

FORUM

Management of children with hemophilia A: How emicizumab has changed the landscape

Guy Young  

Hemostasis and Thrombosis Center,
Cancer and Blood Diseases Institute,
Children's Hospital Los Angeles,
University of Southern California Keck
School of Medicine, Los Angeles, CA, USA

Correspondence

Guy Young, Children's Hospital Los
Angeles, 4650 Sunset Blvd, Mail Stop 54,
Los Angeles, CA 90254, USA.
Email: gyoung@chla.usc.edu

Abstract

The key to having a good quality of life for an adult with hemophilia rests largely on how he or she was managed as children. With effective prophylaxis, young men can begin their adult life with excellent joint function and few, if any, other sequelae from their disease. Unfortunately, this outcome is not always (nor often) attained because of the limitations of the mainstay of treatment, which is factor replacement therapy. In resource-rich countries with an adequate supply of factor concentrates, the treatment burden and formation of inhibitors limit the potential for an ideal outcome, whereas in much of the world, factor concentrates are too expensive to even be an option. The novel agent, emicizumab, which has become available in numerous countries around the world, is reshaping how one approaches the treatment of children with hemophilia A. This Forum Article, based on a State-of-the-Art lecture given at the 2020 International Society on Thrombosis and Haemostasis Virtual Meeting, presents an approach including clinically applicable algorithms for treating children with hemophilia A in the new era with emicizumab.

KEYWORDS

children, emicizumab, hemophilia, immune tolerance induction, inhibitor

1 | INTRODUCTION

Since the first description of hemophilia nearly 2000 years ago, human beings have sought ways to mitigate the harm that this bleeding disorder can wreak. The first such mitigation strategy was described in the Talmud, in which the rabbinical scholars helped mothers prevent the death of their third son by negating the religious requirement for circumcision (apparently, it took the first two sons to die to convince the rabbis to adopt this "unholy" approach). It took until 1840 when a physician named Samuel Lane transfused a boy with severe bleeding symptoms, which led to cessation of that bleed until an effective treatment was described. Last, the infamous

Rasputin drew upon his wisdom to suggest that Alexei Romanov, the son of the last Russian Czar and arguably the most well-known historical figure with hemophilia, avoid aspirin lest it make his bleeds worse. Additional historical context can be found in this review¹ but what binds these three "case reports" is that they all involved children. As we move into the 2020s, treatments for children with hemophilia have evolved significantly and will continue to do so at an even more rapid pace in the coming years. For the past nearly 5 decades, we have been treating hemophilia in what I call *The Factor Era*. Although *The Factor Era* has significantly improved the lives of many children with hemophilia, factor therapy is on the one hand a miraculous innovation yet also immensely problematic. Although it is in

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some sense the ideal treatment—it replaces exactly what the patient is missing—it also has some crucial limitations (more on this later). Thus, in spite of the availability of factor concentrates (in countries that can afford them, which is another major limitation of this therapy), there remain several unmet needs leaving patients and their treaters in search of improved therapeutic approaches. The unmet needs are even more crucial to fulfill in children as the harm caused by untreated or undertreated hemophilia begins in early childhood and accrues throughout the first 2 decades of life. The quality of life and productivity of adults with hemophilia depends largely on the successful prevention of bleeding during their formative years. This Forum Article will be focused on hemophilia A because the only currently available novel therapy, emicizumab, is only approved for treatment of this type of hemophilia. The discussion will first assess the unmet needs of *The Factor Era* followed by a brief review of emicizumab and will close with a discussion of the four classic pediatric patient scenarios (previously untreated patients, previously treated patients, inhibitor patients, and tolerized patients) that characterize the pediatric hemophilia A patient journey along with algorithms one can use in the clinic.

2 | UNMET NEEDS

Until recently, factor therapy has been the only option for the prevention and treatment of bleeding in patients with hemophilia. The development of factor concentrates ushered in an era of vastly improved outcomes for pediatric (and adult) patients. Despite these advances, factor therapy has a number of limitations affecting both safety and efficacy. First, because factor VIII (FVIII) concentrates are immunogenic, neutralizing antidrug antibodies called inhibitors occur with an incidence of about 30%.² When a child develops an inhibitor, it has a dramatic effect on both the treatment and the outcomes. Inhibitor patients suffer from worse joint outcomes³ and, as a result, worse physical functioning.⁴ A detailed review on the management of children with inhibitors can be found elsewhere.⁵ Another important limitation is the treatment burden associated particularly with prophylactic infusions. By this, I mean the time, effort, and pain involved with administration of the infusions that must be given intravenously and repeatedly. For hemophilia A, this typically involves infusing factor two to three times per week depending on which concentrate is used. For young children, a central venous access device is often needed, adding its own risks and complications, and for those who attempt to use peripheral venipuncture, the process for young children can be, frankly, brutal and can result in increased anxiety and distress.⁶ For older children, especially teenagers, adherence, in part because of the time and effort, becomes a major problem.⁷ Furthermore and crucially important, factor therapy may not be as effective as previously thought for the long-term prevention of joint disease.^{8,9} As such, new treatments to overcome these limitations are being developed and one, emicizumab, has been approved in many countries.¹⁰⁻¹⁵ Emicizumab has begun to shift the paradigm for the management of children with hemophilia

A, and because it is the only novel therapy currently available, it will be the focus of this discussion; however, the concepts described here could potentially be applied to other new therapies once they are approved for children.

