Exploring self-management and adherence in haemophilia

Liesbeth Hélène Schrijvers

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Exploring self-management and adherence in haemophilia

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(met een samenvatting in het Nederlands)

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Promotor: Prof. dr. M.J. Schuurmans

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Content

Voor alle mensen met hemofilie

General Introduction

Just another day at the haemophilia clinic…

*"I was already a bit suspicious, because he had many and large haemorrhages. At one moment when he was 1.5 years old, I didn't trust it anymore and I asked the doctor to check his blood levels. And then I received a call… "Your son is affected with haemophilia A". I was in shock, I still remember the feeling. We directly started with frequent clinic visits, it was quite heavy. One year later we started with prophylactic treatment and a couple of months later I started with learning how to infuse him myself. Of course it is very difficult to hurt your own child. I was very nervous and scared. The nurse had a crucial role and supported me at that moment." (*Mother of son with severe haemophilia, 3 years old)

*"My mum is struggling all the time with finding the veins. Sometimes we need to go to the hospital when she failed to infuse. When I wanted to do an activity, I had to stay at home and wait for my mum. I would like to learn how to infuse myself, because I don't want to go to often to the hospital anymore. Yet, I do find it difficult to remember to infuse and I often forget to complete the infusion log." (*Boy with severe haemophilia, 11 years old).

*"I know I have a high pain threshold, and when I have a bleed I just keep going. I have a very strong motto that my body has to listen to me instead of me listening to my body. It is an ongoing battle. This mindset I have to change, but it is so difficult. I don't really want to accept the fact that I have this disease. In many different moments I try to deny that I have it." (*Adult patient struggling with adherence to prophylaxis, 40 years old).

Haemophilia

Haemophilia is an X-linked recessive disease. Lack or absence of clotting Factor VIII (haemophilia A) or IX (haemophilia B) results in excessive bleeding. The severity of the disease is determined by the percentage of clotting factor VIII or IX present in the blood. Patients with mild haemophilia (>5%) are rarely affected by bleeds, only in case of trauma or surgery. Patients with moderate haemophilia (1-5%) have a great variety in symptoms, ranging from no bleeds at all to spontaneous bleeds. Patients with severe haemophilia (<1%) experience spontaneous bleeds in joints, muscles or soft tissue[1,2]. These bleeds can have large consequences: joint bleeds can lead to irreversible joint damage and subsequent arthropathy. Bleeds in the central nervous system may cause motor deficits, neurological problems or even death. Due to under diagnosis in the developing world, the worldwide prevalence differs across the world[3,4]. The current prevalence of haemophilia A in high income countries is 13 per 100 000 males vs. 7 per 100 000 in the rest of the world. For haemophilia B this is 3/ 100 000 vs. 1 per 100 000 in the rest of the world[3,4]. In the Netherlands approximately 1600 people are affected with haemophilia.

Haemophilia treatment (past and present)

In the earlier days, there was no proper treatment for haemophilia[5,6]. Patients suffering from a bleed were imposed to rest and the affected joint was immobilized using plaster cast. Patients with severe haemophilia had a life expectancy of only 16-18 years[7,8]. In the late 1950s, patients were treated with blood or fresh frozen plasma [9]. Since the introduction of cryoprecipitate in 1965 and later clotting factor concentrates the life of the patients with haemophilia completely changed[10]. The life expectancy increased to over 70 years (in Western countries)[11]. The clotting factor replacement therapy could be given on demand (in case of a bleed) or prophylactically to prevent bleeds[12]. For patients with severe haemophilia prophylaxis is the preferred therapy[13]. Many studies have demonstrated the effectiveness of prophylaxis[9,14,15] and the improved patients' autonomy and quality of life[16]. Prophylaxis is usually prescribed three times per week or every other day and is injected intravenously by the patient or his parent[17,18].

