

Profile of Factor VIII Inhibitor Development in Adult Patients With Hemophilia A: An Observational Study in Surabaya, Indonesia

Raditya Rahma Fatih,^{1*} Ami Ashariati,^{2,3} S. Ugroseno Yudho Bintoro,^{2,4} Merlyna Savitri,^{2,4} Arfika Wida Ekacitta,^{5,6} Alfiani Rahmi Mukti^{7,8}

¹Department of Internal Medicine, Muhammadiyah Lamongan Hospital, Lamongan, Indonesia (<https://orcid.org/0009-0002-3640-1394>)

²Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

³Division of Hematology and Medical Oncology, Department of Internal Medicine, Universitas Airlangga Hospital, Surabaya, Indonesia

⁴Division of Hematology and Medical Oncology, Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

⁵Department of Internal Medicine, Sumberrarjo Regional Hospital, Bojonegoro, Indonesia (<https://orcid.org/0000-0002-2114-7840>)

⁶Department of Internal Medicine, Temayang Regional Hospital, Bojonegoro, Indonesia (<https://orcid.org/0000-0002-2114-7840>)

⁷Internal Medicine Specialist Study Program, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia (<https://orcid.org/0009-0009-9032-1039>)

⁸Internal Medicine Specialist Study Program, Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (<https://orcid.org/0009-0009-9032-1039>)

*Corresponding author: Raditya Rahma Fatih, Department of Internal Medicine, Muhammadiyah Lamongan Hospital, Lamongan, Indonesia. E-mail: radityarahmaf@gmail.com

ABSTRACT

Background: Inhibitor development was hemophilia treatment major complication. Inhibitor disturbed clinical response to replacement therapy affecting patient's morbidity and quality of life. Its mechanism was multifactorial, that was patient- and therapy-related. Genetic and inhibitor test weren't done routinely and they were high-priced. Hence risk factor identification was important to predict inhibitor development.

Aim: To know prevalence, socio-demographic and clinical characteristics and inhibitor FVIII development predictors in haemophilia A patients.

Method: This was a cross-sectional observational descriptive research in adult haemophilia A patients in Medical Oncology and Haematology dr. Soetomo General Teaching Hospital Surabaya and its satellite hospital from May until August 2023. FVIII inhibitor development predictors were disease degree, starting age of therapy, replacement therapy type and therapy intensity. FVIII inhibitor level was determined using Bethesda assay.

Result: Out of 30 subjects, inhibitor prevalence was 16,7%. Its median was 5,3 BU. The mean age was 31 years old and 97% of the subjects were male, 40%, 54% and 7% of the subjects were mild, moderate and severe haemophilia, respectively. FVIII inhibitor was detected in all severe haemophilia subjects, 25% subject was given first therapy when they were < 18 years old, 20% subject was given recombinant type and 24% subject had once a week injection.

Conclusion: FVIII inhibitor prevalence was 16,7%. Positive FVIII inhibitor was frequently found in severe haemophilia, starting age of therapy was < 18 years old, recombinant type therapy and had once a week injection.

Key words: inhibitor, FVIII, hemophilia A, human and health, vulnerable.

INTRODUCTION

Hemophilia A is a coagulation disorder caused by a deficiency or dysfunction of factor VIII (F8), which is inherited in an X-linked recessive manner through the X chromosome (X^h).^{1,2} In 2020, the World Federation of Hemophilia (WFH) reported 209,614 hemophilia patients worldwide, 161,379 of whom had hemophilia A, while in Indonesia alone there were 2,334 patients with hemophilia A.³ One of the severe complications in patients with hemophilia A is the development of neutralizing alloantibodies, or inhibitors, against clotting factors—in this case, F8—which frequently occurs in patients with severe disease, thereby affecting their morbidity and quality of life.⁴ The incidence of inhibitor development is 2–3%, or approximately 14.7 per 1,000 person-years.⁵ Factors contributing to the development of F8 inhibitors include the type of genetic mutation, the severity of hemophilia, a younger age at the time of hemophilia diagnosis and initiation of replacement therapy, and higher and more frequent doses of F8; however, the type of replacement therapy—whether plasma concentrate or recombinant—does not influence inhibitor development.^{6–10} Therefore, inhibitor development is a significant challenge in the treatment of patients with hemophilia, making management more difficult and resulting in higher morbidity and increased costs.⁷

