



NATIONAL HEMOPHILIA FOUNDATION

for all bleeding disorders

MASAC Document #268
(Replaces Document #258)

RECOMMENDATION ON THE USE AND MANAGEMENT OF EMICIZUMAB-KXWH (HEMLIBRA®) FOR HEMOPHILIA A WITH AND WITHOUT INHIBITORS

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on March 11, 2022, and adopted by the NHF Board of Directors on April 27, 2022.

A. Introduction

Emicizumab is a recombinant, humanized, bispecific immunoglobulin G4 monoclonal antibody that substitutes for part of the cofactor function of activated factor VIII (FVIIIa) by bridging activated factor IX (FIXa) and factor X (FX). It is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children of all ages, newborn and older, with hemophilia A with and without FVIII inhibitors. The medication is given subcutaneously at a loading dose of 3 mg/kg weekly for 4 doses, followed by one of three subsequent maintenance dose regimens: either 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks.

There is significant reduction in annualized bleeding rates at all doses for all age groups, with or without inhibitors. FVIII and emicizumab are fundamentally different proteins and are regulated differently. Some of the differences are show in Table 1.

Table 1. Comparison of FVIII and emicizumab (Adapted from Lenting P et al. Blood 2017)

| FVIII | Emicizumab |
|--|--|
| Multiple sites of interaction (FIXa, FX and phospholipid surfaces) | Single sites of interaction (FIX/FIXa and FX/FXa) |
| High affinity for enzyme and substrate (low to high nanomolar range) | Low affinity for enzyme and substrate (micromolar range) |
| Full cofactor activity ■ Promote phospholipid binding | Partial cofactor activity ■ Bridges FIXa to FX |
| Enzyme and substrate are in excess over cofactor | Antibody is in excess over enzyme and substrate |
| FVIIIa has on/off mechanism | Emicizumab has no on/off mechanism |
| High level of self-regulation | Low level of self-regulation |
| Administered intravenously | Administered subcutaneously |
| Half-life is hours to days | Half-life is weeks |

B. Clinical Management Guidance

1. Who is appropriate to be considered for treatment with emicizumab?

Physicians/advanced practice providers caring for persons with hemophilia A (PwHA), of any age or severity, with or without inhibitors should discuss this new therapeutic option with

them, including an assessment of the risks and benefits of emicizumab compared to their existing therapy. Emicizumab is approved for PwHA with or without inhibitor of any age.

Based on the clinical trial data, any PwHA with an inhibitor who has spontaneous or traumatic bleeding episodes, whether treated with episodic or prophylactic bypassing agent (BPA), will likely derive significant benefit from emicizumab prophylaxis and it should be considered first-line of therapy. Those on BPA prophylaxis with few bleeding episodes could consider switching from BPA prophylaxis to emicizumab prophylaxis based on overall cost-effectiveness, reduced administration burden and overall superior hemostatic efficacy.

In addition, infants should be considered for prophylaxis with emicizumab at any time after birth given the increased risk of intracranial hemorrhage prior to initiation of FVIII prophylaxis. At this time both FVIII prophylaxis and emicizumab prophylaxis should be considered therapeutic options for primary and secondary prophylaxis. Note, there are currently limited clinical trial data on the use of emicizumab in infants under 6 months of age and the pharmacokinetic exposure is likely to be less than in older infants and children. However, accumulated single institution and sponsored clinical trial experience supports the prophylactic efficacy of emicizumab in infants. We strongly encourage prospective data collection concurrent with its use in this age group through sponsored clinical trials, American Thrombosis and Hemostasis Network (ATHN) studies and the Centers for Disease Control and Prevention (CDC) CDC Registry for Bleeding Disorders Surveillance.