Self-infusion and self-management

Self-management skills are essential to perform and maintain this demanding treatment throughout life. An example of self-management skills patients or parents needs to acquire are self-infusion, bleed recognition, medicine management, pain and risk management and conceptualizing preventative therapy[19]. To learn self-infusion of clotting factor concentrate, patients or parents follow a course provided by the haemophilia nurse[20]. Other self-management skills are learned over time, yet it is unknown when and how patients achieve these skills. Through support of the whole (multi-disciplinary)

team patients are gradually guided towards independent management of haemophilia and prophylaxis[21]. The first part of this thesis aims to provide insight in how to learn and practice these self-management skills.

Non-adherence in haemophilia: a complex problem

Different terms are used to address medication taking behaviour. In the late 1970s, Haynes et al. mentioned compliance as the extent to which the patients' behaviour matched the prescribers' recommendations[22]. However, compliance has been viewed as a negative connotation that patients are subordinate to their prescribers. Nowadays, many professionals prefer the use of the term adherence, which was defined by the WHO as the extent to which a persons' behaviour – taking medication, life style – corresponds with the agreed recommendations of the health care provider[23]. Furthermore, the term 'concordance' is used to define the agreement between patient and prescriber[24].

Non-adherence to medical prescriptions is a problem in the treatment of many chronic diseases. It has been reported that at least 25% of the patients with chronic illnesses do not take their medication as prescribed[25]. A meta-analysis of different chronic diseases (heart failure, HIV and diabetes) showed that non-adherence was associated with an increased morbidity and mortality[26]. Furthermore, this resulted to an increased use of hospital services and increased health care costs[27].

For effective prevention of bleeding in haemophilia, an high adherence to prophylaxis is crucial. Even a single bleed can lead to irreversible damage, especially in a joint or the central nervous system. Inadequate treatment of a bleeding episode (starting too late or a too low initial dose) leads to more damage [28], more pain and prolonged treatment. To prevent bleeding, prophylaxis should be continued without interruption. It has been recently established that young adults who temporarily or permanently discontinued prophylaxis, had significant more arthropathy after 10 years of follow up than patients who never did[29]. Arthropathy leads to a significant reduction of quality of life and labour force participation[30,31] with substantial societal impact. Due to the extremely high costs of clotting factor concentrates (Dutch prices: mean 0.83 Euro/IU [32]), an more adequate treatment of even a single bleed is worthwhile. Immediate treatment is essential for efficient clotting factor use. If an adult with severe haemophilia A has a joint bleed and starts at the first signs of bleeding, a single dose of clotting factor concentrate (e.g. 2000IU) is sufficient. If he waits for 12 hours, the bleed has turned into a major bleed, requiring 5 days of treatment with in total 10000 IU (including additional visits to the clinic, physiotherapist and days lost from work).

From clinical experience, we know that many patients skip or forget prophylaxis, change the prescribed dose, or deviate from the prescribed time of infusion. Little is known about

the scope of non-adherence and the factors influencing adherence in haemophilia. The second part of this thesis aims to describe an assessment of the extent of and underlying reasons for of non-adherence to prophylaxis.

Scope of this thesis:

The first part of this thesis provides insight in how patients with haemophilia learn and practice self-management skills. It starts with a retrospective assessment of learning intravenous infusion (Ch 1). This is followed by an evaluation of the infusion skills and assessment of the time needed for (self-) infusion (Ch 2). Next is a quantification of the achievement of self-management skills of prophylactic treatment in haemophilia (Ch 3).

The second part of this thesis assesses the continuation of prophylaxis, mainly involving aspects of adherence. This starts with a formal Delphi consensus procedure to define (non-) adherence to prophylaxis in haemophilia (Ch 4). This definition was used in the subsequent study to evaluate the adherence levels in haemophilia, including the effects of non-adherence on bleeds and clotting factor concentrate (Ch 5). A systematic literature review was performed to identify the barriers and motivators for non-adherence (Ch 6). This was further explored from a patient' perspective (in Chapter 7). In the last chapter (8) coping in adults with haemophilia was assessed. The general discussion of this thesis involves evidence based recommendations for haemophilia professionals, especially for haemophilia nurses.

