Statements about hemophilia A in Brazil: an expert Delphi panel

Consensos em hemofilia A no Brasil: painel Delphi de especialistas

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ABSTRACT

Objective: Understanding unmet needs related to hemophilia A management in Brazil is critical for supporting decision-making. **Methods:** A modified Delphi consensus panel was conducted. Hematologists with extensive experience treating hemophilia in the Brazilian Public Health System were invited to answer questions regarding indicators of severe hemophilia prophylaxis effectiveness, emicizumab treatment indications, and bypassing agents used to reduce bleeding in patients with inhibitors, immune tolerance induction (ITI) use, and adherence. The consensus was defined as ≥75% of votes in Round 1 or using a 5-point Likert-type scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree) in Round 2, which included questions not reaching minimum cut-off in the first step. **Results:** Nine expert panelists with extensive experience in the Brazilian Public Health System participated. The panel reached an agreement on recommendations about prophylaxis, bleeding treatment patterns, and bleeding sites. From patients' perspectives, venous access and infusion frequency were the most significant barriers to improving patient treatment. According to most experts, emicizumab will not replace ITI or long-term factor VIII therapy. Still, emicizumab was thought to be a good therapeutic option for patients with difficult venous access, patients requiring central venous access, in the presence of inhibitors, or patients experiencing infusion-related pain. **Conclusion:** The information gleaned from this study may be helpful to both decision-makers and those in charge of developing healthcare economic models for the treatment of hemophilia A in Brazil.

Palavras-chave:
hemofilia A, painel Delphi, emicizumabe

RESUMO

Objetivo: É fundamental entender as necessidades não atendidas relacionadas ao manejo da hemofilia A no Brasil. **Métodos:** Foi conduzido um painel Delphi modificado. Foram convidados hematologistas com vasta experiência no tratamento de hemofilia no SUS para responder a perguntas sobre indicadores de eficácia da profilaxia, indicações de tratamento com emicizumabe, uso de agentes de *bypass*, uso de indução de tolerância imunológica (ITI) e adesão. O consenso foi definido como ≥75% dos votos na rodada 1 ou usando uma escala do tipo Likert de 5 pontos (1 = discordo totalmente, 2 = discordo, 3 = não concordo nem discordo, 4 = concordo e 5 = concordo totalmente) na segunda rodada, que incluiu questões que não atingiram o corte mínimo na primeira etapa. **Resultados:** Nove especialistas participaram e houve consenso sobre recomendações para profilaxia, padrões de tratamento de sangramento e locais de sangramento. O acesso venoso e a frequência da infusão foram identificados como as barreiras mais significativas para melhorar o tratamento do paciente. De acordo com a maioria, emicizumabe não substituirá a ITI ou tratamento com fator VIII de longo prazo. Emicizumabe foi considerado uma boa opção terapêutica para

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pacientes com difícil acesso venoso, pacientes que precisam de acesso venoso central, na presença de inibidores ou em pacientes com queixas de dor relacionada à infusão. **Conclusão:** As informações e consensos obtidos neste estudo podem ser úteis tanto para os tomadores de decisão quanto para os responsáveis pelo desenvolvimento de modelos econômicos de saúde para o tratamento da hemofilia A no Brasil.

Introduction

Hemophilia A is a hereditary hemorrhagic disorder caused by the absence or deficient factor VIII (FVIII) activity (Ferreira *et al.*, 2014; Kruse-Jarres *et al.*, 2017). The lack of adequate disease treatment may promote recurrent bleeding, and its episodes result in disability, a negative impact on the quality of life, and eventually death (Mannucci & Tuddenham, 2001; Cao *et al.*, 2009). FVIII replacement is the standard of care recommended worldwide, and in Brazil, other homeostatic agents such as desmopressin and antifibrinolytics are also recommended (Aledort *et al.*, 2019; Brasil, 2015). Brazil has the largest population of hemophilia A patients in Latin America and the third largest in the world. In 2019, 10,821 people were estimated to be living with the condition in the country (WFH, 2020).

