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The Nurse Coordinator's Perspective on Managing Hemophilia Patients With Inhibitors

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Introduction

More than 30 years have passed since the [National Hemophilia Foundation](#) launched its campaign to establish the creation of a network of hemophilia diagnostic and treatment centers across the country.¹ Today, more than 140 federally funded hemophilia treatment centers and programs exist in the United States, and multidisciplinary team care with an emphasis on early diagnosis and intervention to prevent complications has evolved into the norm for the treatment and management of hemophilia.^{1,2}

The comprehensive team care model has become one of the most successful public health initiatives in developed countries. Studies have shown that this model results in significantly improved outcomes for patients and reduced healthcare utilization.³ Within this model, a core treatment team is assembled, consisting of a nurse coordinator, a medical director (usually a hematologist), physiotherapist, and social worker.³ Each member is an integral part of the team, offering specialized care and expertise to hemophilia patients and their families.

The Nurse Coordinator's Role in Hemophilia Team Care

In [Standards and Criteria for the Care of Persons With Congenital Bleeding Disorders](#), the National Hemophilia Foundation outlines the following responsibilities of the hemophilia nurse coordinator:²

- Assessment of patient's general health and bleeding-related issues
- Patient and family education
- Coordination and evaluation of home therapy and home infusion programs
- Development and coordination of patient plan of care
- Interaction with all team members to ensure plan carried out safely
- Participation in quality assurance activities
- Facilitation of data collection and documentation
- Participation in research studies
- Liaison between hemophilia treatment center and community, including primary care providers

The nurse coordinator serves as the link that connects the patient to other members of the care team and extended medical community, including the patient's primary care provider. Nurse coordinators enroll patients in clinical trials about genetic mutations; liaise with outside hospital, inpatient units, and emergency rooms; and function as the first line of triage for patients and their families.

Predicting and Preventing Inhibitor Development

The development of inhibitors is the most serious complication associated with hemophilia. Antibody response to factor VIII can occur in up to 30% of patients with hemophilia A, and in up to 5% of patients with hemophilia B.⁴ Orthopedic complications and the effect on quality of life are more severe in patients with inhibitors, and bleeds are more difficult to control.⁴

Patients with high-titer inhibitors are at increased risk for potentially life-threatening bleeds, which in

turn necessitate complex and costly treatment.⁵ Identifying and understanding those risk factors that are modifiable is essential for the potential prevention of inhibitor development in patients with hemophilia.⁵

Known patient-related risk factors for inhibitor development include ethnicity, family history of inhibitors, and factor VIII gene mutation type (**Tables 1a and 1b**).⁵

Treatment-related risk factors (**Tables 2a and 2b**) include early age at onset of treatment and intensity of treatment, perhaps due to the tissue damage and inflammation that is associated with the major bleeds or surgeries that lead to intensive treatment.⁵

Conversely, some studies have noted a protective effect with prophylactic treatment. In the CANAL study, a retrospective multicenter cohort study performed by Gouw and colleagues, a 60% lower risk of inhibitor development was observed with regular prophylaxis.⁵ Gouw and colleagues also compared the incidence of inhibitor development when recombinant factor VIII products were used as compared with plasma-derived factor VIII products. The authors found no evident difference in inhibitor incidence between plasma-derived and recombinant factor VIII products (**Tables 3a and 3b**).⁶

There was a slightly lower risk of inhibitor development in patients who received plasma-derived factor VIII concentrate, but this risk was not statistically significant. Switching between products also did not appear to affect inhibitor risk.⁶