Definitions used in this thesis:

Self-management:	'*Self-management refers to the individual's ability to manage symptoms, treatment, physical- and psychological consequences, and life-styles changes inherent in living with a chronic condition. Efficacious self-management encompasses the ability to monitor and one's condition and to effect the cognitive, behavioural, and emotional responses necessary to maintain a satisfactory quality of life. Thus, a dynamic and continuous process of self-regulation is established*' [33].
Adherence generic:	'*The extent to which a persons' behaviour - taking medication, life style - corresponds with the agreed recommendations of the health care provider*' [23].
Adherence (haemophilia):	Development of a definition in chapter 6.

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CHAPTER 1

Learning intravenous infusion in haemophilia: experience from the Netherlands

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Abstract

Introduction: Nowadays, nearly all severe haemophilia patients in the Netherlands practise self- infusion at home. Learning intravenous administration of clotting factor requires time and effort. In order to inform patients about the burden and time-investment needed to learn intravenous infusion, we performed a multi-centre retrospective study.

Methods: All data on the learning processes, involving haemophilia patients born between 1980 and 2010 treated in Utrecht or Amsterdam, were extracted from patient files.

Results: 154 patients and their parents were analysed (168 learning processes). Almost all patients had severe haemophilia and started prophylaxis at a median age of 2.7 years. 152/154 patients successfully learned intravenous infusion, including 9 patients who temporarily stopped and succeeded later. Overall, parents or patients needed a median of 8 visits (IQR 4.3-14) in a median of 7 weeks (IQR 4-14.8) to learn self-infusion. Parents who began to infuse by CVAD started at a median age of 1.9 years and succeeded within a median of 12 visits during 7.5 weeks. Parents who learned to perform intravenous infusion started at a median age of 4 years and needed 11 visits during 9 weeks. In 77% of cases, the mother was the first who started learning to infuse the child. Patients started with self-infusion at a median age of 12.9 years, requiring a median of 5 visits in 12 weeks.

Conclusion: The majority of patients and parents were able to learn intravenous infusion, with 50% of all parents and patients succeeding within 8 visits during 7 weeks.

Introduction

In the past forty years, we have seen increasingly rapid advances in the field of haemophilia, in particular of severe haemophilia. First, the introduction of clotting factor replacement therapy (cryoprecipitate and later clotting factor concentrates) has made substitution of the missing clotting factor possible. Second, the introduction of home treatment has enabled prompt treatment of bleeds; this has improved the effectiveness of replacement therapy and greatly enhanced quality of life by promoting patient independence. The idea of home treatment was developed in the United States during the 1970s, because of large distances of the haemophilia treatment centre (HTC) and the general practitioners who mostly did not understand the necessity of prompt therapy [1,2]. The last important step in treatment was the introduction of regular replacement therapy (prophylaxis), starting at an early age to prevent bleeding and subsequent arthropathy [3,4]. Nowadays, the majority of the Dutch severe haemophilia population practice home treatment [5].

Since the introduction of prophylactic treatment, has been initiated at an increasingly younger age in the Netherlands [6]. Currently, prophylaxis for severe patients is initiated after the first joint bleed or a major soft tissue bleed [4] and is usually administered by the haemophilia treatment centre followed by administration by the parents and eventually by the patient himself. Common ways to administer are by peripheral intravenous injections (IV) or by a central venous access device (CVAD). In general, the process will start when it is technically feasible and when parents or patients are ready to start learning. This procedure is guided by a book with six modules (knowledge of haemophilia, home treatment/ self management, products, complications and the technique), developed by the Dutch society of haemophilia nurses in cooperation with the Dutch society of haemophilia physicians and patients. The instruction will be completed with passing an individual practical and a theoretical exam, containing standard examining questions.

It is useful to estimate the time investment needed, for both the patient or parents and the HTC. Therefore, data on this learning process, like age at start of learning, time period, number of training sessions required and the development of needle phobia, are essential information for parents and patients. Although this instruction for home-treatment is standard care, the learning process of self -infusion has not been formally studied. Infusing oneself or one's child also means crossing a considerable psychological threshold [7,8,9]. In order to inform parents and patients about the burden and time investment needed to learn intravenous infusion, we performed a two-centre retrospective study.

