Pediatric Hemophilia in the Era of Subcutaneous Prophylaxis: Translating Hemostatic Innovation Into Safe Everyday Care

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Abstract

Background: Pediatric hemophilia care has moved from episodic rescue toward sustained bleed prevention, yet the growing number of factor and non-factor options has made treatment selection more complex. The clinically relevant question is no longer whether prophylaxis is needed, but how to match a hemostatic strategy to a child's biology, developmental stage, daily activity, family capacity, and local resources.

Aim: To synthesize current evidence on contemporary prophylaxis for children and adolescents with hemophilia A or B and to translate therapeutic advances into a practical safety framework.

Methods: A focused narrative review of international guidance, pivotal trials, long-term extensions, pediatric cohorts, and global registry reports was undertaken. Evidence was organized around treatment goals, product classes, breakthrough-bleed planning, monitoring, adherence, and equity.

Results: Early continuous prophylaxis remains the foundation of care. Extended-half-life factors reduce infusion burden while retaining the measurable pharmacokinetic control of replacement therapy. Emicizumab has established highly effective subcutaneous prophylaxis for hemophilia A across childhood, including inhibitor populations. Rebalancing agents broaden subcutaneous options for adolescents with hemophilia A or B, but require disciplined safety education because breakthrough treatment can shift the balance toward thrombosis. Across all classes, successful care depends on an individualized emergency plan, developmentally appropriate self-management, and comprehensive follow-up.

Conclusion: The best pediatric regimen is not defined by novelty alone. It is the regimen that safely sustains bleed protection while enabling normal growth, activity, schooling, and progressive independence.

Keywords: Hemophilia; Child; Prophylaxis; Emicizumab; Non-factor therapy.

Introduction

Hemophilia A and B are lifelong disorders, but their pediatric natural history is modifiable. Recurrent bleeding during growth can interrupt motor development, schooling, family routines, and the acquisition of independence. International guidance therefore defines regular long-term prophylaxis as the standard of care for children with a severe bleeding phenotype, with treatment goals extending beyond survival to freedom from spontaneous bleeding, preservation of physical function, and participation in ordinary childhood. [1]

The modern therapeutic landscape creates a productive tension. More options can reduce infusion burden and improve protection, yet they also demand greater precision in selection, laboratory interpretation, management of breakthrough bleeding, and communication with emergency teams. The relevant unit of care is consequently not the product but the child-treatment system: medicine, family competence, school preparedness, access to specialist advice, and the capacity to respond correctly when bleeding or surgery occurs. [1,2]

Review approach

This narrative review prioritizes World Federation of Hemophilia guidance, pivotal prophylaxis trials, pediatric extensions, and recent evidence on factor mimetics and rebalancing agents. It focuses on congenital hemophilia A and B from infancy through adolescence. Gene therapy is discussed only as a future pediatric consideration because current clinical use is centered on adults. The review deliberately addresses treatment strategy and safety rather than biochemical or radiological diagnosis of joint disease.

The treatment goal has changed

The randomized Joint Outcome Study established that early regular factor VIII prophylaxis protected joints more effectively than enhanced episodic treatment in young boys with severe hemophilia A. That observation transformed pediatric care: clinically visible bleeds are not an acceptable organizing principle when preventable tissue injury may accumulate between them. Modern practice has moved further, asking whether a child can remain active, avoid treatment-related disruption, and reach adulthood without a legacy of pain or disability. [3]

A low annualized bleeding rate is valuable but incomplete. Bleed counts depend on recognition, reporting, and treatment behavior, and they may not capture restrictions imposed to avoid bleeding. A child who has no recorded bleeds because the family avoids sport, travel, or school activities has not achieved full therapeutic success. Contemporary outcomes therefore include treated and untreated bleeding, target-joint status, physical performance, school attendance, treatment burden, quality of life, and confidence in self-management. [2,4]

Individualized prophylaxis begins with the child

A rational regimen begins with phenotype rather than factor level alone. Baseline severity, previous bleeding, inhibitor status, venous access, pharmacokinetics, activity pattern, weight, comorbidity, planned procedures, and family preferences all influence the benefit-risk balance. Infants require a plan that anticipates mobility and falls; school-age children need protection matched to physical education and play; adolescents require flexibility, privacy, and ownership. Reassessment is essential because the correct regimen at age two may be impractical at age twelve. [1,5]