Table 1a. Risk of Inhibitor Development According to Patient Characteristics

All inhibitors					
	Proportion with Inh (%)	Crude RR (CI)	P	Adjusted RR (CI)	P
Baseline factor VIII activity					
0.01 to 0.02 IU/mL	4/34 (12)	1.0		1.0*	
<0.01 IU/mL	83/332 (25)	2.3 (0.9-6.3)	.10	4.1 (1.0-16.9)	.05
Ethnicity					
White	78/327 (24)	1.0		1.0†	
African	3/8 (38)	1.8 (0.6-5.8)	.31	1.9 (0.6-6.1)	.31
Asian	1/15 (7)	0.3 (0.04-1.9)	.19	0.3 (0.04-2.4)	.27
Other	5/15 (33)	1.5 (0.6-3.6)	.42	2.5 (1.0-6.7)	.06
Family history of hemophilia					
Negative	45/191 (24)	1.0		1.0†	
Positive	42/168 (25)	1.1 (0.7-1.6)	.69	1.0 (0.7-1.6)	.88
Family history of inhibitors					
Negative	29/138 (21)	1.0		1.0†	
Positive	13/24 (52)	3.1 (1.6-6.0)	.001	2.8 (1.3-6.1)	.007
Breast-feeding					
No	12/41 (29)	1.0		1.0†	
Yes	25/91 (27)	0.9 (0.5-1.9)	.88	1.3 (0.6-2.8)	.59
Factor VIII gene mutation type					
Low risk	13/100 (13)	1.0		1.0‡	
High risk	68/212 (32)	2.8 (1.5-5.0)	.001	2.3 (1.3-4.3)	.006

Inh indicates inhibitors.

*Adjusted for ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

†Adjusted for baseline factor VIII activity level, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

‡Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

§Adjusted for baseline factor VIII activity level, ethnicity, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

Adapted from Gouw SC, et al, for the CANAL Study group. *Blood*. 2007;109:4648-4654.

Table 1b. Risk of Inhibitor Development According to Patient Characteristics

High-titer inhibitors*					
	No. of Inh (%)	Crude RR (CI)	P	Adjusted RR (CI)	P
Baseline factor VIII activity					
0.01 to 0.02 IU/mL	2/34 (6)	1.0	.07	1.0 [†]	
<0.01 IU/mL	67/332 (20)	3.8 (0.9-15.3)		6.5 (0.9-47.5)	.06
Ethnicity					
White	63/327 (19)	1.0		1.0 [†]	
African	2/8 (25)	1.5 (0.4-6.2)	.57	1.4 (0.3-6.1)	.62
Asian	1/15 (7)	0.3 (0.05-2.4)	.27	0.4 (0.05-2.8)	.35
Other	3/15 (20)	1.1 (0.3-3.4)	.89	1.7 (0.5-5.7)	.41
Family history of hemophilia					
Negative	36/191 (19)	1.0		1.0 [†]	
Positive	33/168 (20)	1.1 (0.7-1.7)	.78	1.0 (0.6-1.7)	.85
Family history of inhibitors					
Negative	21/138 (15)	1.0		1.0 [†]	
Positive	12/24 (50)	4.0 (2.0-8.2)	<.001	3.5 (1.5-8.1)	.003
Breast-feeding					
No	8/41 (20)	1.0		1.0 [†]	
Yes	23/91 (25)	1.3 (0.6-1.9)	.51	2.1 (0.8-5.5)	.12
Factor VIII gene mutation type					
Low risk	7/100 (7)	1.0		1.0 [†]	
High risk	57/212 (27)	4.3 (2.0-9.5)	<.001	3.7 (1.7-8.3)	.001

Inh indicates inhibitors.

*High-titer inhibitor was defined as clinically relevant inhibitor with a peak titer of at least 5 BU/mL.

[†]Adjusted for ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

[‡]Adjusted for baseline factor VIII activity level, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

[§]Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

[¶]Adjusted for baseline factor VIII activity level, ethnicity, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

Adapted from Gouw SC, et al, for the CANAL Study group. *Blood*. 2007;109:4648-4654.