Methods

Data for this study was collected retrospectively from medical files of all patients (born between 1980-2010) with a inherited bleeding disorder practising home treatment and treated at the Van Creveldkliniek University Medical Centre in Utrecht or at the Academic Medical Centre in Amsterdam, both in the Netherlands. Patients who entered the clinic after the age of five years were excluded because they started IV infusion in a different setting. In addition, incomplete reports concerning the data of learning processes (e.g. regarding who patients who learned to infuse by themselves or from another healthcare professional) were excluded.

Data collected comprised (collected with pre-specified definitions): patient characteristics, person(s) trained, venous access route, frequency and period of visits, result and date of exam. Patients who developed needle phobia during the learning process, were diagnosed by the haemophilia physician and were analysed separately. Furthermore, each first learning process (parent CVAD or parent IV) was analysed apart from the second parent. As treatment strategies varied over time, results were compared according to birth cohorts (1980-1990, 1991-2000, and 2001-2010). Medians and interquartile ranges (IQR) were calculated for the descriptive analyses.

Data on patient characteristics and learning processes were compared across the two centres. In the primary analysis, the characteristics of the learning processes were compared according to subject, venous access route, and between age categories. Normally distributed data were analysed using the Students' T test and data with skewed distributions with using the Mann-Whitney U test (differences considered significant at a P <0.05). All data processing and analyses were preformed with SPSS® software, version 15 (SPSS Inc., Chicago, IL, USA).

Results

In total, data on 154 patients were available for study (N=107 Utrecht, N=47 Amsterdam, Figure 1). In total, 168 of 230 reported learning processes were analysed. 62 learning processes (27%) were excluded, because they were incomplete because patients stopped (N=2) or temporarily stopped learning (N=9) or various other reasons (N=32). 19 processes were lost to follow up: these patients started learning at one of the two clinics, but continued at another hospital (N=15) or with homecare services (N=4), mostly because of the distance and the burden to the family. These learning processes occurred in a significantly earlier period than in the patients who didn't stop the learning process (median 1990 vs. median 1996, P < 0.01). Haemophilia type and severity were comparable between the in- and excluded patients. All timelines presented are the first child with haemophilia in the family.

Patient characteristics of the included population are shown in Table 1. Patient characteristics between both centres were comparable (P = 0.4 - 0.8). Almost all patients had severe haemophilia (142 A, 10 B, 2 von Willebrand Disease type III). Patients started prophylaxis at a median age of 2.7 years (IQR 1.6 - 4.0). In general, parents needed a median of 4.8 months (IQR 1.9 - 10.8) before they were able to perform IV infusion. The most common prophylactic treatment strategy was with a frequency of 2 - 3 infusions per week, after the first joint bleed. The dosage varied from 250-1000 units (median of 500 units) per infusion.

Figure 1: Flowchart of available documentation for analysis in both centres.

