI,** haemophilia B with inhibitors; **HRQoL**, health-related quality of life; **IgG**, immunoglobulin G; **IV**, intravenous; **MSK**, musculoskeletal; **PCC**, prothrombin complex concentrate; **pd-FIX**, plasma-derived factor IX; **PedNet**, Paediatric Network on haemophilia management; **PUP**, previously untreated patient; **rFIX**, recombinant factor IX; **rFVIIa**, recombinant activated factor VII; **RODIN,** Research Of Determinants of INhibitor development; **SHL**, standard half-life; **siRNA**, small interfering ribonucleic acid; **TFPI**, tissue factor pathway inhibitor.

CAPSULE 3B

HAEMOSTATIC AGENTS

NOVEL THERAPEUTIC AGENTS IN HB CARE

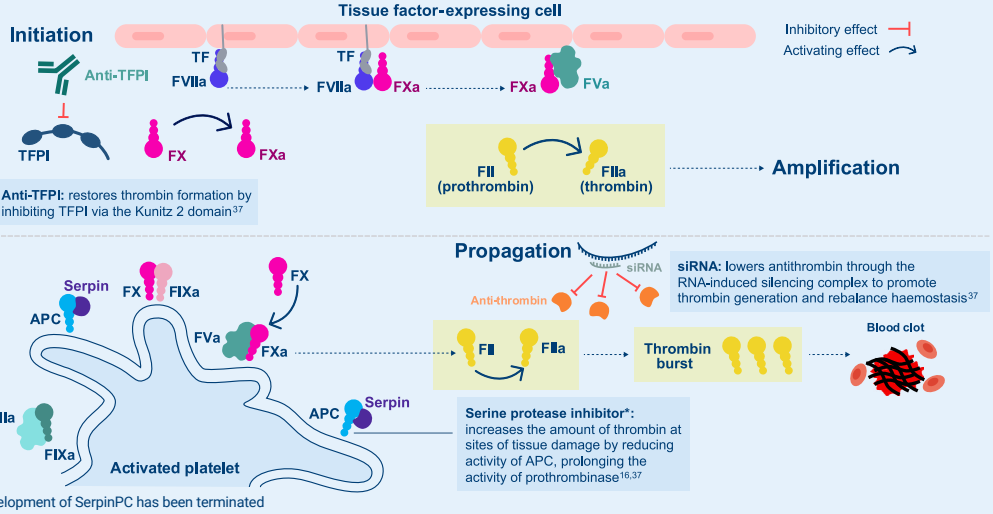
Non-factor therapies

Are designed to increase/restore thrombin generation and rebalance coagulation and reduce treatment burden in people with/without inhibitors[15,33]

In contrast to HA, there are currently no available bispecific antibodies designed to mimic the function of FIX.[15,33] However, FVIII-mimetics have been shown to rescue FIX activity in HB caused by FIX variants that impair assembly of the intrinsic Xase complex[34,35]

May promote HRQoL[15] through subcutaneous administration (some via pen injectors) to improve convenience, and less frequent dosing regimens[33]

MoA of HB treatment classes[16,36,37]

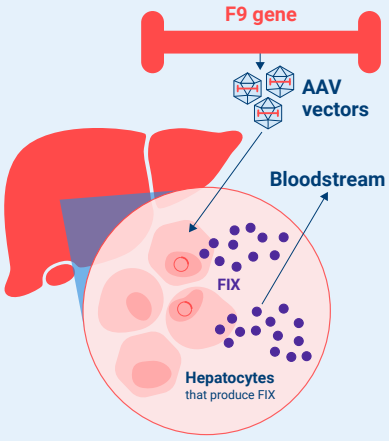


*The development of SerpinPC has been terminated

TREATMENT LANDSCAPE: GENE THERAPY

HB is an ideal target for gene therapy because only a single gene is impacted that is small in size. Gene therapy has the potential to provide long-lasting treatment by delivering a functional copy of the faulty F9 gene to hepatocytes cells where FIX is produced, rather than integrating into the genome, enabling endogenous production of FIX[12,17,18]

Gene therapy vector plasmid and F9 gene[18]



AAV gene therapy was initially associated with packaging constraints; therefore, HB was considered for AAV gene therapy due to smaller gene size[17]

The FIX-Padua variant is utilised in gene therapy for HB as it confers higher activity than that of wild-type FIX, without increasing the risk of thrombosis[12,17]

