


# Factors Involved in the Development of Inhibitory Antibodies in Patients with Hemophilia in Colombia: A Case-Control Study

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## ABSTRACT

**BACKGROUND:** The appearance of inhibitory antibodies against antihemophilic factors is one of the most serious complications related to hemophilia.

**OBJECTIVE:** The objective of this study was to identify variables and factors related to the development of inhibitory antibodies in a group of patients undergoing antihemophilic therapy in Colombia.

**METHODS:** A case-control study in patients with hemophilia treated in Specialized Healthcare Provider Institutions (IPS-E) in 21 cities of Colombia of any age and with a diagnosis of inhibitory antibodies against factor VIII or IX during 2016. Four controls per case paired by age and type of hemophilia were used. Sociodemographic, clinical, and pharmacological variables were identified and analyzed.

**RESULTS:** Seventeen patients with inhibitory antibodies and 68 controls with hemophilia were identified. The mean age was  $28.3 \pm 17.8$  years. A total of 94.1% had hemophilia A, and 88.2% of the cases and 50.0% of the controls had severe hemophilia; 47.1% of the cases and 54.4% of the controls were receiving prophylaxis with coagulation factors. Multivariate analysis showed that having severe hemophilia (OR:17.0, 95%CI:1.32–219.60) and lack of knowledge of the coagulation factor with which the patient was treated before entering the care program in the IPS-E (OR:8.9, 95%CI:1.82–43.75) were significantly associated with a higher probability of developing inhibitory antibodies.

**CONCLUSION AND RELEVANCE:** Coagulation factors associated with the development of inhibitory antibodies were severe hemophilia and lack of knowledge of the type of factor used prior to entering the follow-up cohort.

**KEYWORDS:** Hemophilia A, hemophilia B, blood coagulation factor inhibitors, risk factors, pharmacoepidemiology

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## Introduction

Hemophilia is a recessive hereditary hemorrhagic X-linked disease of low prevalence that is characterized by a quantitative deficiency of coagulation factor VIII (hemophilia A) or IX (hemophilia B), which alters the process of hemostasis. Causative factors may include inheritance of a defective gene or the development of new mutations (1/3 of cases). This pathology usually affects the male population, though in some cases, women may present with a marked bleeding phenotype resulting from low levels of a coagulation factor in the blood.<sup>1,2</sup>

The last global annual report issued by the World Federation of Hemophilia identified a total of 184 723 cases of hemophilia in the 113 member countries, of which 149 764 corresponded to hemophilia A and 29 712 to hemophilia B. Nonetheless, it should be noted that 400 000 cases are estimated worldwide.<sup>3,4</sup> In Colombia, a total of 1705 cases of hemophilia A and 354

cases of hemophilia B have been identified, representing 41.9% and 8.7%, respectively, of the population diagnosed with any coagulopathy, as based on registries from 2016 by the High Cost Account (an institution in charge of analyzing the use and administration of high-cost medications, technologies, and procedures).<sup>5</sup>

One of the most serious complications in the treatment of hemophilia is the appearance of inhibitory antibodies against exogenously administered coagulation factors, which negatively impacts the quality of life and the clinical condition of the patient and has socioeconomic repercussions due to the increase in the cost of treatment.<sup>3,6</sup> Furthermore, development of inhibitory antibodies is associated with a cellular immune response that occurs in the presence of exogenous antihemophilic factor and interactions between antigen-presenting cells (APCs), CD4 T cells and lymphocytes.<sup>7</sup>



Inhibitors are diagnosed by assessing the concentration of antibodies, expressed in Bethesda units (BU), present in a patient's blood. Inhibition should be suspected in patients whose coagulation factor replacement treatment was once effective but who then began to present bleeding without response to infusion of the coagulation factor with the appropriate therapeutic schemes.<sup>8</sup> Inhibitors are classified as low-titer inhibitors if the level is less than 5 BU/mL and high-titer inhibitors if the result is greater.<sup>8</sup> It is estimated that the development of inhibitors occurs more frequently in people with severe hemophilia, representing up to 30% of cases in hemophilia A and up to 8% of cases in hemophilia B.<sup>3</sup>