Shared decision-making should convert these variables into explicit goals. Families should understand what the regimen is expected to prevent, how rapidly protection is established, which laboratory tests remain interpretable, what constitutes a breakthrough bleed, and whom to contact after trauma. A written emergency plan should travel with the child and be available to school staff and non-specialist clinicians. The plan is a safety intervention, not an administrative accessory. [1,5]

Factor replacement remains a precision tool

Standard-half-life factor concentrates remain effective and familiar, and they permit direct measurement of factor activity. Their principal pediatric limitation is treatment burden: frequent intravenous access can be difficult in toddlers and intrusive for families. When adherence is reliable, however, factor

replacement offers a transparent relationship between dose, exposure, activity timing, and rescue treatment. This can be particularly useful in children whose lifestyle benefits from planned peaks of hemostatic coverage. [1,5]

Extended-half-life factor VIII products reduce infusion frequency modestly, whereas extended-half-life factor IX products generally provide a larger extension because FIX biology is more amenable to half-life prolongation. Pediatric trials of rFVIIIFc, pegylated FVIII, rFIXFc, and nonacog beta pegol reported low bleeding rates and acceptable safety in previously treated children. The practical gain is not simply fewer infusions: a less burdensome schedule may improve consistency and allow dose timing around school and sport. [6-9]

Extended-half-life products do not eliminate inhibitor vigilance. Previously untreated children with severe hemophilia A remain at greatest risk during early exposure, and product choice does not remove the need for structured surveillance. The PUPs A-LONG study showed that rFVIIIFc can be used effectively in previously untreated children, while also confirming that inhibitor development remains a central outcome in this population. Families should be taught that loss of treatment effect or unexpected bleeding warrants prompt specialist assessment. [10]

Table 1. Contemporary prophylactic classes and pediatric implications

Class	Pediatric strengths	Key limitations and safety needs
Standard-half-life factors	Direct replacement; measurable activity; flexible dosing around procedures and high-risk activity.	Frequent intravenous access; variable pharmacokinetics; inhibitor surveillance remains essential. [1]
Extended-half-life factors	Lower infusion frequency and longer protection; particularly marked half-life extension for FIX products.	Venous access remains necessary; product-specific assays and pediatric pharmacokinetics must be understood. [6-10]
FVIIIa mimetic (emicizumab)	Subcutaneous prophylaxis for hemophilia A; effective with or without FVIII inhibitors; flexible intervals.	Routine aPTT and one-stage FVIII assays are misleading; breakthrough therapy requires a specific plan. [11-13]
Anti-TFPI antibodies	Subcutaneous prophylaxis can apply to hemophilia A or B and expands options for adolescent inhibitor populations.	Agent-specific titration, rescue limits, and thrombotic surveillance are required. [15,16,20]
Antithrombin-lowering siRNA	Infrequent subcutaneous dosing and activity across hemophilia A or B, with or without inhibitors.	Antithrombin-guided dosing, liver and gallbladder surveillance, and conservative rescue treatment are central to safety. [17-19]

Note: aPTT, activated partial thromboplastin time; FIX, factor IX; FVIII, factor VIII; siRNA, small interfering RNA; TFPI, tissue factor pathway inhibitor.

Emicizumab and the normalization of subcutaneous childhood care

Emicizumab substitutes for the cofactor function of activated factor VIII by bridging activated factor IX and factor X. Its subcutaneous administration and long dosing interval transformed prophylaxis for hemophilia A, particularly for children with inhibitors who previously depended on burdensome bypassing regimens. In HAVEN 2, children with inhibitors achieved marked bleed reduction across weekly, two-weekly, and four-weekly schedules, with a safety profile that supported long-term use. [11]

Pooled HAVEN follow-up demonstrated sustained low bleeding rates over substantial cumulative exposure, including pediatric participants with and without inhibitors. More recent pediatric follow-up from the AOZORA program suggests that low bleeding can be accompanied by maintenance or improvement of joint health over three years. These data support an important principle: convenience and efficacy can coexist, but favorable trial outcomes still depend on correct breakthrough-bleed management and continuing comprehensive care. [12,13]

Emicizumab changes laboratory interpretation. The activated partial thromboplastin time becomes artificially shortened and conventional one-stage FVIII assays are misleading. Bovine-reagent chromogenic assays are required when measurement of endogenous or infused FVIII is clinically

necessary. Every child should have this information in an emergency card because an apparently normal coagulation result can create false reassurance outside the hemophilia center. [1]