AAV gene therapy for HB can achieve durable expression of the FIX transgene, with sustained clinical benefit reported over periods of >10 years so far[38]

Current challenges with gene therapy include:

- Use in inhibitor and paediatric populations*[17]
- Some patients with neutralising antibodies to the AAV serotype*[17,39]
- Close monitoring of liver enzymes is required[17]
- Limited long-term safety and efficacy data for AAV gene therapy[12]
- High cost[17]

*Some challenges with gene therapy may be overcome with CRISPR/Cas9 technology that enables genome editing

AAV, adeno-associated viral vector; **APC**, activated protein C; **CRISPR**, clustered regularly interspaced short palindromic repeat; **FIX**, factor IX; **FIXa**, activated factor IX; **FVa**, activated factor V; **FVIIa**, activated factor VII; **FX**, factor X; **FXa**, activated factor X; **HA**, haemophilia A; **HB**, haemophilia B; **HRQoL**, health-related quality of life; **MoA**, mechanism of action; **siRNA**, small interfering ribonucleic acid; **TF**, tissue factor; **TFPI**, tissue factor pathway inhibitor.

CAPSULE 4A

TREATMENT CHALLENGES

CHALLENGES AND BURDEN OF HB CARE:

Fewer treatments available for HB vs HA, potentially due to the smaller patient population, including few prophylaxis options for HBwI[15,40,41]

Treatment initiation in PUPs with HB is more difficult than HA owing to risk of allergic reactions; it is recommended to start HB treatment in the hospital in case of allergic reactions and other complications[15]

Owing to the high cost of care,[31] **patients in many countries do not have access to regular prophylaxis**[42]

Body weight-based dosing can be complex owing to factors such as body weight changes and miscalculations[13,43,44]

High treatment burden can impact adherence and lifestyle owing to:[15,31,45–48]

- Frequent IV infusions; complex dosing regimens
- Preparation and infusion time: impacts people with haemophilia and their caregivers
- Pain, scarring, infection and venous access difficulties
- Limited storage / portability

CHALLENGES: INHIBITOR DEVELOPMENT (HwI)

Antibodies (inhibitors) against FIX/FVIII are a **serious direct complication** from treatment[1,15] that can neutralise the effect of CFCs for bleed prevention[15]

FIX intolerance is often revealed upon initial exposure to FIX concentrates, e.g. in PUPs[15]

Patients with inhibitors have a poorer prognosis and QoL than those without, including greater rate of bleeding, morbidity and mortality[15,25]

Inhibitor management includes CFC replacement therapy or BPAs to control bleeds, and ITI to eradicate inhibitors[15]

Historically, BPAs were considered standard of care for on-demand treatment of bleeds in HwI; some BPAs are now available as prophylaxis[9,33,35]

For low-responding inhibitors, FIX CFC can be used for acute bleed management. For ITI, frequent infusions of CFC are used to eradicate inhibitors by downregulating the antibody response to establish tolerance[15,40]

NFTs in development are designed to provide prophylaxis for effective bleed prevention in people with HBwI[15]

Characteristics	Haemophilia A	Haemophilia B
Inhibitor incidence[2,8,15,49]	~30%	1.5–10.2% • Occurs more frequently in severe HB,[8,15] whereas it can occur in all severities of HA[49] • Fewer inhibitors may occur in HB than HA because a higher proportion of people with HB are positive for presence of CRM than people with HA[2]
Inhibitor occurrence[15,47]	Within the first 50 EDs to CFCs	Within the first 20 EDs to CFC, typically before the age of 2 years old
Gene characteristics associated with inhibitors[2,15]	Gene has considerable gene deletions and/or intra-chromosomal aberrations	Null mutations
Success rate of clinical response to ITI[9,15]	70–80%	20–30%
Anaphylaxis occurrence[1,2,15,50]	Rare, not associated with inhibitor development	~50–69% Anaphylaxis may be more common in HB owing to size and distribution of FIX and the genetic characterisation of the FIX deficiency,[50] e.g. the FIX gene has fewer gene deletions and/or intra-chromosomal aberrations than FVIII gene[2]
Nephrotic syndrome occurrence in those undergoing ITI[1,15,40,49]	Not reported	30–35% Nephrotic syndrome complicates ITI protocols to eradicate the inhibitors

BPA, bypassing agent; **CFC**, clotting factor concentrate; **CRM**, cross-reactive material; **ED**, exposure day; **FIX**, factor IX; **FVIII**, factor VIII; **HA**, haemophilia A; **HB**, haemophilia B; **HBwI**, haemophilia B with inhibitors; **HwI**, haemophilia with inhibitors; **ITI**, immune tolerance induction; **IV**, intravenous; **NFT**, non-factor therapy; **PUP**, previously untreated patient; **QoL**, quality of life.