3 | EMICIZUMAB

First, to better understand the impact of emicizumab for children, a brief review of its properties and the clinical trial results is needed. Emicizumab is a humanized, bispecific monoclonal antibody that bridges activated FIX and FX, resulting in the generation of activated FX, which then goes on to catalyze the formation of thrombin from prothrombin.¹⁰ Thus, emicizumab essentially substitutes for the function of activated FVIII. Although both activated FVIII and emicizumab ostensibly perform the same function, there are important differences in their properties that were reviewed nicely by Lenting.¹⁶ The phase 3 trials of emicizumab referred to as the HAVEN trials led to the approval in the United States for the treatment of patients with hemophilia A of any age, any severity, and regardless of whether they have an inhibitor or not. In other countries, the approvals vary to some extent with some areas of the world only having approvals for severe hemophilia or only for patients with inhibitors at least for now. As for children, the following trials were conducted: HAVEN 1 included patients ≥ 12 years with inhibitors¹²; HAVEN 2 included patients < 12 years of age with inhibitors¹³; HAVEN 3 included patients ≥ 12 years without inhibitors¹⁴; HAVEN 4 included patients ≥ 12 years with or without inhibitors specifically assessing an every-4-week dosing schedule¹⁵; and HOHOEMI included patients < 12 years without inhibitors.¹⁷ What can be said briefly from these trials is that emicizumab was found to be largely safe and very effective for the prevention of bleeding across the pediatric age spectrum and regardless of whether patients had or did not have inhibitors. Beside the well-described thrombotic events that occurred in the HAVEN 1 study, for which a boxed warning exists in the prescribing information, the other important related adverse event related to emicizumab is the formation of antidrug antibodies, which was published in one patient in the HAVEN 2 study and one additional patient since licensure.^{18,19} A detailed assessment of the safety of emicizumab can be found in this review.²⁰ Furthermore, several large case series have solidified the clinical trial data by providing compelling evidence from real-world use.^{21,22}

Although emicizumab has become an important part of the armamentarium for the management of children with hemophilia, it has also raised a number of important clinical questions for which there are no definitive answers (Table 1). Indeed, there are more questions the clinician is faced with, including the choice of dosing regimens and the follow-up and monitoring of patients who switch to emicizumab, among others; however, the previously presented five questions are the key questions that will be discussed in detail. Clearly, clinical trials, some of which are under way, will hopefully answer some of these questions, but these will take years to complete, and

TABLE 1 Key questions regarding emicizumab use in children and key drivers to decision-making

Key Questions When Using Emicizumab in Children	Key Drivers to Decision-making
At what age should emicizumab be started and should it be used in previously untreated patients (PUPs)?	Before 9 months of age: Very early bleeding requiring long-term prophylaxis when IV therapy is impossible or extremely difficult (intracranial hemorrhage) Parental anxiety regarding the risk for intracranial hemorrhage Beyond 9 months of age Avoidance of central venous access devices Parental preference over factor concentrates
For which noninhibitor patients should emicizumab be prescribed?	Poor responders to factor replacement therapy Poor adherence to factor replacement therapy Lower ABR with emicizumab (based on inpatient comparison from HAVEN 3) Parental/patient preference
Should emicizumab be used to treat all inhibitor patients who failed immune tolerance induction (ITI)?	Bleeding rate Target joint presence Quality of life (for on-demand or prophylaxis bypassing agent patients)
For patients who develop an inhibitor to FVIII, should ITI be initiated, should it be done in all such patients, and what is the role of emicizumab during ITI?	Availability of factor for ITI Parental preference Likelihood of adherence to ITI Availability of emicizumab Understanding of how to use concomitant ITI with emicizumab
For patients who develop inhibitors and are successfully tolerized, can emicizumab be prescribed for them in lieu of ongoing FVIII therapy?	Prescriber and parental preference (no data to support emicizumab alone nor any data that suggesting this would be improper) The PRIORITY is addressing this situation

Abbreviations: ABR, annualized bleeding rate; FVIII, factor VIII; IV, intravenously.

pediatric hematologists are facing these difficult questions and dilemmas now (Table 2). The following section will include four scenarios facing those who treat children with hemophilia: (a) newborns/infants often referred to as previously untreated patients (PUPs); (b) previously treated patients regardless of age (PTPs); (c) inhibitor patients; and (d) inhibitor patients who were successfully tolerized.

4 | PREVIOUSLY UNTREATED PATIENTS/INFANTS WITH HEMOPHILIA A

First, an important caveat for this section in particular. Data on the use of emicizumab in PUPs and in particular infants (children <1 year of age) are scarce and limited to case reports and series. There has been no systematic study of emicizumab in PUPs, although HAVEN 7 (NCT04431726), the Emi-PUPs Study (NCT04030052), and the Hemophilia Inhibitor Prevention Study (NCT04303559) will evaluate emicizumab in PUPs, with each study having different objectives (Table 2). Despite the lack of data, clinicians are already faced with making treatment decisions for PUPs and emicizumab must be part of the treatment option discussions. Until more data are available, the suggestions in the following section and the accompanying algorithm (Figure 1) are by necessity the authors' opinions.