F8 inhibitor is a polyclonal IgG antibody with high affinity for FVIII that is functionally capable of neutralizing F8 activity. Patients with hemophilia A who receive F8 replacement therapy recognize F8 as an antigen and consequently produce antibodies that act as inhibitors.⁴ The inhibitor recognizes F8 epitopes and neutralizes F8 by preventing its interaction with von Willebrand factor (vWF), thrombin, and factor Xa; consequently, F8 is not protected from proteolysis and cannot be activated.¹¹ Meanwhile, F8 inhibitor level testing is not routinely performed in Indonesia due to limited facilities, the time-consuming nature of the testing, and the relatively high cost.¹² Because recurrent bleeding often occurs—particularly in the joints—leading to inflammation, measuring F8 inhibitor levels is necessary to prevent severe complications such as joint deformities and functional impairment.¹³

This study focuses on the profile of inhibitor development, which has been rarely reported in Indonesia—particularly in Surabaya—among adult patients. Therefore, this study aims to describe the profile of F8 inhibitor development in patients with hemophilia A in Surabaya.

METHOD

This study is a cross-sectional study conducted at dr. Soetomo General Teaching Hospital Surabaya and affiliated hospitals in Surabaya, Indonesia, from May to August 2023. The objective of this study is to describe the profile of F8 inhibitor development in patients with hemophilia A. The study protocol follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

This study was approved by the dr. Soetomo General Teaching Hospital Surabaya Ethics Committee (approval number: 0642/KEPK/IV/2023) and the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia (approval number: 70/EC/KEPK/FKUA/2023). This study was conducted in accordance with the Declaration of Helsinki.

Participants were recruited using total sampling, in which all patients with hemophilia A who met the inclusion criteria and did not meet the exclusion criteria were included in the study. The minimum sample size was 26 participants. Inclusion criteria include patients aged 18 years or older who have been diagnosed with hemophilia. Exclusion criteria are patients currently experiencing acute bleeding and those unwilling to participate in this study.

Authors collected data on demographics, family history, comorbidities, clinical manifestations, Body Mass Index (BMI), and inhibitor levels. The research instrument was a data collection form; F8 inhibitor levels were measured using the Bethesda assay. These measurements were performed in the Clinical Pathology laboratory in dr. Soetomo General Teaching Hospital Surabaya. An F8 inhibitor is considered positive if an inhibitor is detected during testing. Hemophilia is classified as severe if the F8 level is < 0.01 IU/mL (<1%), moderate if it is 0.01–0.05 IU/mL (1–5%), and mild if it is > 0.05 IU/mL (>5%).

Statistical analysis was performed using IBM SPSS Statistics for Mac 27.0 (IBM Corp., Armond, NY, USA). Descriptive statistics will be presented in tables showing frequencies, percentages, and medians.

RESULTS

The demographic data are presented in Table 1. Of the 30 participants, there was 1 female patient, and the majority of patients resided in Surabaya. All participants experienced bleeding episodes, with the majority experiencing joint bleeding (63%); the median age at the first bleeding episode was 3 years. A total of 2 participants (7%) had severe hemophilia. Most participants received F8 replacement therapy once a week (70%), and 25 participants (83%) received plasma-derived therapy (Table 2).