CAPSULE 4B

TREATMENT CHALLENGES

CHALLENGES: MILD/MODERATE HB

Patients with mild/moderate HB experience unmet needs, e.g.:[27,28,51]

- Challenging diagnoses
- Variability of bleeds
- Impaired HRQoL

People with moderate HB may report:[15,27,52]

- A severe bleeding phenotype
- Impaired joint health
- Bleeds that require hospitalisation

Patients with moderate HB may have **worse HRQoL** and experience **more pain** than those with severe HB because they are less likely to receive prophylaxis[27]

CHALLENGES: CROSS-REACTIVE MATERIAL

CRM+

Is the presence of detectable FIX antigen (residual protein present but functionally defective) that lacks biological activity, but has antigenic determinants in common with normal FIX[9,14]

More people with HB are CRM+ and have missense mutations than HA, which may explain why a severe disease phenotype is more common in HA than HB[14]

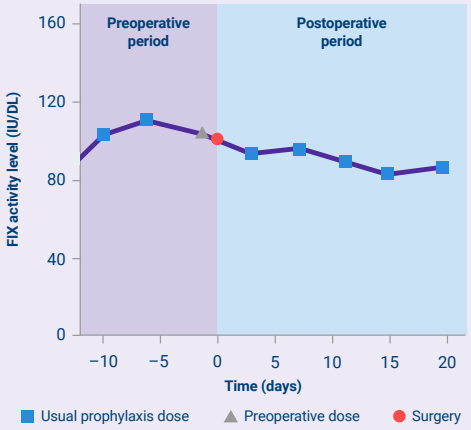
CRM+ may reduce the efficacy of prophylaxis by competing with therapeutic/exogenous FIX for binding sites on collagen type IV[9]

SURGERY

Challenges

- Patients with HB are at an increased risk of excessive bleeding during surgery and require monitoring of factor activity levels and administration of factor replacement[15,40,53]
- Surgery with EHL CFCs in HB differs to HA, i.e. FIX works as a continuous infusion with low doses owing to its distribution in the intra- and extravascular space[15,40,53]
- Limited recommendations exist for surgery in people with HBwI[15]
- Complex biodistribution of FIX complicates monitoring during surgery[15,40]
- Major surgery: additional haemostatic agents may be required, especially for patients receiving NFTs[15,33]

Minor surgery in HB may be managed with a single bolus preoperative dose[15,50]



Minor surgery in HB may be managed with a single preoperative dose to maintain sufficient factor activity throughout the procedure.[50]

In addition, a proportion of patients may not require post-operative infusions because patients can maintain adequate haemostasis or begin a normal prophylaxis regimen.[50]

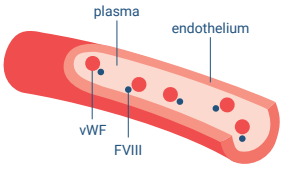
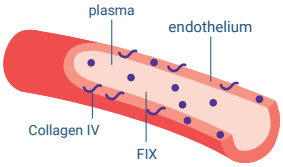
CFC, clotting factor concentrate; **CRM,** cross-reactive material; **EHL,** extended half-life; **FIX,** Factor IX; **HA,** haemophilia A; **HB,** haemophilia B; **HBwI,** haemophilia B with inhibitors; **HRQoL,** health-related quality of life; **ITI,** immune tolerance induction; **PUP,** previously untreated patient; **SHL,** standard half-life.