Table 2a. Risk of Inhibitor Development According to Treatment Characteristic

All inhibitors					
	Proportion of Inh (%)	Crude RR (CI)	P for trend	Adjusted RR (CI)	P for trend
At first factor VIII exposure					
Age at first exposure					
>18 mo	10/57 (18)	1.0	.005	1.0 ^a	.21
12 to 18 mo	16/82 (20)	1.1 (0.5-2.5)		1.2 (0.5-2.9)	
6 to 12 mo	30/130 (23)	1.3 (0.7-2.7)		1.5 (0.6-3.4)	
1 to 6 mo	13/43 (30)	1.9 (0.8-4.3)		1.8 (0.7-4.7)	
<1 mo	16/39 (41)	2.7 (1.2-5.9)		1.6 (0.6-4.1)	
Reason for first factor VIII treatment					
Bleed	65/286 (23)	1.0		1.0 ^a	
Prophylaxis	8/37 (22)	1.0 (0.5-2.0)	.92	1.0 (0.5-2.2)	.95
Surgical procedure	11/17 (65)	3.7 (2.0-7.1)	<.001	2.6 (1.3-5.1)	.007
Peak treatment moment at first treatment episode ^a					
None	44/229 (19)	1.0		1.0 ⁱ	
3 to 4 days	7/36 (19)	1.0 (0.5-2.3)	.98	1.1 (0.5-2.4)	.87
At least 5 days	32/57 (56)	3.3 (2.1-5.3)	<.001	3.1 (1.9-5.0)	<.001
During first 50 exposure days					
After peak treatment moment compared with before	NA	1.6 (1.0-2.7)	.06	1.5 (0.9-2.5) ^h	.14
After major peak treatment moment compared with before	NA	2.0 (1.3-3.1)	.002	1.6 (1.0-2.6) ^h	.03
After major surgical procedure compared with before	NA	1.4 (0.8-2.5)	.21	1.3 (0.8-2.3) ^h	.32
Duration between exposure days ⁱ					
>50 days	NA	1.0	.03	1.0 ^a	.26
10 to 50 days	NA	0.8 (0.4-1.6)		0.8 (0.4-1.6)	
<10 days	NA	1.9 (1.1-3.3)		1.5 (0.8-2.7)	
Dose of factor VIII product ⁱ					
<35 IU/kg	NA	1.0	<.001	1.0 ^a	.01
35 to 50 IU/kg	NA	1.4 (0.7-3.0)		1.2 (0.6-2.6)	
>50 IU/kg	NA	3.3 (1.7-6.5)		2.3 (1.2-4.7)	
Regular prophylaxis	NA	0.4 (0.2-0.8)	.01	0.5 (0.2-0.9)**	.02

Inh indicates inhibitors; NA, not applicable.

^aOnly 2 of the 7 patients who developed inhibitors before the fifth exposure day received treatment with factor VIII on consecutive days (2); the others received treatment on single days before inhibitor development.

ⁱIn patients who were treated on demand during the first 50 exposure days.

^hAdjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, duration between exposure days, dose, prophylaxis, peak treatment moment at first treatment, reason for first treatment, and product type.

ⁱAdjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

^jAdjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, prophylaxis, and product type.

^kAdjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, dose, prophylaxis, and product type.

^lAdjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, prophylaxis, product type, and body weight.

^mAdjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, and product type.

Adapted from Gouw SC, et al, for the CANAL Study group. *Blood*. 2007;109:4648-4654.

Table 2b. Risk of Inhibitor Development According to Treatment Characteristic

High-titer inhibitors*					
	Proportion of Inh (%)	Crude RR (CI)	P for trend	Adjusted RR (CI)	P for trend
At first factor VIII exposure					
Age at first exposure					
>18 mo	9/57 (16)	1.0	.02	1.0 [§]	.63
12 to 18 mo	13/82 (16)	1.0 (0.4-2.4)		1.0 (0.4-2.6)	
6 to 12 mo	23/130 (18)	1.1 (0.5-2.5)		1.1 (0.4-2.6)	
1 to 6 mo	10/43 (23)	1.6 (0.6-3.9)		1.3 (0.5-3.8)	
<1 mo	13/39 (33)	2.4 (1.0-5.6)		1.1 (0.4-3.2)	
Reason for first factor VIII treatment					
Bleed	50/286 (17)	1.0		1.0 [§]	
Prophylaxis	7/37 (19)	1.1 (0.5-2.4)	.82	1.2 (0.5-2.8)	.63
Surgical procedure	10/17 (59)	4.4 (2.2-8.7)	<.001	3.2 (1.6-6.7)	.002
Peak treatment moment at first treatment episode [†]					
None	31/229 (14)	1.0		1.0 [§]	
3 to 4 days	6/36 (17)	1.2 (0.5-2.9)	.66	1.3 (0.5-3.1)	.63
At least 5 days	30/57 (53)	4.3 (2.6-7.1)	<.001	4.1 (2.4-7.0)	<.001
During first 50 exposure days					
After peak treatment moment compared with before	NA	1.7 (1.0-2.9)	.07	1.5 (0.8-2.6) [§]	.18
After major peak treatment moment compared with before	NA	2.3 (1.4-3.7)	.001	1.9 (1.1-3.1) [§]	.02
After major surgical procedure compared with before	NA	1.3 (0.7-2.5)	.43	1.2 (0.6-2.3) [§]	.61
Duration between exposure days [‡]					
>50 days	NA	1.0	.06	1.0 [§]	.62
10 to 50 days	NA	0.6 (0.3-1.4)		0.6 (0.3-1.4)	
<10 days	NA	1.9 (1.1-3.4)		1.3 (0.7-2.5)	
Dose of factor VIII product [§]					
<35 IU/kg	NA	1.0	<.001	1.0 ^{**}	.01
35 to 50 IU/kg	NA	1.7 (0.7-4.0)		1.5 (0.6-3.6)	
>50 IU/kg	NA	4.2 (1.9-9.3)		3.0 (1.3-6.9)	
Regular prophylaxis	NA	0.5 (0.2-0.9)	.03	0.5 (0.2-1.0) ^{††}	.05