Table 1. Sociodemographic Characteristics of the Study Participants

Characteristics	Frequency (Total: 30)
Sex	
Male	29 (97)
Female	1 (3)
Age (year), mean (range)	31 (17-52)
< 31 years	16 (53)
≥ 31 years	14 (47)
Education, n (%)	
Elementary school	1 (3)
Secondary school	5 (17)
High school	12 (40)
Diploma or bachelor	12 (40)
Occupation, n (%)	
Student	5 (16)
Working	23 (77)
Unemployed	2 (7)
Marriage status, n (%)	
Married	16 (53)
Unmarried	14 (47)
Residence, n (%)	
Surabaya	16 (53)
Outside of Surabaya	14 (47)

Table 2. Clinical Characteristics of the Study Participants

Characteristics	Frequency (Total: 30)
Hemophilia Severity, n (%)	
Mild	12 (40)
Moderate	16 (53)
Severe	2 (7)
Age at First Bleeding, n (%)	
< 1 year	8 (27)
≥ 1 year	22 (73)
Median (range)	3 (0.08-35)
Type of Bleeding, n (%)	
Joint	19 (63)
Other than joint	11 (37)
BMI, n (%)	
Underweight	4 (13)
Normal	15 (50)
Overweight	7 (24)
Obesity	4 (13)
Age at which Replacement Therapy was First Initiated, n (%)	
< 18 years	16 (53)
≥ 18 years	14 (47)
Median (range)	18 (2-35)
Frequency of F8 Replacement Therapy Administration, n (%)	
Once a week	21 (70)
Twice a week	9 (30)
Type of F8 Replacement Therapy, n (%)	
Plasma derived	25 (83)
Recombinant	5 (17)

BMI: Body Mass Index; F8: factor VIII

Table 3. Profile of Factor VIII Inhibitor Levels

Inhibitor F8, n (%)	Frequency
Positive	5 (16,7)
Negative	25 (83,3)
Median inhibitor, BU (range)	5,3 (1,3 – 7,0)
Total	30 (100)

F8: factor VIII

Table 5.4 Profile of Factors of Factor VIII Inhibitor Development

Clinical Characteristics	Inhibitor	
	Positive (n=5)	Negative (n=25)
Hemophilia Severity, n (%)		
Mild	0	12 (48)
Moderate	3 (60)	13 (52)
Severe	2 (40)	0
Age at which Replacement Therapy was First Initiated, n (%)		
< 18 years	4 (80)	12 (48)
≥ 18 years	1 (20)	13 (52)
Median (range)	12 (3-28)	22 (2-35)
Frequency of F8 Replacement Therapy Administration, n (%)		
Once a week	5 (100)	16 (64)
Twice a week	0	9 (36)
Type of F8 Replacement Therapy, n (%)		
Plasma derived	4 (80)	21 (84)
Recombinant	1 (20)	4 (16)

F8: factor VIII

Of the 30 participants, 5 (16.7%) had positive F8 inhibitor levels, with a median F8 inhibitor level of 5.3 Bethesda units (BU) (Table 3). Three participants with positive inhibitor levels had moderate hemophilia, and the rest had severe hemophilia. All participants with positive inhibitor levels received weekly F8 replacement therapy, with plasma-derived F8 being the most common type of replacement therapy (Table 4).

DISCUSSION

The development of F8 inhibitors in patients with hemophilia A is a major concern that exacerbates their condition. F8 inhibitors trigger a domino effect on patients' quality of life. Patients often experience frequent bleeding, arthropathy, and disability. Furthermore, treatment costs also become more expensive (14,15). In this study, 16.7% of subjects tested positive for inhibitors, and all patients with severe hemophilia A were positive. Several previous studies have reported similar findings. Approximately 10–15% of patients with hemophilia A have positive inhibitor levels.^{16–18} Severe hemophilia A occurs in 9.5 cases per 100,000 male births. The most common cause of severe hemophilia A is an inversion of intron 22 in the X-linked F8 gene.^{19,20} This mutation results in the absence of F8 in the blood, which can lead to inhibitor development.¹⁵