Breakthrough bleeding on emicizumab is treated with factor VIII in patients without inhibitors or an appropriate bypassing agent in those with inhibitors. Activated prothrombin complex concentrate requires particular caution because excessive cumulative exposure with emicizumab has been associated with thrombotic microangiopathy and thrombosis; recombinant activated factor VII is generally preferred when suitable. Parents and emergency clinicians must know the exact rescue product, dose framework, and threshold for contacting the specialist team. [1,11]

Rebalancing therapies: broader reach, narrower safety margins

Rebalancing therapies increase thrombin generation by attenuating endogenous anticoagulant pathways. Anti-tissue factor pathway inhibitor antibodies and antithrombin-lowering small interfering RNA are attractive because they can provide subcutaneous prophylaxis for hemophilia A or B, irrespective of the missing factor and, for some agents, inhibitor status. This class may be especially important for adolescents with hemophilia B and inhibitors, for whom prophylactic options have historically been limited. [14]

In explorer7, concizumab prophylaxis substantially reduced treated bleeding in adolescents and adults with hemophilia A or B and inhibitors. Explorer8 extended efficacy evidence to patients without inhibitors. These trials also illustrate why rebalancing therapy cannot be managed as "factor by another route": loading, maintenance, and rescue algorithms are product-specific, and the response to additional hemostatic agents is not equivalent to the response observed under baseline hemophilia. [15,16]

Fitusiran lowers antithrombin and demonstrated major reductions in bleeding in ATLAS-INH, ATLAS-A/B, and ATLAS-PPX. Development was shaped by thrombotic events, leading to antithrombin-based dose adjustment and stricter breakthrough-bleed guidance. Marstacimab, another anti-TFPI antibody, has also shown effective prophylaxis in phase 3 programs, including recent inhibitor data. For pediatricians, the lesson is consistent across the class: long dosing intervals reduce visible treatment burden but increase the importance of durable education, accurate medication records, and rapid access to expert advice. [17-20]

Choosing among options

Product selection should be framed as a series of clinical trade-offs rather than a hierarchy. Factor replacement provides measurable levels and flexible peri-activity dosing but requires venous access. Emicizumab offers highly effective low-burden prophylaxis for hemophilia A but alters routine laboratory assays and requires a distinct rescue plan. Rebalancing agents extend subcutaneous prophylaxis to hemophilia B and inhibitor populations, yet their safety depends on close adherence to agent-specific monitoring and bleed-treatment limits. [1,14]

Age and evidence maturity matter. Data derived predominantly from adolescents and adults should not be silently generalized to infants. Growth affects pharmacokinetics, injection volume, activity, and caregiver delivery; developmental change affects adherence and risk perception. When several regimens are clinically reasonable, preference-sensitive factors—route, frequency, privacy, travel, refrigeration, school schedule, and family confidence—can determine whether real-world protection matches trial efficacy. [2,5]

Table 2. A child-centered treatment selection framework

Decision domain	Questions for the consultation	Clinical consequence
Bleeding phenotype	What bleeds have occurred, under which regimen, and during which activities?	Determines required intensity and whether current protection is sufficient.
Development	Who administers treatment now, and which skills should the child acquire next?	Links regimen complexity to caregiver and adolescent capability.
Lifestyle	Which school, sport, travel, or privacy demands threaten consistency?	Guides route, interval, and dose timing.
Safety infrastructure	Are appropriate assays, rescue products, and specialist advice reliably available?	Prevents selection of a regimen that cannot be safely supported.
Family preference	Which trade-offs are acceptable after benefits and uncertainties are explained?	Improves concordance and long-term adherence.
Equity and continuity	Can access be sustained, including during shortages or relocation?	Favors a durable plan over a theoretically ideal but fragile one. [21-23]

Note: The framework should be revisited after major bleeds, growth, lifestyle change, surgery, adherence difficulty, or treatment transition.