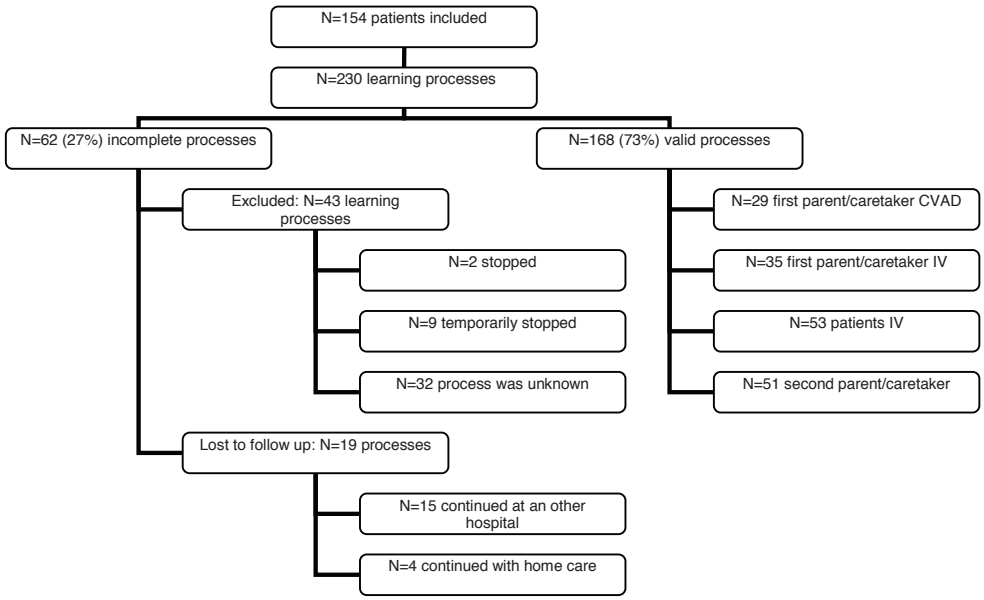


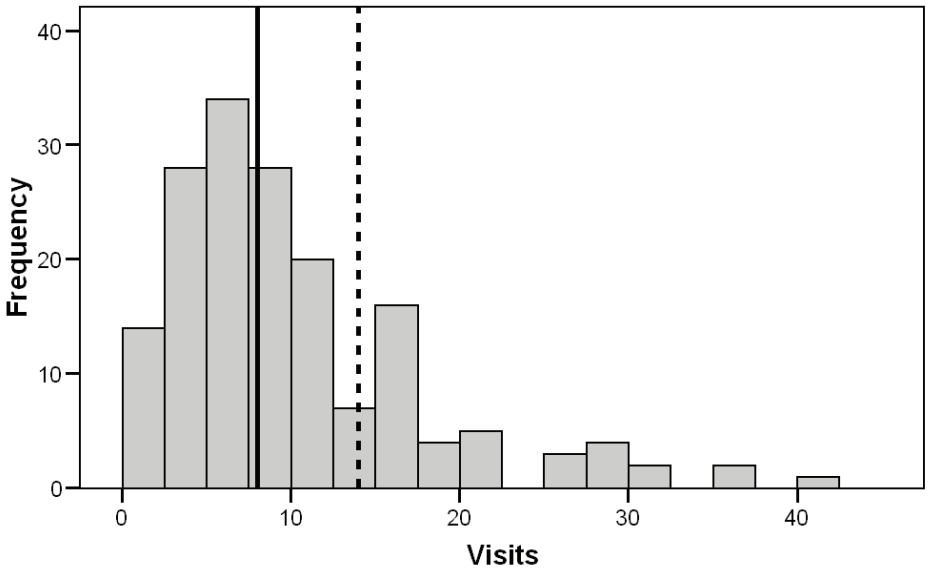
Table 1: Patient characteristics.

Patient Characteristics	Patients *n=154*	Learning processes *n=168*
Diagnosis		
Haemophilia A	142 (92%)	156 (93%)
Haemophilia B	10 (7%)	10 (6%)
Von Willebrand Disease	2 (1%)	2 (1%)
Severity		
Severe (<1%)	149 (97%)	161(96%)
Moderate (1-5%)	5 (3%)	7 (4%)
Mild (>5%)	0 (0%)	0 (0%)

Values are numbers (proportions).

Eventually, in 152 of the 154 (99%) patients or parents were able to learn how and when to administer clotting factor intravenously. Overall (parents CVAD/ IV and IV patients), needed a median of 8
training sessions (range 4.3 - 14) was needed during a median time period of 7 weeks (range 4 -14.8) to learn self-infusion (Figure 2).

Figure 2: Distribution of the number of visits needed for the learning processes from the first parent CVAD and IV, and patients.



Values are frequencies; the black line indicates the median and the dotted line the IQR 75.

Learning process of parents

Characteristics of the learning processes for parents and patients are shown in Table 2. To obtain a more objective perspective of learning, only the learning process of the first parent is presented. The first parent who started to infuse his or her child by CVAD started at a median age of 1.9 years (IQR 1.4 - 2.9). They required a median of 12 training sessions (IQR 9.0 - 16.8) during 7.5 weeks (IQR 5.0 - 10.8).
Parents who first learned IV infusion in a peripheral vein started at a median age of 4 years (IQR 3.0 - 5.0) and needed a median of 11 training sessions (IQR 7.5 - 17.0) during 9 weeks (IQR 4.0 - 14.5).