Patients who have low and high-titer inhibitors can be treated with immunotolerance protocols (different doses of factor and frequency of treatment) in both hemophilia A and hemophilia B. However, in cases involving a high antibody titer, better results have been observed with recombinant activated coagulation factor VII and, with a little less efficacy, with activated prothrombin complex concentrates (aPCCs). Additionally, some therapeutic combinations are effective, such as recombinant activated coagulation factor VII with aPCCs or the combination of antifibrinolytics with an anti-inhibitor Coagulant Complex called FEIBA.<sup>9</sup>

Thus, therapeutic strategies available for patients with inhibitors are focused on the eradication of inhibitory antibodies through the induction of immune tolerance and the treatment of hemorrhagic events using bypassing agents, such as Recombinant Activated Factor VII and aPCCs. These approaches achieve coagulation factor activation by alternate routes.<sup>10</sup>

Because Colombia does not maintain a comprehensive and detailed record of the risk factors related to the development of inhibitors in the hemophilic population, an investigation was conducted to determine the variables associated and to establish their relationship with the development of inhibitory antibodies in patients undergoing antihemophilic therapy from an institution specialized in the care of high-cost pathology in Colombia.

## Methods

A nested case-control study in a cohort was conducted. Cases were defined as patients with hemophilia A or B, of any age, affiliated with the Health System of Colombia in 21 cities of the country and who attend a health care program for hereditary coagulopathies of Specialized Healthcare Provider Institutions (IPS-E) with a diagnosis of inhibitors against coagulation factor VIII or IX between January 1 and December 31, 2016. Four controls for each case were enrolled and were matched for age and type of hemophilia, with a tolerance of 1 year for age. No stratification was made according to coagulation factor levels.

The information was obtained from the hemophilia program database of the IPS-E, which is a high-cost specialized health care center. The data were reviewed by the team of physicians

responsible for patient care and by a medical pharmacologist. The following variables were taken into account:

1. Sociodemographic: age, city of origin.
2. Clinical: type of hemophilia, classification of the severity of hemophilia, family history of hemophilia, age of diagnosis of hemophilia, presence of joint damage, number of affected joints, comorbidities, history of infectious diseases (HIV, hepatitis B virus [HBV], hepatitis C virus [HCV]), history of allergic reaction to the coagulation factor, history of blood transfusions before 1990 and whether more than one transfusion occurred in the last 5 years.
3. Pharmacological: type of coagulation factor under which the patient entered the IPS-E care program, name of the medication, dose, and frequency of use.

The study was approved by the Bioethics Committee of the Universidad Tecnológica de Pereira in the category of risk-free research (approval number CBE-SYR-192016). Personal data of the patients were not recorded, and the principles of confidentiality of information established by the Declaration of Helsinki were respected. Given that the information was collected from clinical records, the bioethics committee exonerated the authors from obtaining informed consent as established by Resolution 8430/93 of the Colombian Ministry of Health.

## Data analysis

Data were analyzed with the statistical program SPSS version 24 for Windows (IBM, USA). Frequencies and proportions were obtained for categorical variables and measures of central tendency and dispersion for continuous variables. Normality was assessed using the Kolmogorov-Smirnov test. Contingency tables were prepared for odds ratio (OR) calculation between the cases and controls for the dependent variable (inhibitor development); for other categorical variables, the  $X^2$  test was applied to evaluate their statistical significance, and differences in continuous variables without normal distribution were examined with nonparametric tests. Multivariate analysis was performed by logistic regression, including the variable inhibitor development and other associated variables in bivariate analyses. A value of  $P < .05$  was considered significant.