Inh indicates inhibitors; NA, not applicable.

*High-titer inhibitor was defined as clinically relevant inhibitor with a peak titer of at least 5 BU/mL.

[†]Only 2 of the 7 patients who developed inhibitors before the fifth exposure day received treatment with factor VIII on consecutive days (2); the others received treatment on single days before inhibitor development.

[‡]In patients who were treated on demand during the first 50 exposure days.

[§]Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, duration between exposure days, dose, prophylaxis, peak treatment moment at first treatment, reason for first treatment, and product type.

[¶]Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, prophylaxis, and product type.

[‡]Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, prophylaxis, and product type.

^{**}Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, prophylaxis, product type, and body weight.

^{††}Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose, and product type.

Adapted from Gouw SC, et al, for the CANAL Study group. *Blood*. 2007;109:4648-4654.

Table 3a. Risk of Inhibitor Development According to Type of Factor VIII Product

All clinically relevant inhibitor development					
		Crude		Adjusted	
NED		RR (CI)	P	RR (CI)	P
Recombinant	8493	1.0		1.0	
Plasma-derived	4425	0.8 (0.5-1.3)	.34	0.7 (0.4-1.1)	.14
Recombinant	8493	1.0		1.0	
Plasma-derived					
Low vWF content*	1272	0.3 (0.1-1.1)	.07	0.4 (0.1-1.1)	.08
High vWF content*	3153	1.0 (0.6-1.6)	.91	0.8 (0.5-1.4)	.45
Kogenate	4267	1.0		1.0	
Kogenate Bayer	378	1.1 (0.2-4.5)	.94	1.2 (0.3-5.4)	.79
Recombinate	1639	1.1 (0.5-2.3)	.75	1.0 (0.5-2.1)	.99
Refacto	2209	1.4 (0.8-2.6)	.24	1.6 (0.9-3.2)	.14

Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose of factor VIII, and regular prophylaxis.

NED indicates number of exposure days on the concerning product type; CI, 95% confidence interval; and RR, relative risk.

*Low vWF content was defined as less than 0.01 IU vWF antigen per IU factor VIII antigen; high vWF content was defined as more than 0.01 IU vWF antigen per IU factor VIII antigen.

Adapted from Gouw SC, et al, for the CANAL Study group. *Blood*. 2007;109:4648-4654.

Table 3b. Risk of Inhibitor Development According to Type of Factor VIII Product

High-titer inhibitor development*					
		Crude		Adjusted	
		RR (CI)	P	RR (CI)	P
Recombinant		1.0		1.0	
Plasma-derived		0.9 (0.5-1.5)	.72	0.8 (0.4-1.3)	.33
Recombinant		1.0		1.0	
Plasma-derived					
Low vWF content†		0.3 (0.1-1.2)	.09	0.3 (0.1-1.3)	.11
High vWF content†		1.1 (0.7-2.0)	.61	0.9 (0.5-1.6)	.79
Kogenate		1.0		1.0	
Kogenate Bayer		1.5 (0.3-6.5)	.60	1.6 (0.3-7.3)	.55
Recombinate		1.4 (0.6-3.1)	.39	1.2 (0.5-2.7)	.70
Refacto		1.5 (0.7-3.0)	.30	1.4 (0.6-3.1)	.38

Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose of factor VIII, and regular prophylaxis.

NED indicates number of exposure days on the concerning product type; CI, 95% confidence interval; and RR, relative risk.

*High-titer inhibitor was defined as clinically relevant inhibitor with a peak titer of at least 5 BU/mL.