The second parent (N=51) who started learning IV or CVAD infusion needed a median of 5 training sessions (IQR 4.0 - 9.0) in a median of 6 weeks (IQR 3.5 - 12.0), when their child had a median age of 4.5 years. Overall, the learning-curve for the CVAD and peripheral access routes were not statistically different.

In 77% of cases, the mother (44/ 57, 7 both) was the first parent to start learning to infuse her child. Gender of the first parent learning, were not associated with the number of training sessions and time needed to learn. On the other hand, significant differences were obtained between the first parent and the second parent who started to learn. The first parents needed more training sessions (P <0.01) and more weeks compared to the second parent. Of 19 parents data were available on both learning by a CVAD and IV infusion, which describes that it was possible to start with intravenous infusion at a median age of 5.6 years old (IQR 4.7 - 6.9).

Learning process of patients

Haemophilia boys mostly started learning during the transition from primary school to high school, before puberty (median 12.9 years, IQR 11.6 - 15.1) and the boys passed the 'self-infusion' exam at a median age of 13.5 years (IQR 12.1 - 15.4; Table 2). This group needed a median of 5 visits (IQR 3.0 - 9.0) during 12 weeks (IQR 1.0 - 28.0). In comparison with parents who learned the technique, patients needed significantly fewer training sessions (P < 0.01), but covered a longer time period (P = 0.67) before they know the practical skills and theoretical background.

Year of birth

Related to the extended period of data collection, the learning processes were divided in three birth cohorts (1980-1990, 1991-2000, 2001-2010). As shown in Table 3, prophylaxis and home treatment started increasingly earlier over the decades, from a median age of 3,9 years in the 1980s to a median age of 1.6 years after 2000 (P < 0.01). After 2000, patients or parents received significant more training (median 9 visits, P <

Table 2: Characteristics of training sessions according to type of learning process:

Learning processes	(1st) Parent CVAD *n= 29*	(1st) Parent IV *n= 35*	Patient IV *n= 53*	Total (all learning processes) *n= 168*
Patient age (yrs)	1.9 (1-3)	4.0 (3-5)	12.9 (12-15)	-
Training sessions (nr)	12.0 (9-17)	11.0 (8-17)	5.0 (3-9)*	8 (4-14)
Time (wks)	7.5 (5-11)	9.0 (4-15)	12.0 (1-28)	7 (4-15)

Values are medians (IQR).
* Significant differences with the other categories in the row ($P < 0.01$).

Table 3: Characteristics of the learning processes according to year of birth.

	Born between 1980-1990 (N=24)	Born between 1991- 2000 (N=67)	Born between 2001- 2010 (N=77)
Age start prophylaxis	3.9 (3-5)	3.2 (2-4)	1.6* (1-3)
Age start home treatment	4.3 (3-5)	4.4 (3-5)	2.1* (2-3)
Visits	5.5* (3-10)	8.0 (4-11)	9.0 (5-16)
Weeks	8.0 (1-45)	8.0 (4-19)	6.0 (4-11)
Age start self-infusion	15.5 (14-19)	12.0* (11-13)	-
Percentage of CVAD's	0%	18%	45%

Values are medians (IQR) and the last row is a percentage.
* Significant differences with the other categories in the row ($P < 0.01$).

0.01) compared to earlier years, but they needed less time (median of 6 weeks). Patients who were born before 1991 started at a later age with self-infusion than patients who were born later (median 15.5 years vs. 12 years, $P < 0.01$).