2. Recommendations for initiation of emicizumab

a. PwHA and inhibitors

Administration of aPCCs should be discontinued at least 24 hours prior to initiation of emicizumab.

b. PwHA and no inhibitors

FVIII prophylaxis continuation during the week after initiation of emicizumab is a common and reasonable approach. However, given that steady-state levels of emicizumab are not achieved until after four weekly doses of 3 mg/kg, it may be reasonable to continue FVIII prophylaxis in select individuals based on their bleeding history and physical activity level, until they are ready to start maintenance dosing.

c. Standard patient education

- i. Loading dose(s) should be given under medical supervision in order to review and observe self-administration technique. If the loading dose (in mg) is different than the maintenance, then patients should be educated about the dose and how to prepare it.
- ii. Emicizumab vials should be visually inspected for particulate matter and discoloration before administration. Emicizumab for subcutaneous administration is a colorless to slightly yellow solution. Do not use if particulate matter is visible or product is discolored and contact the hemophilia treatment center (HTC) and manufacturer so the vial can be returned.
- iii. PwHA should know how to recognize bleeding events, follow the prescribed clotting factor product dose and frequency (FVIII concentrate or BPA for a breakthrough bleed, and reporting all bleeds to the HTC.

- iv. PwHA with inhibitors should understand that rFVIIa is the preferred BPA for management of acute bleeding due to risks of thrombosis and thrombotic microangiopathy (TMA) with activated prothrombin complex concentrate (aPCC). Rarely low doses of aPCCs can be considered in management of acute bleeding events but should be considered in bleeding events refractory to rFVIIa (see Recommendations on acute bleed management section C.iii). PwHA with inhibitors should know how to recognize and seek help for signs and symptoms of thrombosis.

***Full prescribing information is available in the package insert. In addition, the prescribing information contains a boxed warning regarding the risk of thrombotic microangiopathy (TMA) and thromboembolism. These adverse events have occurred in association with the use of activated prothrombin complex concentrates (aPCC) to treat breakthrough bleeding in patients receiving emicizumab. Therefore, for patients with inhibitors and an acute bleed, recombinant FVIIa (rFVIIa) is recommended over aPCC. A bleed management plan should be developed and managed in close coordination with appropriate staff of the patient's HTC, including physicians/advanced practice providers, nurse coordinators, and pharmacy staff. The following recommendations are intended to address clinical management issues that are not addressed fully within the package insert.**

- v. PwHA with FVIII inhibitors should be warned that if they stop emicizumab, residual plasma levels may persist for as long as 6 months, and thus, risk mitigation regarding the use of aPCCs should be considered during that 6-month period to avoid the risk for thrombotic and TMA complications.
- vi. Reminding that when emicizumab is re-ordered, patients must provide their current weight to assure proper dosing and proper vial combinations to achieve the calculated dose. Patient should develop a plan to ensure adequate supply of emicizumab to avoid missed doses of prophylaxis. Instructing patients to give missed dose as soon as they remember and not to give two doses on the same day.
- vii. PwHA must contact the HTC in the event of surgery, whether elective or emergent, to assure a plan for treatment is developed, including if any clotting factor product will be used, and, if so, at what dose and frequency, and if antifibrinolytic agents are advised.
- viii. Regular clinical review of the efficacy for bleed prevention should be conducted once the PwHA has reached the maintenance dosing and every 6 months after initiation of therapy and as clinically indicated.
- ix. Loss of hemostatic efficacy should prompt evaluation for anti-drug antibodies (see below).
- x. PwHA should be counseled to travel with emergency dose(s) of factor concentrate to allow prompt management of any *significant and serious or life-threatening bleeding* (MASAC Recommendation #257).
- xi. Revised ED and travel letters should include:
 - i. Information that the patient is on emicizumab prophylaxis.
 - ii. The potential impact on laboratory assays and acute bleed management.
 - iii. Contact information for the HTC.

- xii. Instructions on Travel:
 - i. Revised travel letter as detailed above.
 - ii. Need to travel with multiple appropriate doses of FVIII concentrate or BPA to manage breakthrough bleeding.
- xiii. Provision of dosing cards or treatment letters that detail the dose and frequency of FVIII concentrate or BPA for management of breakthrough bleeding.
- d. Instructions on when to call the HTC:
 - i. When uncertain about whether or not symptoms are consistent with bleeding and should be treated.
 - ii. For breakthrough bleeding events requiring treatment.
 - iii. For significant trauma including, but not limited to, head trauma.
 - iv. For emergent or scheduled surgery, including invasive dental work.