## Results

From a cohort of 354 patients with hemophilia, we identified 23 (6.5%) patients with a diagnosis of hemophilia and the presence of inhibitors against coagulation factor VIII or IX during 2016 in the IPS-E of Colombia. The mean age of this group was  $29.3 \pm 17.9$  years (range: 2-73 years), and all of the patients were men. Of these 23 patients, 6 were excluded because they already had a diagnosis of inhibitors when they entered the

IPS-E cohort. The sample was therefore limited to 17 subjects as cases and 68 controls, with an average age of  $28.3 \pm 17.8$  years. A total of 15 cases presented high-titer inhibitors (88.2%).

Regarding the geographical distribution of the population ultimately included, 44.8% of the individuals were treated in the city of Bogotá, followed by Cali (14.2%), Pereira (6.0%), Tunja (4.7%), Manizales (3.5%), Barranquilla (2.4%) and 15 other cities (24.4%). Almost all cases had a diagnosis of hemophilia A, mainly classified as severe hemophilia. In addition, most patients were between 19 and 44 years and had some type of joint damage. No patient had a diagnosis of HBV infection or HIV, though 12 of them (14.1%) had HCV infection. The other sociodemographic, clinical and pharmacological variables of the two groups are presented in Table 1.

### Multivariate analysis

Logistic regression to analyze variables related to the risk of presenting inhibitors against coagulation factors VIII or IX showed that having severe hemophilia and lack of knowledge of the factor with which the patient was treated before entering the care program in the IPS-E were significantly associated with a higher probability of developing inhibitors (see Table 2).

### Discussion

The development of inhibitors against coagulation factors VIII and IX used in the management of hemophilia in patients with prophylaxis requirements or treated on-demand is one of the most serious complications. Indeed, there are great impacts on quality of life, clinical progression, the development of complications and both direct and indirect costs associated with treating this pathology. The results obtained in this study, such as the identification of some risk factors associated with the development of inhibitors in the Colombian population, are of interest to attending physicians, patients and local and international entities involved in the process of comprehensive care.

The sociodemographic data for this group of patients with inhibitors and their respective controls show a population with an average age close to 28 years, which is related to the distribution of the different age groups of the population involved in this research.<sup>11</sup> It should be noted that the results reported by the High Cost Account for 2016 show that in Colombia, half of the population with inhibitors is 15 years of age or younger and that for every 100 patients with inhibitors, 75 are under 27 years of age.<sup>5</sup>

There are few epidemiological studies regarding the prevalence of inhibitors against coagulation factors in populations of patients with hemophilia because such studies are focused on patients with severe hemophilia due to their greater frequency. Regardless, the frequency found in this study is comparable to general reports, typically between 5% and 7%.<sup>12</sup> The finding is also similar to more recent studies, such as that of Pinto et al. in India, in which 6.1% of patients had inhibitors,<sup>13</sup> but a slightly greater than the 3.9% reported

by Wang et al in China.<sup>14</sup> According to the results presented by the High Cost Account in Colombia for 2016, among all patients with hemophilia (2,059 cases), 8.5% presented inhibitors, 64.1% did not present them, and 27.4% lacked data for inhibitors.<sup>5</sup>

The association between the presence of inhibitors in patients with severe hemophilia found in our study is completely consistent with the literature, whereby approximately 30% of patients of severe hemophilia A develop inhibitors, with the highest risk in the first month after exposure to coagulation factors, a variable reported as an influencing factor that could not be evaluated in this study.<sup>15,16</sup> It is also recognized that although some risk factors are identifiable, the development of inhibitors and their immunological process remain poorly understood. Indeed, inhibitor development is triggered by different conditions, such as the genetic characteristics of the patient, the type of mutation present and the environment, with the intensity of exposure to coagulation factors being increasingly recognized as an important component.<sup>17,18</sup>