Although any patient who has yet to receive a dose of factor concentrate is considered a PUP, which could include older children who, because of a lack of bleeding or economic reasons, did not receive factor concentrates at a young age, this section is reserved for the youngest patients (i.e., those <1 year of age [infants]). Although some of the concepts such as issues surrounding inhibitor formation likely apply to older PUPs, the main gist of this algorithm revolves around treatment options/approaches for infants in well-resourced countries that can offer emicizumab and factor concentrates to such patients.

Before the availability of emicizumab, the only available agents for prophylaxis of bleeding were FVIII concentrates and the decisions treaters faced were essentially when and how to start prophylaxis and which FVIII concentrate to use. A discussion of when and how to start prophylaxis with FVIII concentrates is beyond the scope of this Forum Article, and an excellent roadmap for how one could approach this issue is presented elsewhere.²³ The major point with respect to this section is that because factor concentrates must be given intravenously, starting prophylaxis much before 1 year of age (e.g., in the first few weeks or months of life) is simply not feasible; it is challenging enough in a 1 year old. Because emicizumab is administered subcutaneously, it is feasible to begin dosing immediately after delivery if desired or at any time in the first weeks/months of

TABLE 2 Currently active studies of emicizumab which are enrolling previously untreated patients (PUPs) or minimally treated patients (MTPs)

Study Name (NCT No.)	Patient Population	Study Design	Primary Outcome Measure	Algorithm addressed
Emicizumab PUPs and NUWIQ ITI study (NCT04030052)	1. Children <3 years 2. FVIII level of $\leq 2\%$ 3. ≤ 2 exposure days to FVIII	Open-label, prospective cohort study using emicizumab and coadministration of weekly or biweekly simoctocog alfa (NUWIQ) Patients who develop inhibitors can remain on study and receive simoctocog alfa for immune tolerance induction	1. Cumulative incidence of inhibitors 2. Number of immune tolerance induction successes	PUP new inhibitor
HAVEN 7 (NCT04431726)	1. Children <12 months 2. Weight <3 kg 3. FVIII level of $\leq 1\%$ 4. ≤ 5 exposure days to FVIII 5. No inhibitor	Phase 3b, multicenter, open-label, single-arm study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab for up to 7 years of follow-up	1. Annualized bleeding rate for various categories of bleeds 2. Hemophilia Joint Health Score (performed at ages 4–7) 3. MRI score of specific joints (performed at ages 5 and 8) 4. Emicizumab trough levels 5. Anti-emicizumab antibodies 6. Anti-FVIII antibodies	PUP
Hemophilia Prevention Trial NCT04303559	1. Children <4 months–4 years 2. FVIII level of $\leq 1\%$ 3. ≤ 3 exposure days to FVII 4. No inhibitor	Phase 3 multicenter, randomized inhibitor prevention trial comparing Eloctate vs. emicizumab to prevent inhibitor formation in severe hemophilia	1. Proportion of patients who develop inhibitors 2. Bleeding events	PUP new inhibitor

Abbreviations: FVIII, factor VIII; MRI, magnetic resonance imaging.