About 30% of patients with the severe disease develop inhibitors against FVIII (FVIII antibodies), rendering such therapy ineffective and increasing the risk of bleeding episodes and death (Schep *et al.*, 2018; van den Berg *et al.*, 2019; Brackmann *et al.*, 2018; Peyvandi *et al.*, 2017). Although emicizumab is an effective treatment capable of partially restoring FVIII function, binding Factor IXa, and Factor X, and promoting effective hemostasis in patients with hemophilia A, it is only reimbursed by the federal government in Brazil for patients who have failed immune tolerance induction (ITI) treatment (Blair, 2019; Anvisa, 2019).

Understanding patients' preferences and unmet needs related to Hemophilia A management in Brazil is critical for better decision-making. As a result, this study was conducted to identify such gaps using a Brazilian expert Delphi panel.

Material and methods

The modified Delphi methodology

The Delphi methodology was chosen to reach a consensus on hemophilia management among experts. This method employs a series of surveys distributed to a group of people to ascertain consensus on statements about a domain of expertise (Dalkey & Helmer, 1963; Hsu & Sandford, 2007).

A modified Delphi consensus was conducted between September and October 2020 (Diamond *et al.*, 2014; Hasson *et al.*, 2000; Powell, 2003). It consisted of the following steps: (a) formation of a steering committee of Brazilian hemophilia experts to determine which topics should be prioritized to improve assistance for patients with hemophilia; (b) establishment of a rationale for authors' validation; (c) validation of the initial statements by the steering committee; (d) discussion of the results by the steering committee; (e) second-round evaluation by first-round participants; and (f) finalization of the consensus-based recommendations. Study steps are shown in Figure 1.

Development of the initial survey

A steering committee with hemophilia experience, representative of various regions in Brazil, recommended by the lead investigators, developed the initial survey based on current knowledge in the field. The survey content was e-mailed to the experts who had two weeks to answer the questions.

The survey asked about prophylaxis, the indications for emicizumab and bypassing agents, how to deal with patients who have inhibitors, ITI use, and adherence. The questionnaires used in both rounds are available in the supplementary material. All steps were completed independently. A committee comprised of authors who identified questions lacking consensus and needing to be addressed in the second round analyzed the results.

Defining consensus

The Round 1 survey required selecting a single item for all questions; the consensus was defined as equal to or greater than 75 percent of votes in agreement. Round 2 focused on the topics on which there was no agreement. In round 2, the

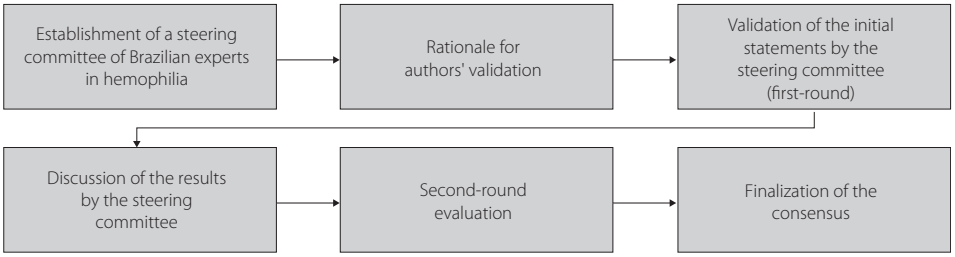

Figure 1. Consensus steps used in the Delphi panel.

experts anonymously expressed their agreement/disagreement on each statement using a 5-point Likert-type scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree).

The number and percentage of participants who scored each item were calculated. In all questions, the answer options were presented invariably (the same pattern, containing a neutral answer, two positive and two negative). Each question specifies whether there was agreement among experts, and the consensus was defined as more than 75% of voters agreeing on a positive or negative response.

Survey refinement

Following the survey round, data was processed and collated, and the level of agreement was determined. Following two rounds of surveying, all statements that achieved or did not achieve consensus were consolidated or described.

Recruitment

All participants were hematologists with extensive clinical experience treating hemophilia in the Brazilian Public Health System. All individuals voluntarily participated in the study and signed the informed consent by e-mail.