Needle phobia

10 children (6.5% of the total) experienced needle phobia during this learning process, apparently unrelated to age (median of 6.8 years, range 2.2 -14.0). 2/ 10 patients were referred to a psychologist, at the age of 11.8 and 14.0 years, respectively. Depending on the situation, the process was individualized. Overall, subjects with needle phobia needed a significantly longer period to learn (median 37.5 weeks, IQR 14.3 - 97.0, $P < 0.01$), but a comparable number of visits (median 8.5 visits, IQR 4.5 - 12.0). Of this group, three patients temporarily stopped learning and one father with a child with needle phobia stopped permanently.

Discussion

To our knowledge, the present two centre retrospective study provides the first quantitative description of the learning process of intravenous infusion taught by the haemophilia nurse. Overall, 152/154 (99%) of the parents or patients successfully learned intravenous infusion, including nine patients who temporarily stopped and succeeded later. Overall, patients and parents needed a median of 8 training sessions during 7 weeks to acquire the technique of IV administration. Parents who began to infuse by CVAD started when their child had a median age of 1.9 years, succeeding within a median of 12 visits during 7.5 weeks. Parents who learned to perform intravenous infusion started at a median age of 4 years and needed 11 visits during 9 weeks. In 77% of the cases, the mother primarily started learning the technique. No gender related differences were seen. Patients started with self-infusion at a median age of 12.9 years, just before puberty, requiring a median of 5 visits in a median of 12 weeks. Patients needed significant fewer training sessions than parents.

Although the data collection was retrospective, 73% of all learning processes could be reliably assessed, while 27% was excluded because of insufficient documentation. The reasons for insufficient documentation appeared to be influenced by other factors than the content of the learning process, such as distance. Pre-specified definitions about the data collection period, frequency and result of the exam were used to reduce information bias. In addition, there might be a risk to confounding by indication, because of the pre-selection of patients with puncture problems who receive a CVAD. Otherwise, the process will much longer and more intensive.
This data represent approximately 60% of all Dutch boys with severe haemophilia starting home treatment in the period of 1980 - 2010. In these two centres, the policy regarding the start of early prophylaxis and the use of educational material for teaching

patients are similar. There are no international guidelines for this process, but the national haemophilia nurses society developed a national protocol. For the external validity, other centres also use comparable educational materials [10].

Although no formal studies on the learning process of home treatment have been performed, there are some studies who reported some data on the patients learning intravenous infusion. Both Lindvall et al. [11] (11.6 years) and Lobato et al. [12] (9.5 years) found a younger age than the 12.9 years in our cohort. It is important to train for independence before puberty: compliance problems resulting in a lack of perceived need are prevalent during puberty [9,11,13].
In addition, Lobato et al. [12] reported a shorter learning period of 4 weeks, including only 3 visits. However, in that study the data was provided through a telephone survey and it is unclear whether the responses were based on experiences of nurses rather than on concrete data. In a Swedish cohort they reported that 80% of the parents needed about 14 months, between the start of prophylaxis and to being able to successful administer prophylaxis [9]. This is longer than the median of 4.8 months in our cohort, may be related to the fact that in the Swedish cohort there was less use of the CVAD. Teitel et al. did not provide specific details, but reported that the time to learn IV infusion generally varies from one week until six months [14]. In addition, they suggested that the actual training period should be individualized.

Rather than it being technically difficult to perform the procedure (99% passes their exam), infusing oneself or one's child means crossing a considerable psychological threshold. In this context, information on the process could create a sense of control and improve their self-efficacy of patients and parents [15]. In addition, these data may be used as a 'benchmark' to identify learning processes that are unusually long or problematic, as well as provide an indicator on when a boy with haemophilia may start learning self-infusion. For future research, a prospective study may confirm these results, but more importantly, identify additional factors which may influence this process.

Conclusion

The majority of the haemophilia patients or their parents who are able to learn how to perform intravenous infusion, with 50% of subjects succeeding in 8 training sessions during 7 weeks. Additional information on the determinants of learning home treatment may help to further individualise the planning of the learning process.