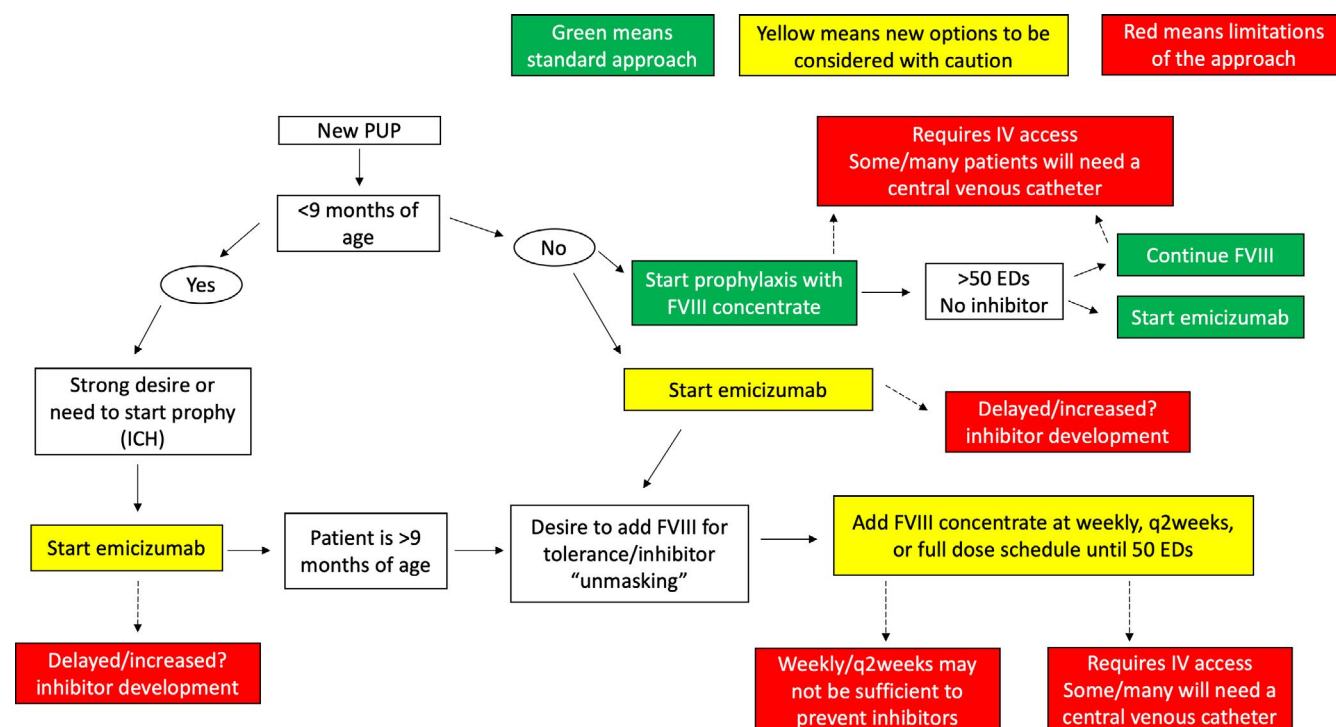


FIGURE 1 Treatment algorithm for the previously untreated patient (PUP). Green boxes indicate the standard of care approach, yellow boxes indicate new approaches to be considered with caution, and red boxes indicate the limitations of any of the recommendations

life; however, whether and in what situations it is appropriate to do so will be discussed later.

The majority of hemophilia patients have a known family history and thus diagnosis can be made within hours after birth (or even prenatally if desired); for those without a family history, diagnosis for the severe form is commonly made within the first week of life because of either bruising/bleeding during birth, excess bleeding from circumcision, or excess bleeding from the heel needle puncture. The important point is that most patients with severe hemophilia will be diagnosed in the first days/weeks of life and therein lies the opportunity to initiate emicizumab at this very early age. Typically, infants with hemophilia will not present with joint or muscle bleeding until at least 9 months of age with the median age of the first joint bleed occurring at 1.9 years of age with an interquartile range of 1.2 to 3 years.²⁴ Experience (supported by the previous data) has compelled the initiation of FVIII prophylaxis at ~1 year of age. But is there a rationale to start prophylaxis before this age? In fact, there is one scenario in which initiating prophylaxis is imperative and one in which starting prophylaxis very early could be considered. For the young infant who has a major bleeding episode such as an intracranial hemorrhage (ICH) postnatally or in the first few months of life, treating the bleed with factor concentrates must occur immediately and, although the duration of therapy is unknown, most treaters would simply continue treatment indefinitely evolving into the usual manner of prophylaxis for older children. However, what about the vast majority of patients who do not experience a severe bleed in the perinatal period or first few months of life—is there a role for initiating emicizumab early to prevent such bleeds? The occurrence of ICH in infants with hemophilia is well known with an incidence of ~6% by 9 months of age for children with severe hemophilia A, after which the incidence flattens out significantly peaking at 8%.²⁵ Although one could argue that such a relatively low rate is not sufficiently high to start all infants on emicizumab, this must be balanced with the potentially devastating neurologic damage that could arise from an ICH no matter how early it is identified and treated. I have asked myself how I would feel if one of my patients develops such an ICH and I had not at least offered emicizumab to the family? The answer has compelled me to have this discussion with the parents of every PUP younger than 1 year of age. That is not to say that it is mandatory to start emicizumab in every infant, but I do recommend that a discussion be had and well documented in the medical record. Clearly, the decision to start emicizumab must be made on a case-by-case basis and will depend on using a shared decision-making approach.

As outlined in the algorithm in Figure 1, the first decision regarding initiating prophylaxis depends on the age of the patient and has been purposely split between PUPs that are more or less than 9 months of age based on the ICH data from the report described previously. It is important to point out here that there are no data (nor likely will there ever be) that can prove that emicizumab is effective in preventing ICH because of the complexities of designing and recruiting enough patients to statistically validate that endpoint. For those patients who have had an ICH, the appropriate immediate treatment is a FVIII concentrate at doses to maintain a FVIII level

between 50% and 100% for the first 1 to 2 weeks following the bleed. As mentioned, the duration needed to treat such a bleed is unknown; however, it is likely that most of these patients will remain on some form of prophylaxis. Ongoing FVIII prophylaxis in a young infant will undoubtedly require a central venous catheter, which has its own set of complications and risks. Thus, is there a role for emicizumab in the subacute phase of managing an ICH? Again, there will likely be no way to definitively prove this; however, taking the data on what is known about the effectiveness of emicizumab in preventing bleeding and with the knowledge that patients are at least converted to a mild hemophilia phenotype, certainly this could be a consideration.^{26,27} As such, one could consider using emicizumab as ongoing prevention of a recurrent ICH after a minimum of 1 to 2 weeks of therapy with FVIII concentrates and with imaging confirming the bleed has improved. The more common scenario will be the newly diagnosed PUP in the first days/weeks of life who may have a non-ICH postnatal bleed (e.g., circumcision) that is treated with a few doses of factor but that has resolved and would not automatically prompt ongoing prophylactic therapy. In this case, the main reason to initiate prophylaxis at an age of <9 months would be to prevent ICH as discussed previously.