3. Recommendations on Acute Bleed Management – PwHA and Inhibitors

Despite the efficacy in the prevention of bleeding events, clinicians and patients should still expect breakthrough bleeding events in persons on emicizumab prophylaxis, which in PwHA with inhibitors will likely mean the need for concomitant use of alternative hemostatic therapies. Due to the serious adverse events observed in the clinical trial program and following completion of the trial, we recommend the following guidance on management of breakthrough bleeding, prevention of and surveillance for thromboembolic and TMA events, and appropriate use of laboratory assays. TMA and serious thrombotic events can largely be avoided by adherence to these management principles as has been observed since commercial availability in pediatric and adult patients. When treating with rFVIIa or aPCC, the patient's prothrombotic risk factors including but not limited to cigarette smoking, obesity, cardiovascular disease, and previous history of venous or arterial thrombosis should be considered due to potential risk of venous and arterial thrombosis.

- a. General approach to breakthrough bleeding: Emicizumab is likely to transform the bleeding phenotype of PwHA to a milder phenotype with a significant reduction in the number of doses of BPA needed for many bleeding events requiring treatment.
Significant and serious or life-threatening bleeding should continue to be treated promptly.
- b. For PwHA and low responding inhibitors acute bleeding events may be managed with high dose FVIII. Surveillance of the inhibitor titer and evaluation of incremental recovery is strongly advised to determine whether high dose FVIII can be effectively used.
- c. Antifibrinolytics may be used in combination with BPA when clinically indicated for mucosal bleeding.

4. Caution with dose and duration of BPA:

- a. Acute bleeding events should be managed with rFVIIa, eptacog alfa (NovoSeven RT) at a dose of 90-120 mcg/kg as an initial dose. The vast majority of bleeds should be able to be managed with 1-3 doses administered at no more frequency than q2h intervals. Alternatively, consideration of rFVIIa, eptacog beta (SEVENFACT) at a dose of 75

mcg/kg as an initial dose. The vast majority of bleeds should be able to be managed with 1-3 doses at no more frequent than q3h intervals. There is significantly more clinical data to support eptacog alfa over eptacog beta. Refer to MASAC Document 233 for details regarding eptacog beta.

- b. Use of aPCC for breakthrough bleed treatment for patients on emicizumab should be avoided if possible, and rFVIIa should be the first option used to treat acute bleeding events as the use in combination with emicizumab does not alter the rFVIIa safety profile. If aPCC is used, it should be limited to no more than 50 IU/kg administered as an initial dose and not exceed 100 IU/kg/day. Duration of aPCC therapy should also be minimized, as prolonged use for >24 hours with doses above 100 IU/kg/day may be associated with thrombosis and TMA.
- c. Repeated dosing of any BPA beyond the above recommendations should be performed under medical supervision with consideration and verification of the severity of the bleeding event prior to continuing to repeat dosing.
- d. For significant bleeding that is not responding to any of the approved BPAs, consider using porcine FVIII. Use of these agents would also allow therapeutic monitoring with the bovine chromogenic assay.
- e. Clinical and laboratory monitoring: All patients on emicizumab prophylaxis who have received aPCC for breakthrough bleeding for more than 24 hrs should do so in close contact with their treatment team for the duration of the aPCC course. They should be evaluated for any clinical symptoms that could be consistent with a thromboembolic event (with a high level of suspicion for atypical sites, e.g. cerebral sinus venous thrombosis), and have clinical evaluation for hypertension and proteinuria to look for evidence for TMA. Laboratory monitoring should include complete blood count, peripheral blood smear analysis to look for schistocytes, D-dimer, prothrombin fragment F1+2 (if available), haptoglobin, bilirubin, serum creatinine, LDH and troponin. For patients who require aPCC beyond the recommended dose and duration guidelines, consider daily laboratory monitoring.
- f. Management of TMA: Use of aPCC should cease immediately. The half-life of emicizumab is >28 days and it will remain in the patient's system for months after discontinuation of emicizumab. Each of the reported cases of emicizumab+aPCC TMA resolved quickly after discontinuation of aPCC with supportive care alone or in conjunction with plasmapheresis. In the 2 cases treated with plasmapheresis, emicizumab was not completely removed and in spite of discontinuation of emicizumab one of these patients had measurable emicizumab laboratory effects for several months. Emicizumab has been restarted successfully in patients without recurrence of TMA.