Breakthrough bleeding, trauma, and procedures

No prophylactic strategy eliminates trauma or surgery. Families should be able to distinguish minor bruising from suspected muscle, joint, head, neck, abdominal, or iliopsoas bleeding and should treat life-threatening sites without waiting for confirmatory testing. A child with head trauma or neurological symptoms requires urgent evaluation even when prophylaxis has been consistent. Treatment records should document time, site, trauma, rescue product, response, and specialist advice so that recurrent events trigger regimen review. [1]

Dental work, circumcision, central-line procedures, orthopedic interventions, and emergency surgery require advance coordination whenever possible. The hemostatic plan must specify the prophylactic agent, additional factor or bypassing therapy, antifibrinolytic use, laboratory method, duration of postoperative cover, and thromboprophylaxis considerations. For children receiving non-factor therapy, the operative team must avoid assuming that routine coagulation tests quantify protection. [1,5]

Adherence is a developmental outcome

Adherence in early childhood is largely a caregiver behavior; in adolescence it becomes a negotiated transfer of responsibility. The treatment team should progressively teach diagnosis, medication name, schedule, injection technique, stock management, bleed recognition, emergency communication, and confidentiality. Skills should be demonstrated, not merely discussed. Simplified schedules can help, but a long interval does not guarantee adherence if the adolescent does not understand why treatment continues in the absence of bleeding. [2]

Digital reminders and electronic treatment diaries can reduce memory burden and improve communication, but they should support rather than replace the clinical relationship. A missed dose should prompt problem-solving rather than blame: competing school demands, needle anxiety, privacy concerns, treatment fatigue, and supply barriers require different solutions. The practical endpoint is reliable protection in the child's actual life, not nominal prescription acceptance. [2,4]

Inhibitors remain a pediatric priority

The therapeutic revolution has not removed the immunological challenge of inhibitors. Risk is greatest in previously untreated children with severe hemophilia A during early exposure to factor VIII, when treatment intensity, genotype, family history, and other variables may interact. Inhibitor screening should follow local protocols and should be performed whenever clinical response is unexpectedly reduced, before major procedures, and after intensive exposure. A child receiving emicizumab may bleed infrequently, so loss of factor VIII efficacy can remain hidden unless exposure and testing are planned. [1,10]

Immune tolerance induction remains the only established strategy for eradicating a persistent factor VIII

inhibitor, although emicizumab can provide bleed protection during the process. The decision to attempt tolerance, the factor product and schedule, venous-access implications, and the role of concomitant prophylaxis require specialist discussion. Families should understand that bleed prevention and inhibitor eradication are related but distinct goals; effective emicizumab prophylaxis does not demonstrate that the inhibitor has disappeared. [1,11]

Hemophilia B inhibitors are less common but can be accompanied by allergic reactions and nephrotic syndrome during immune tolerance. This rare combination makes early recognition and specialist management essential. Rebalancing agents may broaden prophylactic options for adolescents with hemophilia B and inhibitors, yet they do not simplify acute management automatically. Every new treatment must be paired with a new rescue plan. [1,14,15]

Routine pediatrics still matters

Children with hemophilia require the same preventive pediatrics as their peers. Vaccination should be complete, with subcutaneous administration considered when an equally effective licensed route is available and with local pressure after injections. Dental prevention is particularly valuable because avoiding caries and gingival disease reduces future invasive procedures. Families should receive anticipatory guidance on safe analgesics and should avoid unsupervised aspirin and most traditional nonsteroidal anti-inflammatory drugs. [1]

Common childhood illness can expose gaps in coordination. Tonsillitis, gastroenteritis, appendicitis, fractures, and lacerations may present first to clinicians unfamiliar with non-factor therapy. The hemophilia team should make consultation easy, and emergency documents should use generic drug names, state inhibitor status, identify misleading laboratory tests, and specify what should be given before transfer when delay is dangerous. The clarity of this document can be as important as its availability. [1]

Puberty introduces new issues. Increased body size alters dosing; vigorous activity, risk-taking, and travel increase; privacy becomes important; and girls or women with low factor levels may present with heavy menstrual bleeding or procedure-related bleeding. Pediatric services should recognize hemophilia in all genders and provide confidential, developmentally appropriate counseling rather than using a male-only model of care. [1]

Long-term central venous access is less common as subcutaneous therapy expands, but children who retain a device still require infection and thrombosis prevention. Conversely, the absence of a line should not erode competence with emergency intravenous treatment when factor or bypassing therapy is needed. Skills can be distributed across the family and care network, provided responsibilities are explicit. [1,2]

What easier prophylaxis does not solve

A less burdensome regimen can create therapeutic silence: the family sees fewer bleeds and has less frequent contact with the center. This is a success, but it can allow dental care, vaccination, physiotherapy, inhibitor testing, or adolescent counseling to drift. Follow-up should therefore be redesigned rather than reduced, using fewer but more purposeful visits that assess function, participation, adherence, safety knowledge, and changing goals. [1,2]