This study reports that the majority of participants who were under 18 years of age when they began replacement therapy had F8 inhibitors. Several other studies have also reported that the majority of patients with hemophilia A who have inhibitors received their first exposure to F8 during childhood. Previous studies have indicated that receiving replacement therapy for the first time before the age of 12 months is one of the factors contributing to inhibitor development.^{8,12,21–23} Internationally, a cohort study of more than 1,000 previously untreated patients showed that the median age at first exposure to F8 was 1.1 years, with 99.3% receiving their first exposure within 75 days.²³ Meanwhile, none of the participants in this study were younger than 2 years old at the time of their first replacement therapy (the earliest being 18 months). However, this cannot be confirmed with certainty because the participants underwent their first inhibitor screening only during the course of this study. This situation is similar to that in China, where, due to economic constraints, F8 inhibitor screening is not a routine test and medical resources are limited.¹⁵

The higher proportion of patients who receive their first treatment before the age of 18 can be explained by several factors. First, severe hemophilia A generally manifests clinically from an early age, usually in the form of spontaneous bleeding in joints or soft tissues as soon as children become physically active, so that the diagnosis and indication for replacement therapy are established as early as infancy or toddlerhood. Second, modern management guidelines encourage the early initiation of prophylaxis in severe hemophilia to prevent joint damage (hemophilic arthropathy) and improve long-term quality of life. Third, increased awareness among families and healthcare providers regarding a family history of hemophilia allows for earlier screening and diagnosis, even before major bleeding episodes occur. Conversely, the group that received their first therapy in adulthood (≥ 18 years) likely consists of patients with milder or moderate hemophilia phenotypes, who did not require routine replacement therapy from childhood and were only exposed to F8 upon experiencing trauma, surgical procedures, or significant bleeding in adulthood; it may also reflect delayed access to diagnosis and comprehensive hemophilia care, particularly in areas with limited screening facilities, as also described in the context of hemophilia care in Indonesia.^{12,24}

Differences in the age of first exposure are related to the maturity of the immune system and the immunological context at the time exogenous F8 is first recognized as a foreign antigen. In infants and young children, the adaptive immune system, which is not yet fully mature, is often more prone to mounting a strong immune response to exogenous F8 if the first exposure occurs concurrently with danger signals such as infection, inflammation, vaccination, or invasive procedures. Furthermore, patients with severe F8 gene mutations, such as intron 22 inversion, large deletions, or nonsense mutations, tend not to produce any endogenous F8 protein at all; consequently, exogenous F8 is fully recognized as a foreign neoantigen from the very first exposure, which typically occurs at an early age due to their severe hemophilia phenotype. Conversely, in patients who are first exposed as adults, the immune response to FVIII is more frequently triggered by short-term, intensive exposure, such as surgery, which acts as the primary trigger, regardless of the maturity of the immune system in question.^{24,25} Furthermore, inhibitors also form due to the breakdown of previously established tolerance. Patients experience a longer “exposure period” to replacement therapy.²⁶

Several studies have reported the use of low-frequency F8 replacement regimens, particularly in countries where factor concentrates are available. Toure et al.,²⁷ in a three-year prospective study in Senegal, found that low-dose F8 prophylaxis administered once or twice a week reduced the annualized bleeding rate (ABR) from 7.53 to 1.33 and decreased joint bleeding from 3.6 to 1.4 episodes per year. A study reported that in eastern India, the implementation of very low-dose prophylaxis—administered once weekly (15 IU/kg)—in children with severe hemophilia A resulted in a significant reduction in the ABR from 23.73 to 1.87 events per year ($p < 0.001$). The prevalence of once-weekly dosing is most likely due to limited access to and the cost of F8 concentrate, which

remain major challenges in developing countries. In addition to cost considerations, once-weekly dosing also reduces the frequency of hospitalizations, thereby potentially improving adherence to long-term therapy, as demonstrated by improved quality-of-life scores.²⁸