5. Recommendations on Acute Bleed Management – PwHA without inhibitors

Despite the efficacy in the prevention of bleeding events, clinicians and PwHA should still expect breakthrough bleeding events in patients on emicizumab prophylaxis, which in PwHA without inhibitors will likely mean the need for concomitant use of FVIII replacement therapy. No serious adverse events have been observed related to concomitant use of FVIII concentrates in patients on emicizumab prophylaxis. Specifically, no thrombotic or TMA events have been observed. Below are some specific guidelines for consideration in this patient group.

- a. General approach to breakthrough bleeding: Emicizumab is likely to transform the bleeding phenotype of PwHA without inhibitors to a milder phenotype with a significant reduction in bleeding events requiring treatment. *Significant and serious or life-threatening bleeding should continue to be treated promptly.*
- b. All FVIII concentrates (plasma-derived and recombinant standard half-life and extended half-life) may be used for breakthrough bleeding events. Dosing should follow the same recommendations as when the patient was on FVIII replacement therapy (MASAC Recommendation #257).
- c. Antifibrinolytics may be used in combination with FVIII concentrates when clinically indicated for mucosal bleeding or for minor oral procedures.

6. Recommendations on laboratory assays while on emicizumab

Although emicizumab mimics the function of FVIIIa, it is biologically different from FVIIIa, having a much lower affinity for factor IXa and X, not requiring activation, and not deactivated by the protein C/S pathway. These fundamental differences affect interpretation of clotting assays.

- a. Laboratory monitoring of emicizumab is not required while on routine prophylactic dosing.
- b. aPTT-based assays, including clot-based FVIII activity assays, should not be performed while on emicizumab, as they will yield misleading results (ie. artefactually shortened aPTT and very elevated FVIII activity).
- c. Chromogenic FVIII activity assays will only provide an assessment of emicizumab activity if the assay includes all human reagents, but these are not widely available. A chromogenic FVIII assay that uses bovine reagents may be used to assay the FVIII activity of any additional FVIII concentrate administered or endogenous FVIII.
- d. The clot-based Bethesda assay cannot be utilized to assess for a FVIII inhibitor. However, a bovine-reagent chromogenic-based inhibitor assay can report out a FVIII inhibitor titer. If samples are submitted to the Centers for Disease Control and Prevention (CDC) for central laboratory testing, they must be clearly identified that the patient is on emicizumab.
- e. Exploratory laboratory assays include thromboelastography/thromboelastometry/thrombin generation and clot waveform analysis. These and other assays under continued investigation are likely to allow for quantitation of emicizumab concentration from plasma. However, due to the intrinsic differences between emicizumab and FVIII, this complicates assignment and interpretation of FVIII-equivalent activity. Caution should remain in extrapolating clinical correlates using 'FVIII-equivalence' from such assays until further clinical data is available. It may be useful in determining whether a patient may potentially have an anti-drug antibody and to determine how much emicizumab may be available in the patient.
- f. Anti-drug antibodies:

- i. The prescribing information for emicizumab includes important safety information on the risk for anti-drug antibodies (ADAs). Use of any therapeutic protein carries the potential for the development of ADAs. These were observed within the global clinical trial program with emicizumab and are described within the US and European Union (EU) emicizumab product labels. The immunogenicity of emicizumab was evaluated using an enzyme-linked immunosorbent assay or an electrochemiluminescence assay. In the dose-finding trial (n = 18), four patients tested positive for ADAs. In the pooled clinical trials, 5.1% of patients (34/668) tested positive for anti-emicizumab antibodies and <1% developed ADAs with neutralizing potential (based on declining pharmacokinetics). One patient from HAVEN 2, who developed an ADA, experienced loss of efficacy after 5 weeks of treatment. There was no clinically apparent impact of the presence of ADAs on safety. Two of 88 children in HAVEN 2 developed ADAs with one patient having loss of emicizumab efficacy.
- ii. The development of an anti-drug antibody to emicizumab is distinct from the development of an inhibitor to FVIII. Notably, anti-drug antibodies directed against emicizumab may affect how it works in the patient but will not affect the person's underlying hemophilia or inhibitor status, nor the ability to manage bleeding events with their conventional therapies, including BPA.
- iii. Continued diligence in evaluation of clinical efficacy of emicizumab as would be expected for any hemophilia therapeutic. Loss of efficacy of emicizumab may be manifest by an increase in breakthrough bleeding events. Patients concerned about a loss of efficacy should seek prompt evaluation by their provider.
- iv. We have provided information on assays that may be utilized for evaluation of the activity of emicizumab, utilizing a chromogenic FVIII activity assay with human reagents that are recognized by emicizumab. However, the widely available conventional aPTT and clot-based FVIII activity assays can be used in evaluating a case of loss of efficacy. The aPTT should be within the normal range in all persons with hemophilia when obtained during ongoing treatment with emicizumab; similarly, clot-based FVIII activity assays will be well above the normal range. In the course of evaluating a reported loss of efficacy, a prolonged conventional aPTT assay and/or a low FVIII activity (by clot-based assay or chromogenic assay using human reagents) in a person treated with emicizumab should be a useful initial evaluation for the presence of a neutralizing anti-drug antibody directed against emicizumab in cases of near complete neutralization. Therapeutic levels of emicizumab are around 45-60 mcg/mL and the aPTT will be normal until the emicizumab level drops below 3 mcg/mL. Additional information regarding laboratory assays may be found within the prescribing information.
- v. There are no commercially available assays in the US for determination of anti-drug antibodies directed against emicizumab. Should a patient and provider have suspicion of an anti-drug antibody outside of the ongoing clinical trial program, they should contact the manufacturer (<https://www.gene.com/contact-us/submit-medical-inquiry>) for guidance on subsequent evaluation.
- vi. Recommend that patients and providers continue diligence in reporting any unanticipated adverse events. Available reporting mechanisms can be reviewed here

7. Recommendations on surgical management with emicizumab

Emicizumab is approved for prophylaxis, but how this extends to surgical prophylaxis remains to be fully understood. While it improves hemostasis, it does not normalize hemostasis. This is especially important when planning hemostatic control in the surgical setting. Within the clinical trials, some patients had adequate hemostatic control with emicizumab alone for minor surgical procedures while others did not. This is like what has historically been seen in patients with mild hemophilia.

- a. Surgeries should be conducted at centers with appropriate experience and access to necessary laboratory monitoring assays for concomitant use of hemostatic agents.
- b. Elective surgeries should be conducted after PwHA have completed the loading dose phase and are at steady state maintenance dosing (following week 5).
- c. Emicizumab alone should not be presumed to be adequate for major procedures where current standards of care are to maintain factor levels within the normal range for a period of days.
- d. Close monitoring of bleeding control as well as access to appropriate laboratory assays to monitor therapy (eg. chromogenic FVIII assay with FVIII replacement) is very important when determining treatment plans for patients on emicizumab needing surgical procedures.
- e. For major surgeries and procedures where bleeding could result in serious complications, patients should be provided rFVIIa or FVIII replacement pre- and post-operatively to maintain adequate hemostasis at the discretion of the treating physician. Anti-fibrinolytics may also be part of the perioperative management plan. Further research/experience is needed to form better defined treatment plans for different surgical procedures.
- f. Providers are cautioned to consider that bleeding complications from surgeries in patients with hemophilia still greatly outweigh thrombotic complications in frequency and morbidity/mortality.

8. Recommendations on concomitant use of emicizumab during immune tolerance induction.

There are limited data on the concomitant use of emicizumab prophylaxis during immune tolerance induction (ITI). Batsuli et al. described a case series of children with hemophilia A and inhibitor who underwent ITI in combination with emicizumab prophylaxis (Atlanta Protocol), and 2 larger clinical trials of this protocol are underway. MASAC recommends that the pros and cons of the various approaches for PwHA and inhibitors be part of a patient/clinician shared decision-making and ITI should remain an option for their care. It is reasonable to offer ITI regardless of age and previous attempts without the combination of emicizumab. We also recommend that long term follow-up and interventional trials that include the concomitant use of emicizumab with ITI should be encouraged. If ITI with concomitant emicizumab prophylaxis will be pursued, we provide the following recommendations:

- a. No more than 50-100 IU/kg per dose of FVIII for ITI be administered unless observation will occur within a clinical trial. This relates to the uncertainty as to any potential incremental risk of an elevated FVIII level, even transiently, in patients on emicizumab who may need treatment with a BPA for breakthrough bleeding during ITI.
- b. Data on the use of emicizumab prophylaxis with ITI should be conducted under a clinical trial or as part of existing databases collecting data on the natural history of emicizumab use within the US (see below).