Requires further research

CAPSULE 5

PHARMACOKINETIC PROPERTIES AND MONITORING

INTRAVASCULAR AND EXTRAVASCULAR DISTRIBUTION OF FIX

Characteristics	HA	HB
Characterisation[13,14]	The PK of FVIII is well characterised	The PK of FIX is less well characterised than FVIII
Clinical phenotypes[14]	Correlates well to PK parameters of FVIII	Does not correlate as well to PK parameters of FIX
Location[13,14]	**FVIII:** Mainly intravascular 	**FIX:** Both intra- and extra-vascular  Upon infusion, FIX moves from the intravascular to extravascular space[9]
Binding[13]	Circulates in a stable complex with vWF owing to size	FIX is a smaller protein than FVIII and is not bound to vWF so can be distributed more widely.[2,9] FIX may bind to collagen IV in the extravascular space for haemostatic function[2,13]
Recovery and half-life[13]	The half-life of FVIII is 12–14 hours	FIX is reported to have a longer half-life of FIX is 18–20 hours, requiring less frequent administration than FVIII. FIX may travel from intravsacular to extravascular space, and back again, lengthening the half-life

PK-TAILORED PROPHYLAXIS IN HB

- Increasing factor levels to within the non-haemophilic range (**>40%**) may reduce bleed frequency[15]
- Intravascular FIX is measured from plasma samples and correlate with clinical outcomes (higher FIX levels confer better protection against bleeds), whereas extravascular FIX is not measurable, but may also have a role in haemostatic function because it extends the FIX MRT[2,13]
- Extravascular distribution of FIX may contribute to variations in PK profile, bleeding phenotypes and response to factor replacement[40]
- HB guidelines recommend targeting FIX trough levels of **>3–5%** or higher to help prevent subclinical and spontaneous bleeds and maintain joint health[15,54]
- EHL FIX molecules are designed to provide FIX trough levels in the range of **5–10%** to convert people with HB from a severe to mild phenotype[31]

Factor activity in a patient with severe HB following prophylaxis[13]*

EHL FIXs have a **longer** half-life: **~82–101 hours** and slower recovery

VS

EHL FVIIIs' half-life: **~14–19 hours**

Therefore, a lower dosing frequency of FIX EHLs is required, which confers reduced treatment burden[13,45]

*Red indicates the area under the curve.

CHALLENGES WITH PK-TAILORED PROPHYLAXIS[9,13]

MONITORING

Monitoring PK for dosing/therapy comparison is challenging for FIX replacement therapies owing to differences in extravascular distribution between patients, therapies and over time[40]

Chromogenic assays can be used to measure circulating FIX plasma levels; there may be some variability with one-stage assays[40]

Laboratory assessments will not reflect extravascular collagen-bound FIX reservoirs; extravascular distributions of EHL FIX treatments are not yet fully understood, but are thought to be treatment dependent[40]

Blood group is a determinant of plasma factor levels of FVIII and vWF; however, it is not the case for FIX[55]

EHL, extended half-life; **FIX**, factor IX; **FVIII**, factor VIII; **HA**, haemophilia A; **HB**, haemophilia B; **MRT**, mean residence time; **PK**, pharmacokinetic; **vWF**, von Willebrand factor.

Requires further research

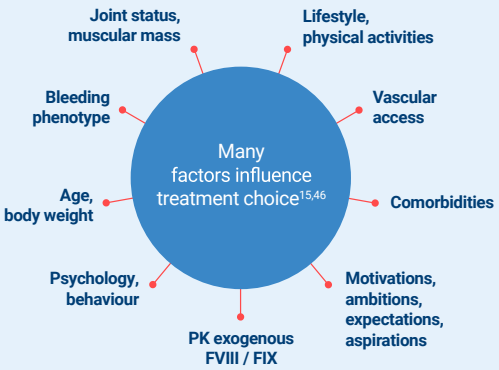
CAPSULE 6

TREATMENT INDIVIDUALISATION AND SHARED DECISION-MAKING

TREATMENT INDIVIDUALISATION

With a new era of haemophilia treatments in development, patient expectations and treatments goals are changing[54]

With increasing numbers of HB treatments, it is possible to further individualise care according to the patient's clinical characteristics, lifestyle, preferences and local healthcare environment[15]



Driving factors for individualisation choice[46,56]

Patient-related

- High treatment burden
- Patient physical activity level
- Treatment administration issues
- Patient support network, especially paediatric/adolescent patients
- Patient preference
- Poor compliance
- Portability/storage requirements
- Ease of access to hospital

Clinical

- Bleed history / continued bleeds
- Patient's metabolic profile
- Presence / development of inhibitors
- History of adverse events / reactions
- Presence of non-haemophilia-related comorbidities

Logistical

- Cost
- Insurance companies
- Local/hospital guidelines

SHARED DECISION-MAKING

Shared decision-making involves a collaborative effort between patients, families and clinicians on clinical evidence and patient priorities[46]