The frequency of F8 replacement therapy is essentially determined by the need to maintain sufficient F8 activity over a specific period. F8 products with a standard half-life are generally eliminated from the circulation more quickly, so they conventionally require administration two to three times per week. In contrast, F8 products with an extended half-life (EHL) allow factor levels to be maintained for longer periods and extend the dosing intervals. The World Federation of Hemophilia states that the frequency of therapy can be adjusted based on individual pharmacokinetics, F8 levels, bleeding patterns, physical activity, age, and treatment goals. Once-weekly administration does not necessarily imply lower treatment intensity but may reflect the use of a product with a longer half-life or an individually tailored treatment strategy.⁷

The discovery of F8 replacement therapy for patients with hemophilia A is significant because it can improve patients' quality of life. The administration of plasma-derived therapies carries a lower risk of inhibitor development. Various studies have reported that inhibitor development frequently occurs in patients receiving recombinant therapy.^{29,30} However, this was not the case in this study. As many as 80% of participants with inhibitors were recipients of plasma-derived replacement therapy. There have been cases in Europe of previously treated patients (PTPs) receiving plasma-derived therapy who developed inhibitors. The cause is that these plasma-derived products undergo a prolonged pasteurization process for viral inactivation, resulting in structural changes to F8 and the development of neo-immunogenicity.³¹ The involvement of immune responses, such as human leukocyte antigens and proteins like cytokines, is one of the causes of inhibitor development. Plasma-derived products can induce tolerance in patients with hemophilia A as an immunomodulator.³²

This study is a descriptive study aimed at identifying the factors contributing to the development of FVIII inhibitors in patients with hemophilia A, namely the severity of hemophilia, age at the start of FVIII therapy, type of replacement therapy, and treatment intensity. The most ideal design for a study on this topic would be a prospective cohort study; however, this design was not feasible due to time and resource constraints. In addition to a prospective cohort study, a case-control study could also have been conducted; however, this design could not be implemented due to limitations in the study population. This study did not include other predictors of inhibitor development, such as gene mutations; therefore, the researchers could not account for them as potential predictors influencing the risk of inhibitor development.

CONCLUSION

Only a small proportion of patients with hemophilia A have F8 inhibitors. All patients with severe hemophilia A, most patients who received replacement therapy before the age of 18, most patients who received plasma-derived replacement therapy, and most patients who received replacement therapy once a week have F8 inhibitors. This serves as a reminder to clinicians and policymakers to pay closer attention to the health of hemophilia patients who are living longer, as they still frequently experience bleeding episodes, especially those living in areas far from tertiary care centers.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent form. In the form, patient has given his consent for his clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil

Conflict of interest

The authors declare no conflict of interests

AUTHOR CONTRIBUTION

Conceptualization, RRF, AA, SUYB, MS; Methodology, RRF, AA, MS, AWD; Validation, AA, SUYB, MS; Data Curation, RRF, AWD; Writing – original draft preparation, RRF, AWD, ARM; Reviewing and editing, AA, MS, AWD, AFM; Supervision, AA, SUYB, MS; Project Administration, AWD

DATA AVAILABILITY

The data supporting this case report are available from corresponding author upon reasonable requests.