For patients in whom the choice is made to start prophylaxis with emicizumab in the first few months of life, the next decision point in the algorithm is when the patient is older (>9 months) and revolves around initiating FVIII concentrate therapy. A major limitation of using emicizumab alone is that it alters the typical history of inhibitor development. Historically, when patients with severe hemophilia A started prophylaxis with FVIII concentrate, they would quickly (within months) reach 50 exposure days, the point at which nearly all patients who develop inhibitors will be found to have an inhibitor. If one chose to initiate prophylaxis with emicizumab alone and did not incorporate any FVIII, it could take >13 years to even reach 20 exposure days because of the effectiveness of emicizumab in preventing bleeding.²⁸ Thus, for such patients, there will be a prolonged at-risk period. Furthermore, whether or not such an approach alters the likelihood of developing an inhibitor (higher, lower, or similar incidence) is unknown. Therefore, in patients who do start emicizumab at a very young age, one could consider adding an FVIII “tolerizing” regimen with the caveat that there are no data to suggest that such an approach that deviates from the usual two to three times per week dosing will offer a tolerizing affect. The Emi-PUPs study (NCT04030052) will aim to address this important question.

For PUPs who have reached the age at which factor prophylaxis can be initiated (>9 months in the algorithm) and have not started emicizumab, the options are to start FVIII prophylaxis, which is the standard/traditional approach, or to start emicizumab. The major concern with starting emicizumab for such patients is the same as for the younger patients revolving around the development of inhibitors as described, and the flow of the algorithm, in fact, merges for both age groups. With respect to factor prophylaxis, the limitations of this approach are the same ones that have been discussed previously regarding both the treatment burden and efficacy in preventing long-term joint damage. Clearly, emicizumab does not require

intravenous access and has a lower treatment burden and although it is presumed to improve adherence, this is not as yet proven. In addition, there are no long-term data on emicizumab, and whether it can prevent joint damage is unknown; however, emicizumab converts patients to a mild hemophilia phenotype^{26,27} and most patients with mild hemophilia do not suffer permanent joint damage. Of course, patients can start prophylaxis with FVIII concentrates and be transitioned to emicizumab at any time if the treatment burden issues become prohibitive. Last, once patients reach 50 exposure days (and are no longer a PUP), they can transition to emicizumab if they so choose without having to be concerned about inhibitor formation (they are, in fact, PTPs at this point).

5 | PREVIOUSLY TREATED PATIENTS

For the sake of this discussion, a PTP is a patient of any age who has reached 50 exposure days to an FVIII concentrate. Although there are data that suggest the inhibitor risk continues until 75 exposure days, the vast majority of inhibitors do occur by 50 exposure days.² The reason for distinguishing PTPs from PUPs lies in the risk for developing an inhibitor. The previous discussion on PUPs delved into the issues of how emicizumab could alter *The Factor Era* natural history of inhibitor formation; however, once a patient is a PTP, the concern for inhibitor formation no longer takes precedence. Keeping this discussion to the prophylaxis situation, by definition, a PTP on prophylaxis will enter this phase of life on FVIII concentrate

therapy. As such, this algorithm (Figure 2) splits the patients into those that are responding well and adherent to those that are not responding well meaning they are having breakthrough bleeding and/or are not adherent. For those that are doing well, they certainly can continue on factor prophylaxis. Despite the earlier comments regarding the lack of prevention of joint damage with FVIII prophylaxis as was seen in some studies, other data suggest that factor prophylaxis can prevent long-term joint damage and result in adults with perfectly functioning joints.²⁹ For those patients who are not doing well with factor prophylaxis as evidenced by breakthrough bleeding or lack of adherence that clearly also will result in breakthrough bleeding, the option to switch to emicizumab should be entertained. The algorithm offers three possibilities including continuing with the current factor product either with a dosing regimen change or if adherence is an issue, support for improved adherence, but in my experience these solutions do not help, especially in the long-term, leaving two other options. If a patient is on a standard half-life FVIII concentrate, switching to an extended half-life concentrate may improve the outcomes. Alternatively, one could switch the patient to emicizumab. One case series noted that the vast majority of switches to emicizumab from factor in a largely adult PTP cohort was due to the lack of efficacy of FVIII therapy to prevent bleeding.³⁰ The limitations of the factor approach are the same as previously discussed, noting in particular that long-term data on the use of extended half-life FVIII concentrates (beyond 5 years) are lacking because it is for emicizumab that the lack of long-term data are the primary limitation.