In our population, it was found that lack of knowledge of the type of factor used at entry into the cohort was associated with a higher probability of developing inhibitory antibodies, an important finding because some information suggests that the risk is higher when using recombinant factors<sup>19-22</sup>; however, a conclusion has yet to be reached, and there are contradictory data.<sup>20</sup> There is more information about the risk during the first days of exposure to the factor, especially at higher doses, which can be associated with immunological phenomena that lead to the development of inhibitors.<sup>23</sup> It would be essential to explore other danger signals such as the stimulation of dendritic cells with factor VIII in combination with bacterial molecule lipopolysaccharide that induce a strong activation of these cells, which may explain a strong response of CD4+T lymphocytes, which would be the signal that increases the innate and adaptive response toward factor VIII products. It is unknown whether the patients who developed inhibitors in this cohort were exposed to danger signs such as infections, surgeries or the previous intensity of treatment that could be involved in the generation of immunogenicity against the administered factor VIII.<sup>24,25</sup> It should also be considered that, in real life conditions, patients may not communicate the treatment they were previously receiving to a new clinic responsible for their care if they change institutions; a patient may be treated with a completely different drug, and this is a determining variable.

Some studies have shown that early prophylaxis in at-risk patients can be important for decreasing the incidence of inhibitor development, a condition of almost 10% of the subjects of this study, but a problem arises when the coagulation factor used for the treatment is unknown.<sup>26-28</sup> The low proportion of patients receiving primary prophylaxis can be explained by the procedures of the Colombian health system; in which there are delays in the delivery of medicines and in care and follow-up, and many patients receive treatment even when

**Table 1.** Sociodemographic, pharmacological and clinical characteristics of patients with inhibitors against factor VIII and IX and their controls, Colombia, 2016.

CHARACTERISTICS OF PATIENTS	CASES WITH INHIBITORY ANTIBODIES (N=17)	CONTROLS (N=68)	P VALUE
Age			
Mean age - years (SD)	28.1 (18.2)	28.4 (17.9)	.95
Age group - No (%)			
0-4y	2 (11.8)	7 (10.3)	
5-14y	3 (17.6)	13 (19.1)	
15-18y	0 (0.0)	1 (1.5)	
19-44y	9 (52.9)	31 (45.6)	
>45y	3 (17.6)	16 (23.5)	
Family history of coagulopathy - n (%)	6 (35.3)	43 (63.2)	.037
In self-infusion scheme - n (%)	4 (23.5)	8 (11.8)	.213
Clinics			
Type of hemophilia - n (%)			1.000
Hemophilia A	16 (94.1)	64 (94.1)	
Hemophilia B	1 (5.9)	4 (5.9)	
Severity - n (%)			
Mild	1 (5.9)	17 (25.0)	.106
Moderate	1 (5.9)	17 (25.0)	.106
Severe	15 (88.2)	34 (50.0)	.005
Age at diagnosis (years) - mean (SD)	2.8 (3.2)	4.7 (7.6)	.135
Type of prophylaxis - n (%)			
Currently in prophylaxis	8 (47.1)	37 (54.4)	.587
Primary	2 (11.8)	6 (8.8)	.710
Secondary	1 (5.9)	15 (22.1)	.127
Tertiary	5 (29.4)	16 (23.5)	.615
Days of factor administration - n (%)			
1 d a wk	0 (0.0)	1 (1.5)	.615
2 d a wk	0 (0.0)	7 (10.3)	.336
Every other day	8 (47.1)	28 (41.2)	.661
Everyday	0 (0.0)	1 (1.5)	1.000
Presence of joint damage - n (%)	11 (64.7)	33 (48.5)	.233
Number of affected joints - n (%)			
Any	6 (35.3)	34 (50.0)	.277
1 joint	0 (0.0)	10 (14.7)	.200
≥2 joints	11 (64.7)	24 (35.3)	.028
History of central nervous system injury	1 (5.9)	1 (1.5)	.362

(Continued)