REFERENCE

1. Rotty LWA, Hendratta LCA, Lasut PFC. Hemofilia A dan B. In: Buku Ajar Ilmu Penyakit Dalam. VII. Jakarta: PIPInterna; 2024. p. 3312–20.
2. Salen P, Babiker HM. Hemophilia A. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Oct 13]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK470265/> PubMed PMID: 29261993.
3. Stonebraker JS, Bolton-Maggs PHB, Brooker M, Evatt B, Iorio A, Makris M, et al. The World Federation of Hemophilia Annual Global Survey 1999–2018. *Haemophilia*. 2020 Jul;26(4):591–600. doi:10.1111/hae.14012 PubMed PMID: 32497379.
4. DiMichele D. Inhibitors to factor VIII/IX: immune tolerance. In: Textbook of Hemophilia. II. West Sussex: John Wiley & Sons, Ltd., Publication; 2010. p. 64–70.
5. Kempton CL. Inhibitors in previously treated patients: a review of the literature. *Haemophilia*. 2010 May;16(102):61–5. doi:10.1111/j.1365-2516.2010.02235.x
6. Ragni MV, Ojeifo O, Feng J, Yan J, Hill KA, Sommer SS, et al. Risk factors for inhibitor formation in haemophilia: a prevalent case-control study. *Haemophilia*. 2009 Sep;15(5):1074–82. doi:10.1111/j.1365-2516.2009.02058.x PubMed PMID: 19563499; PubMed Central PMCID: PMC2734871.
7. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020 Aug;26 Suppl 6:1–158. doi:10.1111/hae.14046 PubMed PMID: 32744769.
8. Lorenzo JI, López A, Altisent C, Aznar JA. Incidence of factor VIII inhibitors in severe haemophilia: the importance of patient age. *Br J Haematol*. 2001 Jun;113(3):600–3. doi:10.1046/j.1365-2141.2001.02828.x PubMed PMID: 11380444.
9. Gouw SC, van den Berg HM, Oldenburg J, Astermark J, de Groot PG, Margaglione M, et al. F8 gene mutation type and inhibitor development in patients with severe hemophilia A: systematic review and meta-analysis. *Blood*. 2012 Mar 22;119(12):2922–34. doi:10.1182/blood-2011-09-379453 PubMed PMID: 22282501.
10. Chambost H, Gaboulaud V, Coatmélec B, Rafowicz A, Schneider P, Calvez T, et al. What factors influence the age at diagnosis of hemophilia? Results of the French hemophilia cohort. *J Pediatr*. 2002 Oct;141(4):548–52. doi:10.1067/mpd.2002.128115 PubMed PMID: 12378196.
11. Saint-Remy JMR, Jacquemin MG. Inhibitors to factor VIII-immunology. In: Textbook of Hemophilia. II. West Sussex: John Wiley & Sons, Ltd., Publication; 2010. p. 52–6.
12. Simatupang GNA, Windiastuti E, Oswari H. Faktor Risiko Timbulnya Inhibitor Faktor VIII pada Anak dengan Hemofilia A. *SP*. 2016 Nov 16;14(5):320. doi:10.14238/sp14.5.2013.320-5
13. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet*. 2016 Jul 9;388(10040):187–97. doi:10.1016/S0140-6736(15)01123-X PubMed PMID: 26897598.
14. Kim JY, You CW. The prevalence and risk factors of inhibitor development of FVIII in previously treated patients with hemophilia A. *Blood Res*. 2019 Sep 30;54(3):204–9. doi:10.5045/br.2019.54.3.204
15. Sun J, Li Z, Huang K, Ai D, Li G, Xie X, et al. F8 gene mutation spectrum in severe hemophilia A with inhibitors: A large cohort data analysis from a single center in China. *Research and Practice in Thrombosis and Haemostasis*. 2022 Apr;6(4):e12723. doi:10.1002/rth.12723
16. Borhany M, Kumari M, Shamsi T, Naz A, Farzana T. Frequency of Factor VIII (FVIII) Inhibitor in Haemophilia A. *Journal of the College of Physicians and Surgeons Pakistan*. 2012;22(5):289–93.
17. Chen YC, Hu SH, Cheng SN, Chao TY. Genetic analysis of haemophilia A in Taiwan. *Haemophilia*. 2010 May;16(3):538–44. doi:10.1111/j.1365-2516.2009.02180.x PubMed PMID: 20236351.
18. Al-Beldawi DH. The Risk Factors of Inhibitor Development and Hepatitis C Virus among Hemophilic Patients in Children Welfare Teaching hospital. *JFacMedBagdad*. 2010 Apr 4;52(1):4–8. doi:10.32007/jfacmedbagdad.5211036
19. Lim MY, Ardila J, Castaman G, Dargaud Y, Fijnvandraat K, Gualtierotti R, et al. Diagnosis and management of hemophilia A and B. *Journal of Thrombosis and Haemostasis*. 2026 Jul;24(7):2341–54. doi:10.1016/j.jth.2026.04.005
20. Abdulqader AMR, Mohammed AI, Rachid S, Ghorashizadeh P, Mahmood SN. Identification of the Intron 22 and Intron 1 Inversions of the Factor VIII Gene in Iraqi Kurdish Patients With Hemophilia A. *Clin Appl Thromb Hemost*. 2020 Jan 1;26:1076029619888293. doi:10.1177/1076029619888293
21. Goudemand J, Rothschild C, Demiguel V, Vinciguerratt C, Lambert T, Chambost H, et al. Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A. *Blood*. 2006 Jan 1;107(1):46–51. doi:10.1182/blood-2005-04-1371