Statistical analysis

The consensus was determined by the simple frequency (percentage) of the agreement for each survey round. Descriptive statistical analysis, proportion, central tendency, and dispersion were calculated using Microsoft Excel.

Results

Interviewee profile

A total of nine physicians who, on average, had graduated in the past 26 years (Standard Deviation [SD]: 10.03) and specialized in hematology for the past 18.1 years (SD: 3.4) participated in this study. The participants have been working throughout Brazilian Public Hemophilia treatment centers (HTC), including the Northeast (N = 3), Midwest (N = 1), Southeast (N = 4), and South (N = 1) regions.

Round 1

As part of the first round, participants were asked about hemophilia patients' profiles in their respective regions (Table 1).

According to expert opinion, most patients assisted at HTC are older than 30 years (28%), present severe disease (57%), receive secondary prophylaxis (31%), and 93% have no inhibitors. Joints appear as the leading bleeding site (57%) and the knee as the most frequently affected one (47.2%), followed by the ankle (31.1%) and elbow (18.3%). Half of the participants reported a probability of using a central venous catheter, ranging from 1 to 20%. The other half stated no need to use a central venous catheter in their centers; the heterogeneity is likely related to patients' profiles, as a central venous catheter is typically indicated for young children.

In addition to the patient's characteristics, the initial questionnaire addressed topics related to therapeutic strategies. The experts ranked the criteria to suggest treatment for patients with hemophilia A without inhibitors in the following order: (1) efficacy; (2) safety; (3) dosage convenience; (4) route of administration; (5) patient/caregiver preferences; and (6) cost of treatment. While for patients with inhibitors, the ranking factors were similarly classified, except for (4) "dosage convenience" and (3) "route of administration" that appeared in inverted positions.

Table 1. Patients profile according to expert's opinion

Variables	%
Age group	
0-3 years old	12
4-12 years old	18
13-18 years old	20
19-30 years old	22
>30 years old	28
Disease severity	
Mild	19
Moderate	24
Severe	57
Prophylaxis	
Primary	20
Secondary	31
Tertiary	23
On demand	26
Probability of central venous catheter insertion	
0%	50
1 to 20%	50
Inhibitors	
Yes	7
No	93
Bleeding site	
Joints	57
Muscles	26
Mucosa	13
CNS	4
Joint bleeding site	
Knee	47.2
Ankle	31.1
Elbow	18.3
Shoulder	7.1
Hip	6.3

CNS: central nervous system.

Asked about procedures performed routinely in the first hemarthrosis event, FVIII administration is recommended by all (100%) specialists and physical therapists by 67%. However, other procedures such as hospitalization, red blood cells transfusion, tests such as blood count, activated partial thromboplastin time (aPTT)/partial thromboplastin time (PTT), and biochemistry, imaging tests, radiography, and computed tomography, would not be recommended by specialists.

In terms of the annual rate of bleeding that would shift the therapeutic approach from on-demand to prophylactic therapy, most specialists (57%) would change the treatment at an annual rate of two to three bleedings. For 29%, this change would happen at an annual rate higher than three bleeds and for 14% with only one bleed per year.

Table 2 shows specialists' preferential treatment by different subgroups.