†Low vWF content was defined as less than 0.01 IU vWF antigen per IU factor VIII antigen; high vWF content was defined as more than 0.01 IU vWF antigen per IU factor VIII antigen.

Adapted from Gouw SC, et al, for the CANAL Study group. *Blood*. 2007;109:4648-4654.

Preparing Patients for Immune Tolerance Induction

When patients develop inhibitors, immune tolerance induction (ITI) is the only proven method of eradication. Carcao et al report a 60% to 80% success rate with ITI. ITI therapy regimens involve regular infusions of replacement factor, with the goal of inducing antigen-specific tolerance, which allows patients to reinstitute factor replacement therapy.⁴

Patients who may be candidates for ITI need effective education and counseling so they can make informed decisions, and in order for optimal outcomes to be achieved. Key points for the nurse coordinator to relay to patients include the costs, time commitment, and lifestyle changes associated with ITI, as well as the potential for adverse effects. Adverse effects generally are related to the factor concentrate used, the type and quantity of bypassing agent employed, the administration of any immunosuppressive agent, and the use of central venous access devices.⁴

Preparing Patients for Surgery

Traditionally, all but the most essential surgeries have been avoided in hemophilia patients with inhibitors because of concerns that adequate hemostasis could not be achieved or maintained in such patients. As a result, many patients were denied procedures that could greatly improve their quality of life, such as orthopedic procedures.⁷

Recently, however, a movement has been underway to offer more surgeries to hemophilia patients with inhibitors provided that adequate preoperative and postoperative measures are employed to ensure patient safety. These include preoperative screening for the presence of inhibitors, notification of all members of the hemophilia treatment team of any impending surgeries, and assurance of adequate laboratory and blood bank support. Factors to consider in surgical hemophilia patients with inhibitors are listed in [Table 4](#).⁷

Table 4. Surgery in inhibitor patients: factors to consider

- Age of patient
- Inhibitor titre and anamnestic response
- Relevant co-morbidities
- Indication for surgery
- Urgency of the surgical procedure
- Type of surgical procedure
- Experience of surgeon
- Availability of multidisciplinary team of experts experienced in perioperative management of haemophilia (haemophilia treatment centre)
- Risk factors for thrombosis (age, type of procedure, thrombophilic genotypes)
- Patient and family preferences
- Sufficiency of supply of replacement and bypassing products
- Cost of replacement and bypassing products to national blood system, patient, or third-part insurer

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Elective surgical procedures should always be performed in coordination with the hemophilia treatment team. The nurse coordinator can then ensure the availability of adequate laboratory support for reliable monitoring of clotting factor level. It is recommended that elective surgery be scheduled early in the week and early in the day in order to allow for optimal laboratory and blood bank support as well as the availability of sufficient quantities of clotting factor concentrates and bypassing agents.⁸

Preoperative prophylaxis in inhibitor patients involves high-dose factor VIII replacement by intermittent bolus injection or continuous infusion: a bolus infusion of FEIBA of 50-75 IU/kg⁻¹ or immediate bolus infusion of factor VIIa.⁷

Postoperative management involves clinical monitoring, FEIBA or recombinant factor VIIa infusions, and coordination of factor delivery to the patient's home or long-term care facility. The patient's home environment and therapeutic requirements must be assessed prior to discharge and caregivers must be educated on postoperative rehabilitation. Nurse coordinators should also ensure reimbursement for long-term care and clotting factor usage, the availability of adequate amounts and appropriate vial sizes of clotting factor, and patient follow-up post-discharge.

[Listen to expert commentary derived from the symposium titled "Multidisciplinary Team Care in Hemophilia: Elective Orthopedic Surgery in Patients With Inhibitors," which was held at the National Hemophilia Foundation \(NHF\) Annual Meeting on October 31, 2009. In this CME activity, Prasad Mathew, MD, FAAP, and James V. Luck, Jr, MD, offer their perspective as team members of hemophilia treatment center \(HTC\) programs.](#)

Presurgical Management of Hemophilia Patients With Inhibitors: Key Points

- Know the type of surgery
- Emergent or planned?
 - Orthopedic or nonorthopedic?
- Screen for presence of inhibitors
 - If present, high or low responder?
- Historical response to factor concentrates
- Communicate appropriate treatment plan to treatment team

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