**Table 1.** (Continued)

CHARACTERISTICS OF PATIENTS	CASES WITH INHIBITORY ANTIBODIES (N= 17)	CONTROLS (N=68)	P VALUE
Allergic reaction attributable to the factor	1 (5.9)	6 (8.8)	1.000
Infectious comorbidity	3 (17.6)	9 (13.2)	.699
Hepatitis C virus infection	3 (17.6)	9 (13.2)	.699
Transfusion before 1990	7 (41.2)	26 (38.2)	.824
>1 transfusion in the last 5y	3 (17.6)	20 (29.4)	.329
Pharmacological			
Type of factor with which patient received before entering the program - n (%)			
Unknown	11 (64.7)	17 (25.0)	.002
Plasma-derived	4 (23.5)	27 (39.7)	.268
Recombinant	2 (11.8)	24 (35.3)	.079

**Table 2.** Variables associated with the development of inhibitory antibodies against factor VIII or IX in binary logistic regression models, Colombia, 2016.

VARIABLES	P VALUE	OR	95% CI	
			LOWER	UPPER
Severity				
Mild		Ref		
Moderate	.509	2.79	0.13	58.17
Severe	.030	17.03	1.32	219.60
Type of factor upon entry				
Plasmatic		Ref		
Recombinant	.416	0.46	0.07	2.98
Unknown	.007	8.92	1.82	43.75

Adjusted by: age, sex, severity, and number of affected joints. Abbreviations: OR, odds ratio; 95%CI, 95% confidence interval; Ref, reference group.

prophylaxis is indicated. However, in some groups of patients with hemophilia in Colombia, this problem has been mitigated with incorporation into specialized management centers, where early access to drugs is guaranteed, and according to the indication, at the appropriate dose, without delays and traceability. Such measures avoid indiscriminate exposure to different coagulation factors or high doses that might be involved in the development of inhibitors.<sup>26</sup>

Arthropathy is one of the most common outcomes of patients with hemophilia, and causes functional limitations and even deformities; it is related to the severity of the disease, the number of intra-articular bleeds, the age at which the diagnosis was made, and treatment options available and received.<sup>29</sup> The finding of a significantly higher proportion of patients with

two or more affected joints in the group of cases that developed inhibitors is associated with the severity of hemophilia, which was also found in this cohort.

This study presents a first approach to determining possible factors that influence the development of inhibitors. However, there are some limitations inherent to the methodological design and the lack of some data that could be of interest. For example, no information about family history of inhibitors was available. Some conditions that lead to prolonged exposures to high doses of clotting factors, such as periods of surgery or having suffered severe bleeding, have been identified that can increase the risk of developing inhibitors, so this history should not be known before this group of patients was admitted to this cohort may limit the interpretation of the findings. In addition, the case sample was small, and there was a lack of knowledge regarding the management prior to admission to the cohort and a lack of genetic studies on coagulation factor-specific mutations. Nevertheless, patients with hemophilia who produce inhibitors were clearly identified, and a close follow-up was performed once they entered the cohort, which guarantees that the information collected during the time of the study is reliable.

## Conclusion

It can be concluded that in this cohort of patients with a diagnosis of hemophilia, a small proportion have inhibitors against coagulation factors VIII and IX and that factors associated with the development of inhibitors were severe hemophilia and lack of knowledge of the type of factor used prior to entry in the cohort, a condition that forced us to delve more deeply into the clinical history, allowing us to identify risk in a timely manner. Therefore, it is suggested that inhibitor development may be prevented by better follow-up. The detailed information in this work is useful for decision makers regarding access and choice of treatment owing to the potential implications,

complications and increased costs for patients who develop inhibitory antibodies against coagulation factors.

### Author Contributions

JEMA participated in the drafting, description of results, discussion, critical revision of the article, and evaluation of the final version of the manuscript. LACQ participated in the drafting, data collection, data analysis, description of results, discussion, MEMD participated in the data collection, data analysis, description of results, discussion. AGM participated in the data collection, data analysis, description of results, discussion, JDWG participated in data collection, discussion, critical revision of the article, DRAO participated in data collection, discussion, critical revision of the article.

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