Table 2. Expert's opinion on therapeutic strategies

Management	**Response**	
Age group and hemophilia A treatment		**%**
Should prophylaxis be instituted at a young age (before bleeding episodes) or postponed until a specific time point?	Regardless of age group, including patients <12 years old	100
	Patients >12 years old	0
	Patients >18 years old	0
	Other	0
Prophylaxis		**Ranking**
When indicating prophylaxis, what would be the best prophylactic therapy in a scenario where all technologies were available at SUS?	Extended half-life FVIII	1
	Emicizumab	2
	Recombinant FVIII	3
	Plasmatic FVIII	4
Bypass agents		**%**
Which factors determine the intermittent prophylaxis indication with bypass agent for patients with inhibitors?	Bleeding rate	89
	Bleeding site	78
	ITI impossibility	78
	Age group	11
	FVIII level	0
Inhibitors testing		**%**
Which signs or symptoms determine the patient's test for inhibitors?	Routine test	100
	Bleeding inadequate response to FVIII replacement	89
	Increased bleeding rate	78
	Other	0
How often do your patients with inhibitors take intermittent (short-term) prophylaxis?	<3 months	33
	<6 months	33
	<12 months	33
ITI		**%**
In which of these situations would you not consider ITI therapy for a patient with inhibitors?	No venous access	67
	No patient/caregiver compliance	67
	No adherence	56
	Young child	11
	Presence of predictive factors for failure	11
	No	11
	High-titer inhibitor	0
Blood products and contamination risk		**%**
Concern about contamination is still a significant factor in indicating an alternative product such as emicizumab?	Yes	56
	No	44

FVIII: factor VIII; ITI: immune tolerance induction.

The experts unanimously agreed that prophylaxis should be instituted regardless of the patient's age. Bleeding sites and bleeding rates were the most frequently cited factors for indicating intermittent prophylaxis with bypass agents in patients with inhibitors. Most respondents (56%) reported that blood products contamination is still a concern and a potential indication for emicizumab. The preferred therapy was long-acting FVIII, followed by emicizumab, in a scenario with all technologies available at SUS.

Experts unanimously reported inhibitor testing should be done regularly. However, most of them test again if there is an inadequate response to FVIII replacement (89%) and bleeding frequency increases (78%).

In patients with inhibitors, the frequency of short-term intermittent prophylaxis is similarly distributed between less than three months, less than six months, and less than 12 months (33% each). Experts say ITI would not be indicated for patients with inhibitors with no venous access (67%) and no patient/caregiver compliance (67%).

At the end of the first round, participants were asked to answer questions about emicizumab. When ranking the most relevant indications for prescribing the drug, the following order was observed: (1) presence of inhibitors; (2) need for central venous access; (3) gains in quality of life; (4) bleeding rate; (5) pain during venous infusion; and (6) joint involvement.

Table 3 shows experts' agreement on the emicizumab indication for different scenarios. Most participants (67%) agreed that emicizumab prevents and reduces bleeding in patients with inhibitors. In addition, most experts (67%) believe this drug should be restricted to ITI non-responders and that this is a good option as prophylaxis during ITI (67%).

Table 3. Experts' agreement on the emicizumab indication in different situations

	Emicizumab indication	
Scenarios indications	**Yes (%)**	**No (%)**
Bleeding prevention in patients with inhibitors	67	33
Bleeding reduction in patients with inhibitors	89	11
Bleeding prevention in patients without inhibitors	33	67
Bleeding reduction in patients without inhibitors	56	44
Emicizumab is restricted to ITI non-responders	67	33
Emicizumab is a good option for prophylaxis during ITI	67	33

TI: immune tolerance induction.

Experts were asked to identify and rank possible indications for emicizumab regarding patients without inhibitors. The following order of relevance has been defined: (1) difficulty in venous access (89%); (2) high bleeding phenotype (56%); (3) short pharmacokinetics (FVIII) (44%); (4) family history of inhibitor development (44%); (5) primary prophylaxis (11%); and (6) children (11%).

Round 2

The same experts were invited to participate in the second round; six agreed, and the consensus was defined as at least five concordant responses. Table 4 shows the results of the second round. Overall, all experts recommended prophylaxis, regardless of age, bleeding treatment pattern, or bleeding sites. Venous access and infusion frequency were the most considerable barriers to patient treatment. Emicizumab was unanimously considered an excellent therapeutic option for patients with difficult venous access, who require central venous access, or in the presence of infusion-related pain. Even if available in the Brazilian Public Health System, most experts (67%) believe that emicizumab will not replace ITI or long-term FVIII therapy.

The consensus was not achieved on some statements regarding emicizumab recommendation for patients with moderate or severe hemophilia A without inhibitors or restricted only to patients with moderate or severe hemophilia A with a high-titer inhibitor. There was no consensus on emicizumab recommendations for pediatric patients with moderate or severe hemophilia A without inhibitors, regardless of age (Table 4).