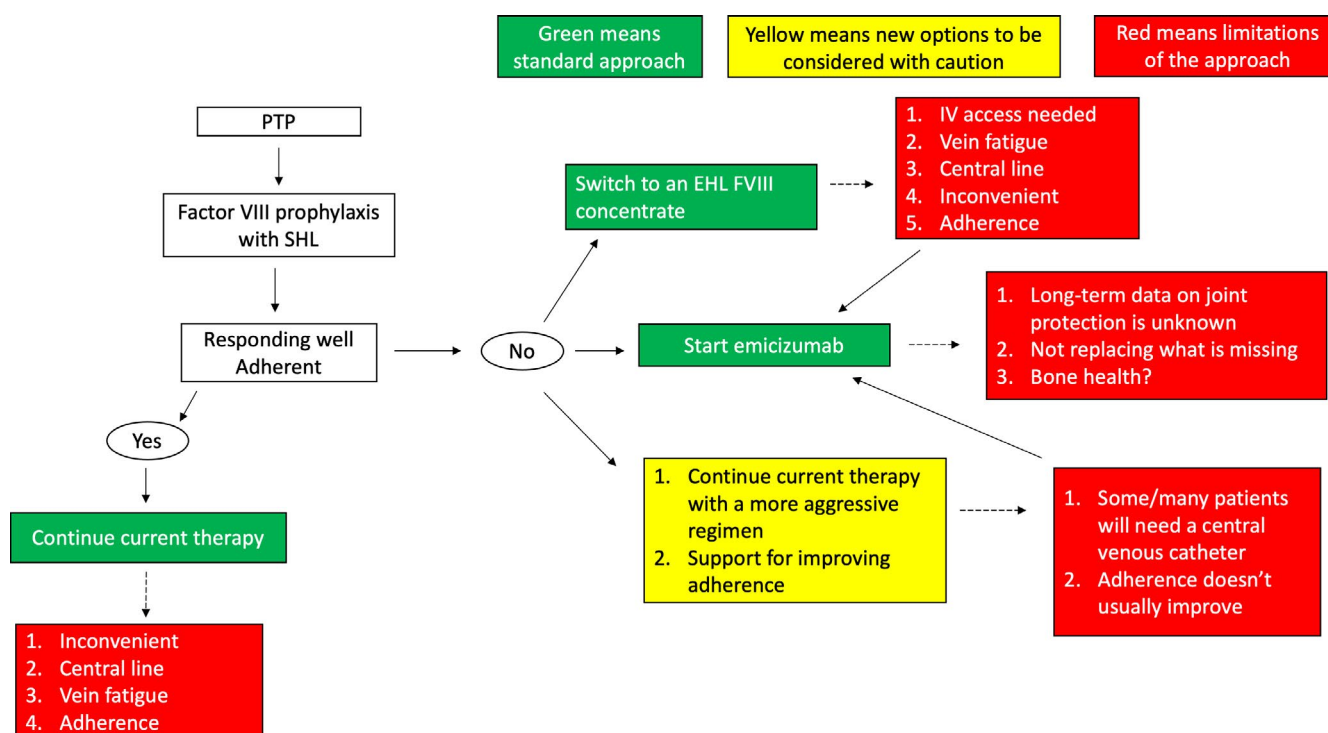


FIGURE 2 Treatment algorithm for the previously treated patient (PTP). Green boxes indicate the standard of care approach, yellow boxes indicate new approaches to be considered with caution, and red boxes indicate the limitations of any of the recommendations