It is different between HA and HB owing to the differing available treatments[46]

Establishing effective shared decision-making[46,47]

- Identification and management of patient expectations
- Collaboration between patients and the entire MDT
- Need for patient education/empowerment
- Value decision-making tools
- Regular reassessment of the ability of the selected treatment modality to achieve these new ambitions

People with haemophilia rarely achieve a 'haemophilia-free mind' owing to haemophilia-related concerns. The concerns of people with haemophilia will differ depending on factors such as the severity of their haemophilia, the treatment modality they are receiving and the mental burden.[57]

FIX, factor IX; **FVIII**, factor VIII; **HA**, haemophilia A; **HB**, haemophilia B; **MDT**, multidisciplinary team; **PK**, pharmacokinetic.

CAPSULE 7

CARRIERS OF HAEMOPHILIA AND FUTURE AREAS OF RESEARCH

CARRIERS OF HAEMOPHILIA AND FEMALES WITH HAEMOPHILIA

Females can be carriers of HB and be affected by symptoms[58]

In females, haemophilia diagnosis is based on the same baseline FVIII/FIX activity levels as in males[22]

Genotype positive females can bleed regardless of factor levels; therefore, genotype positive females with factor levels ≥40 IU/dL are termed **symptomatic carriers**, whereas those without bleeding are **asymptomatic**[22]

Gender inequality in haemophilia[22,59–61]

Females with haemophilia and carriers

Factor levels	Inheritance	Diagnosis	Access to care	Access to treatments
Baseline factor levels not systematically measured Carriers can be asymptomatic or symptomatic	50/50 chance of transmitting affected X chromosome to their children Often not aware of carrier status	Often undiagnosed, not confirmed, informed or counselled, or there is a delay in diagnosis as symptoms can be mild **Of females with haemophilia (factor levels <40%):** **96%** Mild HA/HB **4%** Severe/moderate HA/HB	Are often not provided with haemophilia management and care	Females are often underrepresented and excluded from haemophilia clinical trial research
Baseline factor levels routinely measured	Transmit affected X chromosome to every daughter	Are more likely to receive a diagnosis than females	Often have access to multidisciplinary care	Often have access to current and new treatments

Males with haemophilia

The prevalence of carriers of haemophilia is underestimated[22]

For **one** male with haemophilia, there are:

2.7–5 potential carriers of haemophilia

1.5 somatic carriers

0.3–1.0 carriers with FVIII/FIX <0.4 IU/mL who are infrequently included in national databases[59]

Females represent **~6%** of the HB population[61]

29.5–47% of carriers of HB have **FIX levels <40%**[60,62]

Challenges

Pregnancy

- FIX levels do not rise during pregnancy as observed with FVIII levels; therefore, pregnant HB carriers have higher risk of bleeding than pregnant HA carriers[21,22]
- Prophylaxis may be required for delivery in settings capable of managing any haemophilia-related outcomes, and post-partum[22,47]
- DDAVP boosts plasma levels of FVIII and vWF and is used to prevent bleeds in mild/moderate HA, including for pregnant carriers of haemophilia; however, DDAVP does not affect FIX levels[15]

Further research is required to improve awareness, identification and screening, diagnosis, management and access to treatment for carriers and females with bleeding disorders[22,58]

REMAINING RESEARCH QUESTIONS AND UNKNOWNS

- What are the implications/role of extravascular FIX and FIX binding to collagen IV on clinical outcomes?
- What is the role of positive vs negative CRM on HB treatment and management?
- How will NFT dosages and schedules be adapted according to individual patient needs in HB?
- What is the long-term efficacy and safety of HB gene therapies?
- What impact do non-factor therapy molecules have on long-term joint health in HB?
- How can HB treatments be tailored for paediatric patients?
- How can strategies be developed to aid the prevention and management of inhibitors?
- How will new treatments impact people with HB, including carriers and females with HB?
- How can barriers to accurate diagnosis in females with HB be overcome?
- What are the implications of being a carrier of HB, e.g. the effect on bleeding tendencies and health?

CRM, cross-reactive material; **DDAVP**, desmopressin; **FIX**, factor IX; **FVIII**, factor VIII; **HA**, haemophilia A; **HB**, haemophilia B; **IV**, intravenous; **NFT**, non-factor therapy; **vWF**, von Willebrand factor.

Requires further research

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SUPPLEMENTARY MATERIAL

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