9. Other unresolved issues and potential new avenues of research

- a. MASAC recognizes the potential utility of emicizumab prophylaxis in patients with severe Type 3 VWD with inhibitors to von Willebrand factor. An investigator-initiated study is underway and hemostatic efficacy has been reported in limited case reports.
- b. ATHN TRANSCENDS is a natural history including PwH treated at US HTC. Data collection includes data on PUPs as well as PwH treated with emicizumab.
- c. We encourage additional investigations to determine potential safe and efficacious dosing of aPCCs with concurrent emicizumab. There are multiples studies investigating the optimal dose of aPCC to achieve targeted thrombin generation while on emicizumab.
- d. We encourage the continued accumulation of management of surgical experiences in patients prescribed emicizumab.
- e. Important clinical trial data are being collected in mild and moderate hemophilia A without inhibitors. HAVEN 6 is a study to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in participants with mild or moderate hemophilia A without FVIII inhibitors (NCT04158648). Interim analysis suggests that emicizumab is hemostatically efficacious in non-severe hemophilia A. The exact FVIII level in which there is diminishing returns is unclear at this time.
- f. There are insufficient data on the level of protection provided by emicizumab prophylaxis to patients who participate in high impact activities/organized sports and MASAC encourages additional research to study this. The STEP study is an observational cohort study seeking to compare FVIII and emicizumab for the prevention of bleeding in persons with moderate and severe hemophilia A participating in sports (NCT 05022459).
- g. The Hemophilia Inhibitor Prevention trial (NCT 04303559) is a phase III multi-center randomized clinical trial in which prophylaxis with rFVIIIc will be compared with emicizumab, using an adaptive design, to prevent inhibitors in persons with severe hemophilia A without an inhibitor.
- h. The Hemophilia Inhibitor Eradication trial (NCT 04303572) is a phase III multi-center randomized clinical trial in which rFVIIIc ITI plus Emicizumab will be compared with rFVIIIc ITI alone to eradicate inhibitors in persons with severe hemophilia A and inhibitors.
- i. The use of emicizumab prophylaxis in ITI will be explored in the MOTIVATE study (NCT 04023019). The purpose of the study is to capture different approaches in the

- management of persons with hemophilia A and FVIII inhibitors, document current immune tolerance induction approaches, and evaluate the efficacy and safety of immune tolerance induction, including the combination of FVIII and emicizumab.
- j. There is theoretical data on the role of low dose structured FVIII exposure in mitigating the risk of FVIII inhibitors in PUPs. Efforts on mitigating the risk of inhibitors have largely failed other than the use of plasma-derived FVIII in PUPs at low risk for inhibitor development. In 2010, Kurnik published their data on 26 consecutive PUPs receiving low dose (25 U/kg) FVIII infusions peripherally once weekly at the sign of any bleeding tendency. After >100 EDs, only 1 of 26 (4%) PUPs developed an inhibitor, compared with 14 of 30 (47%) also consecutive PUPs in the historical comparator group. A sponsored study was attempted and prematurely terminated due to futility and a similar inhibitor prevalence was demonstrated (42.1%) as historical controls. This concept was revived following the approval of emicizumab in young children. Limiting bleeding events in a PUP on emicizumab prophylaxis while introducing low dose FVIII weekly or every other week potentially could mitigate the risk of inhibitor development in certain unknown populations. At this time there is no data to support this strategy, but it is under investigation. The Emicizumab PUPs and Nuwiq ITI study (The Atlanta study; NCT04030052) is a two-part study that will investigate the role of structured low dose FVIII in PUPs to reduce the incidence of FVIII inhibitors while on emicizumab prophylaxis. In part two of the study the role of 100 units/kg three times a week human cell line derived recombinant FVIII in inhibitor eradication.
 - k. The PRIORITY trial (NCT04621916) is a study that will evaluate the inhibitor recurrence with or without ongoing FVIII exposure in patients with hemophilia A on emicizumab prophylaxis after a successful immune tolerance induction.

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