22. Chalmers EA, Brown SA, Keeling D, Liesner R, Richards M, Stirling D, et al. Early factor VIII exposure and subsequent inhibitor development in children with severe haemophilia A. *Haemophilia*. 2007 Mar;13(2):149–55. doi:10.1111/j.1365-2516.2006.01418.x PubMed PMID: 17286767.
23. Van Den Berg HM, Fischer K, Carcao M, Chambost H, Kenet G, Kurnik K, et al. Timing of inhibitor development in more than 1000 previously untreated patients with severe hemophilia A. *Blood*. 2019 Jul 18;134(3):317–20. doi:10.1182/blood.2019000658
24. Lawrenti H. Hemofilia dan Perkembangan Terapinya. *Cermin Dunia Kedokteran*. 2021 Sep 1;48(9):362–7. doi:10.55175/cdk.v48i9.129
25. Miller CH, Rice AS, Boylan B, Payne AB, Kelly FM, Escobar MA, et al. Characteristics of hemophilia patients with factor VIII inhibitors detected by prospective screening. *Am J Hematol*. 2015 Oct;90(10):871–6. doi:10.1002/ajh.24104 PubMed PMID: 26147783; PubMed Central PMCID: PMC4642843.
26. Hay CRM, Palmer B, Chalmers E, Liesner R, Maclean R, Rangarajan S, et al. Incidence of factor VIII inhibitors throughout life in severe hemophilia A in the United Kingdom. *Blood*. 2011 Jun 9;117(23):6367–70. doi:10.1182/blood-2010-09-308668
27. Touré SA, Seck M, Sy D, Senghor AB, Faye BF, Diop S. Clinical outcome and incidence of inhibitor development in severe hemophilia patients receiving low-dose prophylaxis: a 3-year follow-up study in Senegal, West Africa. *Hematology, Transfusion and Cell Therapy*. 2023 Jul;45:S95–100. doi:10.1016/j.htct.2022.04.004
28. De D, Datta SS. Very low-dose prophylaxis in children with hemophilia A. *Asian J Transfus Sci*. 2024;18(2):369–70. doi:10.4103/ajts.ajts_159_22 PubMed PMID: 39822679; PubMed Central PMCID: PMC11734790.
29. Kohar K, Prayogo SA, Wiyono L. The Impact of Recombinant Versus Plasma-Derived Factor VIII Concentrates on Inhibitor Development in Previously Untreated Patients With Hemophilia A: A 2021 Update of a Systematic Review and Meta-Analysis. *Cureus*. 2022 Jun 16. doi:10.7759/cureus.26015
30. Franchini M. Plasma-derived versus recombinant Factor VIII concentrates for the treatment of haemophilia A: recombinant is better. *Blood Transfusion*. 2010. doi:10.2450/2010.0067-10
31. Miri S, Rosendaal FR, Kavakli K, Eshghi P, Moghaddam SM, Scardo S, et al. Inhibitor development upon switching from plasma-derived to recombinant factor VIII in previously untreated patients with severe hemophilia A: the PUP-SWITCH study. *Research and Practice in Thrombosis and Haemostasis*. 2024 Nov;8(8):102595. doi:10.1016/j.rpth.2024.102595
32. Peyvandi F, Miri S, Garagiola I. Immune Responses to Plasma-Derived Versus Recombinant FVIII Products. *Front Immunol*. 2021 Jan 22;11:591878. doi:10.3389/fimmu.2020.591878