Subcutaneous administration also changes the psychology of treatment. Young children may grow up without memories of regular intravenous infusions or major bleeding, which can reduce fear and stigma. At the same time, they may reach adolescence with limited understanding of the consequences of missed prophylaxis or the complexity of emergency treatment. Education should anticipate this “success paradox” and use age-appropriate simulations and teach-back to preserve competence. [2]

Finally, pharmaceutical innovation cannot substitute for continuity of supply. A long-acting or highly specialized regimen becomes unsafe when access is interrupted without a bridging plan. Centers should discuss travel, relocation, shortages, and insurance or financing before problems occur. In resource-constrained settings, the best program may be the one that can reliably deliver prophylaxis, rescue treatment, and follow-up to the largest number of children. [21-23]

Global equity and rational implementation

Therapeutic progress is unevenly distributed. Analyses of global programs and the World Bleeding Disorders Registry show profound differences in diagnosis, prophylaxis, and outcomes between high-resource and lower-resource settings. A regimen that depends on unavailable assays, fragile supply chains, or inaccessible rescue products may be less safe than a simpler strategy that can be delivered consistently. Equity therefore belongs inside clinical decision-making, not only in policy discussions. [21-23]

Sustainable pediatric programs combine diagnosis, reliable product supply, home treatment, family education, physiotherapy, surgery pathways, data collection, and emergency access. Humanitarian programs demonstrate that predictable access can convert donated product from episodic rescue into prophylaxis and planned surgery. The priority is not to recreate high-income practice uncritically, but to build locally durable systems that protect childhood development. [21,23]

Monitoring success without overtreatment

Follow-up should answer four questions: Is protection sufficient? Is treatment safe? Is the regimen sustainable? Is the child living more freely? Bleed diaries and medication records remain important, but they should be interpreted with activity exposure. One treated bleed during frequent vigorous sport may represent a different clinical problem from one spontaneous bleed during ordinary daily life. The trend over time and the circumstances of each event are more informative than an isolated annualized number. [1,2]

Treatment intensification is appropriate when spontaneous or recurrent site-specific bleeding persists, but it should not be reflexive after every injury. The team should examine adherence, administration technique, dose timing, pharmacokinetics where relevant, growth, trauma pattern, and whether pain was truly caused by bleeding. Escalation without clarifying the mechanism may increase cost and treatment burden without solving the problem. [1,5]

Safety surveillance is therapy-specific. Factor replacement requires inhibitor awareness and product-appropriate activity testing. Emicizumab requires recognition of assay interference and safe use of bypassing therapy. Anti-TFPI and antithrombin-lowering agents require adherence to their monitoring, dose-adjustment, and rescue protocols, with attention to thrombotic symptoms. A standardized clinic checklist can prevent safety knowledge from becoming fragmented as children switch regimens. [1,14-20]

Patient-reported outcomes can reveal treatment failure before bleeding data do. Fear of activity, treatment fatigue, missed school, caregiver distress, or reluctance to travel may persist despite excellent hemostatic control. These outcomes should lead to targeted intervention rather than automatic pharmacological escalation. Sometimes the next therapeutic advance is physiotherapy, psychological support, school advocacy, or a simpler plan rather than a different molecule. [2,4]

Research priorities

The next generation of pediatric evidence should compare strategies using outcomes that matter to children: zero spontaneous bleeding, activity participation, pain-free days, school attendance, treatment workload, caregiver burden, and safe emergency management. Longitudinal studies are needed to determine whether very low recorded bleed rates under non-factor prophylaxis translate into normal musculoskeletal health across decades. Trials should also include girls and women with hemophilia, non-severe phenotypes, and children from regions where current evidence is sparse. [2,14]

Comparative effectiveness research should address switching, combination rescue, surgery, adherence after the novelty of a regimen fades, and the consequences of interrupted access. Pediatric pharmacovigilance is particularly important for therapies that rebalance coagulation because rare thrombotic events may not be fully characterized in preapproval cohorts. Registries capable of linking treatment exposure to patient-reported, functional, and safety outcomes will be essential. [14,22]

Conclusion

Modern prophylaxis can release children with hemophilia from much of the visible burden that once defined the disease. The clinical task is to convert pharmacological possibility into dependable everyday

safety. This requires matching therapy to the child, teaching a precise rescue plan, interpreting laboratory tests correctly, and measuring success in growth, participation, and independence. A regimen is truly effective when it protects the child not only from bleeding, but also from a childhood organized around fear of bleeding.

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