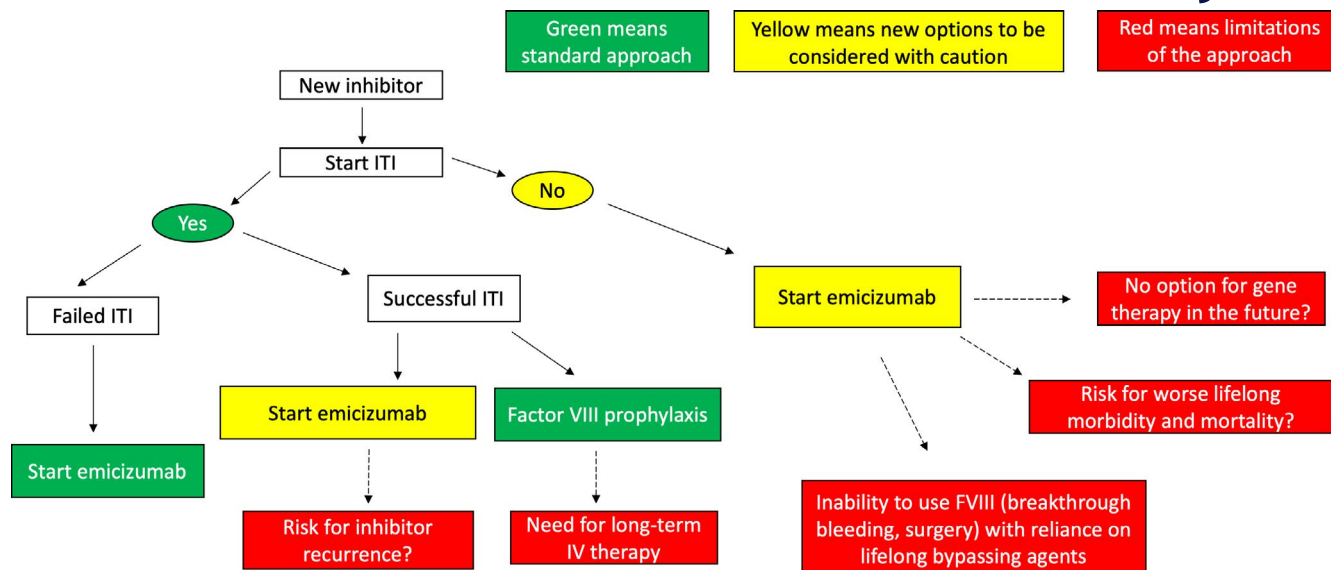


FIGURE 3 Treatment algorithm for new inhibitor patients. Green boxes indicate the standard of care approach, yellow boxes indicate new approaches to be considered with caution, and red boxes indicate the limitations of any of the recommendations

6 | INHIBITOR PATIENTS

The patient that develops an inhibitor to FVIII concentrates remains a vexing problem. Nearly all new inhibitor patients present in the first few years of life, corresponding with when they initiate FVIII therapy. About 70% of inhibitors will present within the first 20 exposure days and >95% by 50 exposure days.² Thus, once factor therapy, especially in the form of prophylaxis, is initiated, it takes only several months to reach these exposure days. Once an inhibitor is identified, the treatment must follow a two-pronged approach, including inhibitor eradication and bleed management. Although the new era has led to some debate regarding whether inhibitor eradication via immune tolerance induction (ITI) should even be performed, the general consensus at least as of now is that eliminating the inhibitor is an important goal.³¹⁻³³ Nevertheless, the algorithm for the newly diagnosed inhibitor patient (Figure 3) offers both options, although the suggestion not to do ITI is in yellow, meaning it should be considered with caution and incorporate the limitations in the red boxes that follow that option. For patients who undergo ITI yet do not have their inhibitor eliminated, the clear option is to start emicizumab. It has been shown in both the HAVEN 1 and 2 studies to be far superior to either an episodic approach or a bypassing agent prophylaxis approach.^{12,13} For those in whom ITI is successful, they are left with a quandary that will be discussed in the next section.

A detailed discussion of ITI is outside the scope of this Forum Article; however, the following reference goes into much more detail.⁵ The questions facing the clinician today with the availability of emicizumab beyond whether to perform ITI at all revolve more around how to perform ITI. This question dovetails with the bleed management approach. It is now considered the standard approach to start all high-titer inhibitor patients on emicizumab. It has been shown in the HAVEN 2 study to reduce the likelihood of bleeding in children with

inhibitors by 99%.¹² As such, if emicizumab is going to be prescribed for newly diagnosed children with inhibitors, this changes the considerations regarding the most appropriate ITI regimen. The International ITI study demonstrated that both the high-dose ITI regimen (200 IU/kg/day) and the low-dose ITI regimen (50 IU/kg every other day) were ultimately equally effective at inducing tolerance.³⁴ The study was stopped early because subjects on the low-dose arm had more bleeding events. Notably, the higher dose regimen resulted in more rapid tolerization; however, if emicizumab can almost completely prevent bleeding events, then one must question whether the burden of daily factor infusions and the substantially (eight-fold) higher cost of the high dose regimen is worth achieving tolerance just a few months faster. It is just such discussions that have led to the adaptation of an ITI approach that incorporates the low-dose regimen (or at least a lower dose than 200 IU/kg per day) along with emicizumab as novel treatment strategy for newly diagnosed inhibitor patients. This has been put forth both by the Future of Immune Tolerance Group³¹ and the Atlanta group,³⁵ and an extensive discussion regarding ITI in this new era can be found in those references.

7 | THE TOLERIZED PATIENT

The fourth and final algorithm (Figure 4) builds off of Figure 3 and is for patients who were successfully tolerized. Before the availability of emicizumab, patients who were successfully tolerized would be transitioned to FVIII prophylaxis with the notion (though with no data to support it) that the ongoing exposure of the immune system to FVIII was “maintaining” their tolerance. In fact, the only study that addresses this issue at all, albeit a retrospective case series, hints that ongoing FVIII treatment may not be necessary.³⁶ With the availability of emicizumab, one now has the option to treat with