Discussion

This study was carried out to identify patients' unmet medical needs in the management of hemophilia A in Brazil through a consensus provided by a Brazilian Delphi panel of experts who considered in their decisions their experience relating to patients' preferences and reasons for discontinuing treatment. Understanding the main concerns of all stakeholders in clinical practice is critical for decision-making. As a result, the findings of this study are essential for hemophilia A care in Brazil.

In this Brazilian Delphi panel, venous access, infusion-related pain, and frequency were reported as the most significant barriers to patient's treatment in Brazil, representing the primary unmet needs. It is an essential finding since, according to the Hemophilia Guideline proposed by the Brazilian Ministry of Health in 2015, the replacement of the deficient coagulation factor (derived from human plasma or recombinant) and the use of other homeostatic agents such as desmopressin and antifibrinolytics are recommended. Most of these strategies are administered intravenously (Brasil, 2015).

Table 4. Definitions obtained through the Brazilian Delphi panel

		Scale* (N)				
Recommendations	**Consensus**	**1**	**2**	**3**	**4**	**5**
Should SUS patients with severe hemophilia A receive prophylaxis even in the absence of bleeding?	Yes	-	-	-	-	6
Prophylactic therapy is recommended for patients without inhibitors on-demand therapy who have more than one annual episode of spontaneous bleeding.	Yes	1	-	-	4	1
Long-term FVIII, if available at SUS, would be the first option for patients with moderate/severe hemophilia A without inhibitors and a high bleeding rate.	Yes	-	1	-	3	2
Emicizumab, if available at SUS, would be the first treatment option for patients with moderate/severe hemophilia A without prophylaxis and with high-titer inhibitor and bleeding rates.	Yes	-	1	-	3	2
Emicizumab, if available at SUS, would be the first treatment option for patients with moderate/severe hemophilia A with prophylaxis and with high-titer inhibitor and bleeding rates.	Yes	-	1	-	4	1
Emicizumab is the first option for patients with moderate / severe hemophilia A and inhibitors with a high bleeding rate.	Yes	-	1	-	4	1
The bypass agent is the first option for patients with moderate / severe hemophilia A and inhibitors with a high rate of bleeding.	Yes	-	1	-	4	1
In your experience, what percentage of patients adhere to treatment when prescribing ITI?*	Yes	-	-	-	5	1
Even without bleeding (hemarthrosis or muscle bleeding), patients with high-titer inhibitors should be treated with ITI.	Yes	-	-	-	1	5
I would prescribe emicizumab (if available at SUS) for patients undergoing ITI and who need prophylaxis to prevent bleeding during ITI treatment.	Yes	-	1	-	1	4
I would consider emicizumab, if available at SUS, restricted to patients with moderate/severe hemophilia A and a high-titer inhibitor with ITI failure.	Yes	-	1	-	4	1
In the previous round, intravenous administration and infusion frequency were the main factors limiting patients' adherence to treatment.	Yes	-	-	-	1	5
If available at SUS, I would recommend emicizumab for patients with moderate/severe hemophilia A and difficult venous access, regardless of inhibitors.	Yes	-	-	-	4	2
If available at SUS, I would recommend emicizumab for patients with moderate/severe hemophilia A and central venous access need, regardless of inhibitors.	Yes	-	-	-	5	1
I would consider emicizumab, if available at SUS, to be restricted only to patients with a high-titer inhibitor or without venous access.	Yes	-	-	1	5	-
If available at SUS, I would recommend emicizumab for patients with moderate/severe hemophilia A without inhibitors and prophylactic therapy.	No	-	2	2	1	1
I would prescribe emicizumab, if available at SUS, for patients with moderate/severe hemophilia A receiving bypass agents and with poorly controlled bleeding episodes.	Yes	-	-	-	2	4
I would consider emicizumab, if available at SUS, restricted only to patients with moderate/severe hemophilia A with a high-titer inhibitor.	No	-	3	-	2	1
I would consider emicizumab, if available at SUS, restricted to patients with moderate/severe hemophilia A with a high-titer inhibitor and not eligible for ITI.	No	-	2	-	2	2
I would consider emicizumab, if available at SUS, to be restricted only to patients with moderate/severe hemophilia A not eligible for ITI.	No	1	1	-	4	-
In the pediatric population with moderate/severe hemophilia A, I would consider emicizumab a good therapeutic arsenal option, if available at SUS, for patients under three years old with high-titer inhibitors.	Yes	-	-	1	3	2
In the pediatric population with moderate/severe hemophilia A, I would consider emicizumab a good therapeutic arsenal option, if available at SUS, for patients under three years old without inhibitors.	No	-	2	-	4	-
In the pediatric population with moderate/severe hemophilia A, I would consider emicizumab a good therapeutic arsenal option, if available at SUS, for patients aged 3-6 years with high-titer inhibitors.	Yes	-	-	-	5	1
In the pediatric population with moderate/severe hemophilia A, I would consider emicizumab a good therapeutic arsenal option, if available at SUS, for patients aged 3-6 years without inhibitors.	No	-	2	1	3	-
In the pediatric population with moderate/severe hemophilia A, I would consider emicizumab a good therapeutic arsenal option, if available at SUS, for patients aged 6-12 years with high-titer inhibitors.	Yes	-	-	-	2	4
In the pediatric population with moderate/severe hemophilia A, I would consider emicizumab a good therapeutic arsenal option, if available at SUS, for patients aged 6-12 years without inhibitors.	No	-	2	1	3	-

