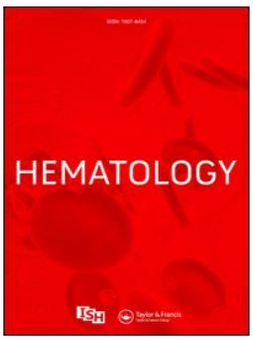

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Re-personalization and stratification of hemophilia care in an evolving treatment landscape

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ABSTRACT

Hemophilia therapeutics are evolving rapidly. Comprehensive care must also evolve to embrace this change. Online tools and guidelines are widely available to optimize prophylaxis with conventional clotting factor concentrates using an individual's predicted pharmacokinetic profile. Novel hemostatic agents (e.g. biphenotypic antibody) are also becoming widely available, with other agents with differing mechanisms of action in final stages of trial. Contemporary issues including challenges of prophylaxis; bleed treatment; laboratory monitoring and inhibitor risk/surveillance are summarized in this narrative review, focusing on how a re-personalization of education and treatment will be necessary to meet these challenges of the rapidly changing therapeutic landscape.

KEYWORDS

Hemophilia; prophylaxis; personalization; pharmacokinetic; comprehensive care; factor; emicizumab; optimize

'*Personalization*' and '*Stratified Medicine*' are commonly used terms in many areas of contemporary medicine, most notably oncology, aligning the power of genomic dissection of disease subtypes (*e.g.* breast cancer) to best match with an ever increasing portfolio of molecular or targeted therapies. Hemophilia A care has arguably always had a multidisciplinary, personalization intent with the evolution of comprehensive care, but only recently begun to implement individualized pharmacokinetics (PK) into the formulation of FVIII prophylaxis prescribing practices. The hemostasiologist/hematologist now appreciates the substantial variation of time to baseline FVIII levels (48–109 h) after a standard 30 u/kg dose of standard half-life FVIII clotting factor concentrate (CFC) [1]. The availability of online tools implementing population pharmacokinetic (popPK) algorithms now enables the identification of an individual person with hemophilia (PWH)'s own PK profile as a standard of care, with recent ISTH SSC guidance on the subject [2,3]. Individualized-PK guided dosing has delivered annualized bleed rates (ABR) of zero in excess of 40% and even >80% for spontaneous bleed freedom in clinical trial settings [4,5]. Current attempts to optimise prophylaxis benefit many PWH, but also identify a substantial minority who continue to bleed despite such a personalized approach. Arguably, this will become the contemporary stratification step in hemophilia care as the therapeutic landscape evolves. However, it should also be remembered that the ABR metric, although commonly used, is not the complete story of protection for patients. The concept of subclinical bleeding leading to musculoskeletal damage despite no overt joint bleeds requires continued attention [6,7].

The remaining important area to stratify hemophilia care is the prediction of inhibitory antibody occurrence and/or the outcome of immune tolerance induction. It has long been known that the *F8* mutation is relevant in this area [8] and also now contributory to interpreting the benefit of a plasma-derived fVIII CFC at the very first exposure to treatment in a previously untreated patient (PUP) [9]. The minority of individuals with less disruptive *F8* genotypes may benefit from a pdFVIII over a recombinant product, but for the majority with more disruptive mutations, including Intron 22 inversion, this stratification on *F8* alone does not hold [10]. Antibody affinity maturation and class switching to IgG4 have been identified as an important step to discriminate clinically meaningful inhibitory antibodies from non-inhibitory or transient ones [11]. Multiple additional immune-modulatory polymorphisms have been identified [12,13,14,15] but not yet converted to aid the stratification of early treatment choices in clinical practice, not least that for the majority of baby boys these markers are not available at the time of first treatment. Studies are ongoing to further understand the early molecular steps in inhibitor induction at first exposure to CFC.

There is currently a rich pipeline of therapeutic agents in clinical trials or early approval for hemophilia treatment [16,17,18]. The majority have mechanisms of action that modulate hemostasis, but the therapeutic agents are not themselves factor replacements [19].