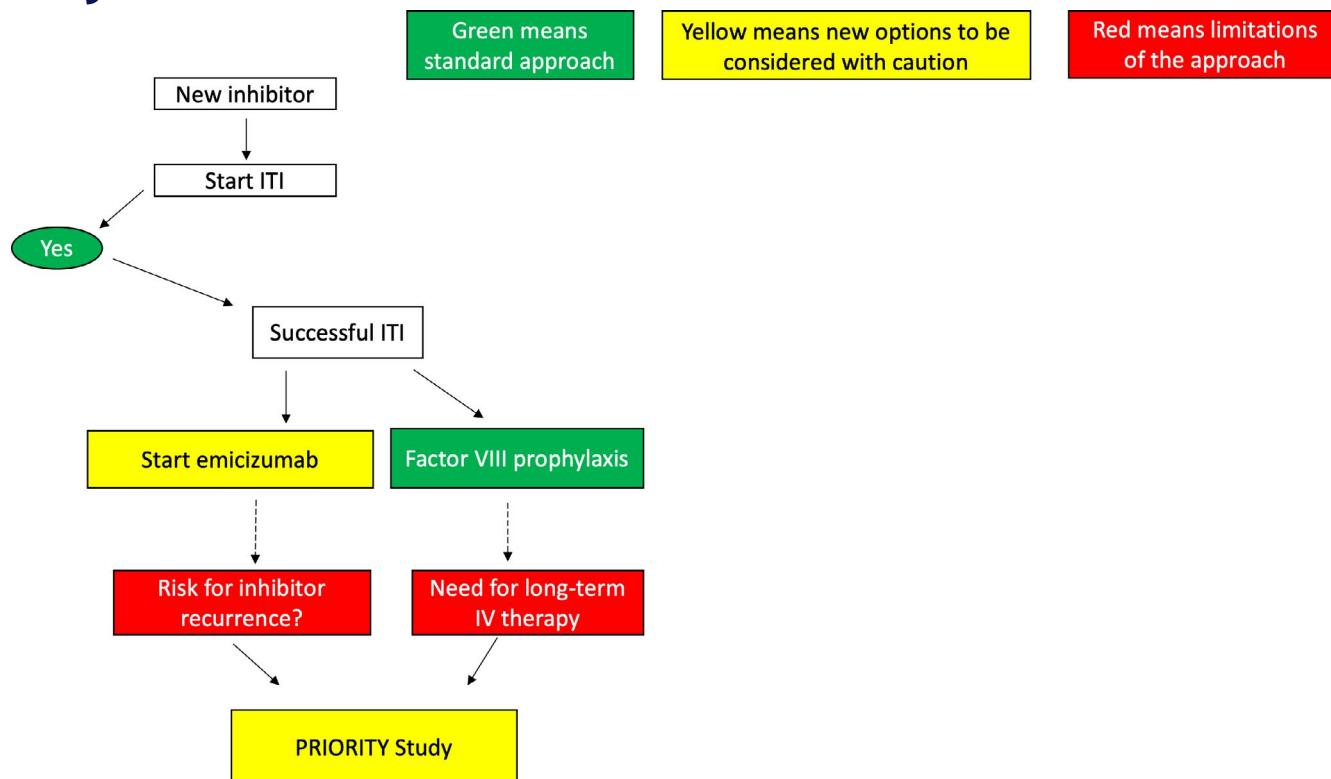


FIGURE 4 Treatment algorithm for tolerized inhibitor patients. Green boxes indicate the standard of care approach, yellow boxes indicate new approaches to be considered with caution, and red boxes indicate the limitations of any of the recommendations

either FVIII prophylaxis or emicizumab. The limitations of ongoing FVIII in this now-tolerized patient have been previously discussed. Although the decision to simply switch to emicizumab at this point may seem straightforward given its advantages over FVIII therapy, the issue here revolves around the risk for inhibitor recurrence. Simply put, there are no data that can support either side of this argument. The PRIORITY study (NCT04621916) is a new study that will randomize successfully tolerized patients to emicizumab alone or emicizumab plus weekly “tolerance-maintaining” FVIII treatment. It will take a few years in all likelihood to complete this study; thus, it is not possible at this time to recommend either FVIII prophylaxis or emicizumab and short of having these patients participate in the PRIORITY study, the clinician will have to make a decision on which approach they and their patient prefer on a case-by-case basis.

8 | CONCLUSION

In summary, the availability of emicizumab has significantly up-ended the traditional approach to the management of children with hemophilia A affecting every leg of the patient journey from PUP to PTP and for those who develop inhibitors, from pre-ITI to ITI to post-ITI. There are strong data to suggest emicizumab has become the standard of care for patients with inhibitors. For the majority of patients that do not develop inhibitors, and so have the option of FVIII concentrates, for whom and when to use emicizumab remains

controversial. Even for patients with inhibitors, although emicizumab should be prescribed to prevent bleeding, issues surrounding whether, in whom, and how to perform ITI remain, and for those who have been successfully tolerized, how to move forward with either FVIII or emicizumab or some combination of both is entirely unclear. For some of these scenarios (PUPs, ITI, and post-ITI), clinical trials are under way, but for other scenarios (prevention or treatment of ICH), it is unlikely that definitive studies are feasible. Regardless, the addition of emicizumab to the armamentarium of treaters who care for children with hemophilia has been a very welcome addition, albeit one that has presented new challenges. Finally, emicizumab is only effective in hemophilia A and thus the discussion of patient scenarios will only apply to hemophilia A patients; however, once other subcutaneously administered therapies that can also be used in hemophilia B are made available such as fitusiran, concizumab, marstacimab, and others, similar questions will arise. Therefore, although the algorithms in the subsequent section are written for hemophilia A patients, I encourage the reader to visualize similar algorithms for hemophilia B patients once novel agents that are safe and effective in hemophilia B are made available.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Guy Young developed the algorithms and conceived of the idea and wrote and edited the manuscript.

ORCID

Guy Young  <https://orcid.org/0000-0001-6013-1254>

TWITTER

Guy Young  @GuyYoungMD

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