*5-point Likert-type scale: = less than 10%, 2 = around 25%, 3 = around 50%, 4 = around 75%, and 5 = next to 100%. FVIII: Factor VIII; ITI: immune tolerance induction; SUS: Brazilian Public Health System.

The need for technologies that use alternative routes of administration was highlighted by experts who saw it as an unmet need among patients. As a result, if emicizumab with its subcutaneous route of administration became widely available in the Brazilian Public Health System, it would fulfill the preference of a sizable proportion of hemophilia patients. In agreement with this statement, the Practical Guidance of the German, Austrian and Swiss Society for Thrombosis and Haemostasis Research (GTH), as well as World Federation of Hemophilia (WFH) guidelines (2020), proposed the use of emicizumab as a prophylactic approach in patients with hemophilia A with or without inhibitors of all ages based on patients' situation including venous access issues (Holstein *et al*., 2020; Srivastava *et al*., 2020).

Unmet needs related to hemophilia A care were previously reported considering different perspectives. Mahony *et al.* (2017) conducted a survey to obtain information on hemophilia care and treatment availability in 37 European countries. They reported a lack of access to psychosocial care and poor preparation for an aging hemophilia population (von Mackensen *et al*., 2017). They also assessed patients' unmet needs and reported that most individuals from Germany, Switzerland, and Austria perceived short half-life and frequent injections as disadvantages of the current treatment. Differences observed in the studies highlight the need to conduct an unmet needs analysis considering different perspectives.

Delphi approach was used (Dalkey & Helmer, 1963; Hsu & Sandford, 2007) to define a consensus on Brazil's unmet disease needs. There are two strategies of analysis using this method: classic and modified Delphi. Classic Delphi proposes the performance of four rounds among participants, the first one composed of a questionnaire including open answers, using a qualitative approach. The modified method allows the first round to consist of focus groups or face-to-face interviews that use content analysis or a structured form with quantitative questions based on the literature or previous research. Subsequent rounds are similar in both strategies and use the analysis of prior rounds to compose further questions until the minimum consensus is reached (Massaroli *et al*., 2018).

Despite the important results shown in this study, some limitations need to be highlighted. The first is related to the representativeness of the study sample since no experts from the North region were included. In addition, although experts from all other areas were included, most participants were from the Northeast and Southeast. Finally, despite the Delphi method being a universally used strategy, results are based on expert opinion, and information obtained through real-world analysis could be more representative of reality.