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Rather, they either mimic the hemostatic function of the FVIII protein, *e.g.* biphenotypic antibody binding factor IXa and X (emicizumab, Roche) [16] or modulate the hemostatic equilibrium through interference with regulatory molecules, *e.g.* antithrombin knockdown (siRNA, Fitusiran, Sanofi) [17] or Tissue Factor Pathway Inhibitor (TFPI) interference (*e.g.* Concizumab, Novo-Nordisk) [18]. The apparent added values of all these molecules are a combination of a less demanding route of administration, subcutaneous (SC) rather than intravenous (IV), and long half-lives that enable both less frequent dosing (up to once a month) together with a continuous hemostatic level of protection thought to be well into the mild hemophilia equivalent range of FVIII activity (FVIII:C). However, modulating the clotting cascade in these ways is not without uncertainty and risk, recognizing the multiple interactions between cascade molecules, and that wild-type FVIII is arguably the most tightly regulated molecule in the entire cascade. Although co-administration of the bypassing agent (BPA) Factor Eight Bypassing Activity (FEIBA, Takeda) with emicizumab is thought as the likely precipitant of the unusual thrombotic and Thrombotic MicroAngiopathic (TMA) events seen in the HAVEN 1 emicizumab trial [16], the lack of a necessary activation step and absence of negative control (*e.g.* activated Protein C) for functional mimics contrasts to the requirements for the wild-type FVIII molecule. The pathophysiology of these TMA events remains obscure and time to resolution uncertain. Additionally, novel agents have half-lives that will require weeks or months of wash out if needing to be stopped electively or in an emergency in the absence of any antidotes. Novel agents are not quantifiable in any current, standard hemostatic assay, whilst validated product-specific assays are yet to become available. Risk of anti-drug antibodies (ADA) against these agents appear to be low [16] but loss of efficacy and a confirmed ADA case using emicizumab highlights need for ADA surveillance strategies for all new monoclonal therapies.

Novel agent efficacy appears to be sufficient for prophylaxis, but not for maximal hemostatic protection for serious trauma or major surgery. As such, we are entering an era of requiring different agents for baseline prophylaxis and on-demand treatments. Conventional CFC and BPA will remain the on-demand therapeutics of choice in non-inhibitor and inhibitor settings respectively. The absence of validated assays to give a clinician a meaningful readout from patients' plasma with simultaneous novel and conventional hemostatic agents on board remains a concern, particularly for less experienced clinicians or laboratory scientists who may not be aware of these potential confounders to assay interpretation and consequent risk to clinical management. This further supports the assertion that these new agents should be overseen by experienced comprehensive care centers despite the convenience of administration that paradoxically encourages detachment from such an expert center in favor of a more local, less specialist facility. It is notable that both reported deaths in the novel agent trials (Emicizumab and Fitusiran) occurred in facilities distant to their comprehensive care trial centers [16].

Conversion to a continuous level of hemostatic protection equivalent to mild hemophilia with a novel agent meets one of the prophylaxis challenges conventional factor concentrates has arguably struggled to deliver for decades – namely maintaining a minimal level of FVIII:C well above the minimum prophylaxis level (1 iu/dL) defined in the 1960s [20,21]. Analysis of those living with non-severe hemophilia A in a Dutch cohort describes the ever decreasing risk of spontaneous joint bleeding as the baseline FVIII:C levels rise through 5 iu/dL then past 10 iu/dL, confirmed by a recent, large US cohort [22,23]. PWH (severe) and their families currently require CFC prophylaxis IV training and CFC supply from early in life, with continuous and frequent life-long CCC contact to encourage adherence, evaluate more serious bleeds and oversee surgical interventions. Musculoskeletal complications have inevitably occurred in the majority of adults and centers oversee outcome measurement collection throughout the decades of life. It is conceivable that novel agents started early enough in life will circumvent the necessity for early, intensive medical involvement, resulting in a more distant relationship with their CCC akin to current mild hemophilia A cohorts. If these novel agents do indeed demonstrate a steady hemostatic threshold and superiority in efficacy, such a distance from the CCC risks a depersonalization in hemophilia care. This brings both advantage and disadvantage, discussed below. However, a notable early advantage is the re-establishment of equity in treatment efficacy between those living with or without a chronic inhibitor. In this particular niche of chronic inhibitors, novel molecules such as emicizumab (HemLibra®) appear to demonstrate a superior efficacy over conventional BPA prophylaxis in adults [16,24], albeit with need for significant caution in times of co-administration of BPA [25].

Spontaneous or traumatic bleed avoidance with CFC prophylaxis has been demonstrated to be meaningful in both children and adults living with severe HA [6,7]. The stereotyped view of mild hemophilia A is of being infrequent hospital/emergency department (ED) attenders, often diagnosed later in life, free of spontaneous bleed risk with rare need for the expertise of their CCC. However, in times of crisis, anecdotally, emergency pathways are often less clear for these individuals, often presenting later than those with more severe hemophilia with consequent risk of avoidable morbidity and potential mortality. This principle is already borne out in the 'treated' and 'all bleed'

metrics introduced in novel-agent, open-label clinical trials [16] which has de-escalated the urgency of hemostatic treatment for perceived non-serious injuries or symptoms. This contrasts to the current CFC convention of 'treat first, ask later'. Additionally, the majority of those living with mild hemophilia do not have the skill to self-administer intravenous factor concentrate at home or whilst traveling, thus increasing their hospital dependency at times of crisis. A recent UK cohort of over 800 non-severe hemophilia A PWH retrospectively analyzed treatment burden over a 2-year period. Forty-four percent (377/853) of non-severe PWH required at least one hemostatic treatment in the 2-year study period, 79% (296/377) of whom received FVIII CFC [26]. Despite the Dutch and US papers' prediction of minimal spontaneous joint bleeding in the mild hemophilia population [22,23], the UK cohort suggests treatment for bleed treatment, surgery or procedures is more frequent than previously recognized.

Those using novel prophylaxis agents in the future will still need 'top up' on demand treatment with conventional CFC or BPA for significant trauma or procedures. This introduces a new challenge for treating hemophilia teams. New educational strategies will be required to transition PWH to these new agents, manage their expectations of how active they may wish to become if their musculoskeletal status allows, whilst retaining a close enough relationship to keep the communication pathways open in the event of emergencies. Over time, with sufficient prophylaxis efficacy, these patients may not even keep a supply of CFC or BPA at home at all, as is the case for the majority of PW non-severe hemophilia. This will become a re-personalization era, during which treaters re-focus individuals and families on how to manage their severe hemophilia, minimizing new risks in the era of these novel agents whilst highlighting the comprehensive care need beyond just CFC supply and treatment, maintaining true holistic, multidisciplinary care [27,28].

True primary prophylaxis in severe hemophilia starts early, often in the first year of life. Complete joint bleed avoidance is the key to guarantee long-term musculoskeletal health. However, it is well recognized to be challenging to implement with CFC, requiring intravenous access, often by an implanted venous access device and intensive training of the parents to ultimately be able to treat at home. Those with a family history and confirmation of severe hemophilia on the day of birth without bleed complication currently have an uncertain wait for months until first exposure to CFC. There are ad hoc ED attendances and often multiple, emotionally traumatic attempts to administer CFC intravenously in a small child. There is an ever-present risk of intracranial hemorrhage in this first year, in the absence of prophylaxis [29]. The early treatment of these previously untreated patients (PUPs) requires a systematic surveillance for inhibitory antibody responses against the infused therapeutic CFC [30]. This period is challenging for the treating team and family, but as a result, the intensity embeds a solid foundation of trust in the hemophilia care team, with clear, open and well-tested emergency care pathways. A therapeutic agent that could be administered by a parent more simply than intravenous CFC, e.g. subcutaneously, avoiding the need for implanted venous access devices, could enable a true primary prophylaxis to be instituted earlier for musculoskeletal protection, additionally reducing ICH risk. For those with a family history of severe hemophilia, this could/should arguably be from the day of diagnosis. Earliest intervention with a novel agent from first day, week or month of life needs both short- and longer term study data to demonstrate safety and efficacy in such young individuals. The efficacy of biphenotypic antibody therapy (e.g. emicizumab) is well documented now in the context of human physiology with a mature liver [16,31,32] but lacking in the context of an immature neonatal/infant liver, with lower substrate levels of both FIX and FX with potential efficacy implications. Similarly, the novelty of the interfering RNA (iRNA) therapeutic has accrued data in individuals with mature livers, albeit with some LFT derangement in some with a chronic history of HCV [17] A similar challenge to 'earliest intervention' in a neonate with such a therapeutic demands the necessary PUP-equivalent clinical trial to be performed in the youngest patients. It is not clear that such studies are planned as yet. Longer term trials are also required, akin to the CFC international joint outcome study [6], to demonstrate long-term MSK benefit of such early intervention. In contrast to the current adult, previously treated patient (PTP) cohort who will live with the legacy musculoskeletal damage of the last decades of treatment, the emerging PUP cohort may benefit from a more complete, life-long musculoskeletal protection and bleed avoidance.