Conclusion

The Brazilian Delphi panel revealed critical unmet needs to fulfill patients' preferences in managing hemophilia A in Brazil. Venous access and infusion frequency were the most considerable barriers to patients' treatment, and emicizumab was considered an excellent therapeutic option. Thus, the results of this Brazilian Delphi panel may be helpful for health policymakers in developing new strategies for better disease management in the country.

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References

Aledort L, Mannucci PM, Schramm W, Tarantino M. Factor VIII replacement is still the standard of care in haemophilia A. Blood Transfus. 2019;17(6):479-86.

Anvisa – Agência Nacional de Vigilância Sanitária. Registro Anvisa emicizumabe [Internet]. 2019. Available on: https://consultas.anvisa.gov.br/#/medicamentos/25351624847201781/?nomeProduto=hemcibra. Accessed on: Oct 8, 2020.

Blair HA. Emicizumab: A Review in Haemophilia A. Drugs. 2019;79(15):1697-707.

Brackmann HH, White GC, Berntorp E, Andersen T, Escuriola-Ettingshausen C. Immune tolerance induction: What have we learned over time? Haemophilia. 2018;24 Suppl 3:3-14.

Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Especializada e Temática. Manual de hemofilia. Brasília: Ministério da Saúde; 2015. 80p.

Cao O, Loduca PA, Herzog RW. Role of regulatory T cells in tolerance to coagulation factors. J Thromb Haemost. 2009;7(Suppl 1):88-91.

Dalkey N, Helmer O. An experimental application of Delphi method to use experts. Manag Sci. 1963;9:458-67.

Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014;67(4):401-9.

Ferreira AA, Leite IC, Bustamante-Teixeira MT, Guerra MR. Hemophilia A in Brazil – epidemiology and treatment developments. J Blood Med. 2014;5:175-84.

Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000;32(4):1008-15.

Holstein K, Albisetti M, Bidlingmaier C, Halimeh S, Heine S, Klamroth R, et al. Practical Guidance of the GTH Haemophilia Board on the Use of Emicizumab in Patients with Haemophilia A. Hamostaseologie. 2020;40(5):561-71.

Hsu CC, Sandford BA. The Delphi technique: Making sense of consensus. Pract Assessment Res Eval. 2007;12(10):1-8.

Kruse-Jarres R, Kempton CL, Baudo F, Collins PW, Knoebl P, Leissinger CA, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol. 2017;92(7):695-705.

Mahony BO, Savini L, Hara JO, Bok A. Haemophilia care in Europe – A survey of 37 countries. Haemophilia. 2017;23(4):e259-66.

Mannucci PM, Tuddenham EG. The Hemophilias – From Royal Genes to Gene Therapy. N Engl J Med. 2001;344(23):1773-9.

Massaroli A, Martini JG, Lino MM, Spenassato D, Massaroli R. Método Delphi como referencial metodológico para a pesquisa em enfermagem. Texto Contexto Enferm. 2018;26(4):1-9.

Peyvandi F, Ettingshausen CE, Goudemand J, Jiménez-Yuste V, Santagostino E, Makris M. New findings on inhibitor development: from registries to clinical studies. Haemophilia. 2017;23:4-13.

Powell C. The Delphi technique: Myths and realities. J Adv Nurs. 2003;41(4):376-82.

Produtos Roche Químicos e Farmacêuticos S.A. Hemcibra (emicizumabe) [bula]. 2019. 28p.

Schep SJ, Schutgens REG, Fischer K, Boes ML. Review of immune tolerance induction in hemophilia A. Blood Rev. 2018;32(4):326-38.

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;26(S6):1-158.

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;134(3):317-20.

von Mackensen S, Kalnins W, Krucker J, Weiss J, Miesbach W, Albisetti M, et al. Haemophilia patients' unmet needs and their expectations of the new extended half-life factor concentrates. Haemophilia. 2017;23(4):566-74.

WFH – World Federation of Hemophilia. Report on the Annual Global Survey 2019. WFH; 2020.