Inhibitor occurrence remains the predominant challenge of implementing prophylaxis in a young boy. If novel agents offer a potential of true bleed avoidance and musculoskeletal protection, might they also offer inhibitor avoidance too? Superficially, this would seem to be possible given the avoidance of early CFC exposure. However, the previously cited non-severe HA data suggests a substantial need for on demand CFC exposure in non-severe HA [26]. Additionally, given a novel agent may be implemented as the prophylaxis agent, without sufficient efficacy to treat a significant trauma or cover major surgery, these episodes will require on demand management with CFC exposure. Gouw et al. have demonstrated an increasing risk of inhibitor occurrence in the first 50ED to CFC if prophylaxis is not implemented by 20EDs [33]. Indeed the higher than expected inhibitor rates in

both arms of the SIPPET randomized controlled trial are in part attributable to longer on demand exposure in a majority [9]. Taken together, the on demand exposure to CFC in the context of novel agent prophylaxis may paradoxically increase inhibitor rates and also delay inhibitor occurrence to later in childhood or even adulthood depending on frequency of on demand CFC requirements. This brings additional challenges to the care team, given the inhibitor screening will be spread out over years rather than the current months, more akin to that after CFC exposure in non-severe HA. However, inhibitor screening in non-severe HA is already suboptimal with conventional assays [26]. Inhibitor screening in individuals with novel agent therapeutics on board will need specific assay considerations [25]. We may be at a time when the standard inhibitor assay (Bethesda) is no longer the first choice assay and an immunological assay (unaffected by the novel hemostatic agent), *e.g.* ELISA, applied for screening and then a bovine reagent-modified Bethesda used to determine inhibitory relevance of ELISA positive results.

If the current estimated 30–45% of individuals to experience an inhibitor were to arise at a later time point in childhood, there will be very different challenges to considering and implementing immune tolerance induction (ITI) as the definitive goal of treatment. Long-term tolerance to either FVIII or FIX remains the crucial status for a PWH to ensure the most efficacious hemostatic treatment in a time of crisis, particularly significant trauma, surgery or head injury. Additionally, the normalized or near normalized FVIII:C and FIX:C levels in recently reported adeno-associated viral (AAV) gene therapy studies highlight a real, transformational promise of this one-off intervention in the non-inhibitor setting [34,35]. Achieving tolerance to wild-type FVIII or FIX will likely remain a pre-requisite for eligibility for gene therapy in the medium term.

This evolving landscape of new agents and continued inhibitor risk will require a very deliberate, re-personalized care strategy from the current strategies treaters are familiar with. Conversion to an intensive intravenous CFC ITI, having had early years on a SC novel agent prophylaxis agent, will not only have health economic demands for a heavier, older patient, but the physical and psychological impact on the older boy and family will be very different to those in the younger boys of current practice. Despite these challenges, it is crucial that as a treating community, we do not avoid the short-term challenges of considering and implementing ITI, thereby guaranteeing the benefit of long-term tolerance in the majority [36]. Whether ITI can occur with lower dose CFC, concurrently with a novel agent prophylaxis agent on board, is another area requiring additional data, as is the means by which tolerance would be maintained thereafter.

Finally, an unintended consequence of delay in first CFC exposure if novel agents are used for primary prophylaxis is that it affords treaters time in all patients to describe the *F8* genotype and possibly for the first time start to use immunological polymorphism data in a more meaningful way within this new time window [12–15]. Thus it may be that our time to apply stratified medicine in hemophilia is truly upon us, to identify at risk individuals, counsel about and possibly intervene differently to avoid inhibitor occurrence. Whilst for those older individuals, stratifying access to novel agent prophylaxis agents initially on bleed phenotypes after personalized popPK optimization on existing CFC prophylaxis. This can provide a logical transition to identify who could/should use new agents early and enable data acquisition to identify both efficacy and life quality advantage. Meticulous, collaborative adverse-event reporting for these emerging cohorts should be a priority with careful consideration of attributions of causality for any event, including deaths. All of the scenarios discussed will require proactive re-personalization of how we counsel, stratify and prescribe treatments for our patients and families living with hemophilia in the coming years.

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