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CHAPTER 2: SHORT REPORT

Self-infusion of prophylaxis: evaluating the quality of its performance and time needed

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Submitted

Short report

Prophylactic replacement therapy is the cornerstone of treatment in severe haemophilia. Regular infusions with clotting factor concentrate have been proven effective to prevent bleeding, subsequent (joint) damage, and positively affect the impact of haemophilia on daily life [1]. Patients or parents of younger patients learn to infuse clotting factor concentrate in a peripheral vein (IV) or a central venous access device (CVAD) [2].

As even a single bleed may cause irreversible damage, prophylaxis requires lifelong adherence and well-developed self-management skills [3]. The UKHCDO guidelines (United Kingdom Haemophilia Centre Doctors Organisation) described that competence in venous access technique as an important aspect of successful prophylaxis [4]. Currently, these skills are learned in a short course with an average of eight sessions [2]. After passing the exam patients or parents are qualified to perform intravenous treatment independently [2, 5]. There are no follow-up sessions and the quality of the procedure is never formally evaluated. In addition, many patients stated that they did not 'have enough time' to infuse in the morning [6], leading to non adherence. However, the time needed for self-infusion has never been studied. The aim of this study was to quantify adherence to (self) infusion guidelines [5] as well as the time needed for prophylaxis in haemophilia.

This study comprised a cross-sectional observational study, which was embedded in the nursing consultation of three large Dutch Haemophilia Treatment Centres (Utrecht, Amsterdam and Rotterdam). Patients of all ages with a congenital clotting factor deficiency using prophylaxis with a minimum frequency of once weekly were eligible for inclusion. Convenience sampling was used: during outpatient clinic visits patients were asked to administer their regular prophylaxis, while nurses observed the quality and duration of self-infusion procedure according to a checklist. The checklist was based on the Dutch guidelines for learning IV or CVAD infusion with a non-sterile (1 centre) and sterile approach (2 centres) [5]. Concomitantly, the time needed for self-infusion was recorded with a stopwatch and comprised the entire procedure from the start of preparation of the materials to completion of the infusion diary. Patient characteristics collected were: year- and month of birth, the person performing the procedure (patient or parent), diagnosis (haemophilia A, B or Von Willebrand type III), current treatment (prescribed frequency and -dose), venous access route (IV or CVAD) and certification for (self-) infusion (present/ absent, including date).
Descriptive statistics were performed separately for IV and CVAD infusion. Due to the skewed distributions the data was analyzed using the Mann-Whitney U test (significant at $P<0.05$). All analyses were performed with SPSS® software, version 20 (IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA)).

Overall, 161 infusion procedures in 132 patients or parents were evaluated in the three centres (Utrecht n=94, Amsterdam n=57 and Rotterdam n=10), comprising 48% of the total population on prophylaxis in these centres. Patient characteristics are presented in Table 1. Patients learning to self-infuse were excluded from analysis (n=26), as infusion took significant longer (13:00 min, p>0.001). For 31/ 161 procedures only time assessment was performed. The patients had a median age of 13.7 years (Interquartile (IQR): 9.7-23.3). The majority of the patients were diagnosed with haemophilia A (84%), and the majority had severe haemophilia (91%). Most patients (47%) followed a prophylactic regimen of 3.0 times per week with 1000 IU per infusion.

Table 1: Patient and treatment characteristics*.

	Total infusions *(n=161)*
Number of assessments	
One	132
Two	13
Three or more	16
Age (med, IQR)	13.7 yrs (9.7-23.3)
Diagnosis	
Haemophilia A	135 (84%)
Haemophilia B	16 (10%)
Von Willebrands Disease	10 (6%)
Severity	
Severe haemophilia	146 (91%)
Moderate haemophilia	7 (4%)
Type III Von Willebrands Disease	8 (5%)
Route of administration	
IV	147 (91%)
CVAD	14 (9%)
Treatment	3.0 (2-7)
Frequency prophylaxis (med, range)	
Dose prophylaxis (med, range)	1000 (250-3000)

Values are reported as frequencies or medians (interquartile-range).
*26 patients were excluded from final analysis, because they were engaged in learning self-infusion.

The mean experience with self-infusion was 4.9 years (range 0-25.6 years). The evaluation of the quality and timing of infusion procedures is shown in Table 2. Almost all patients and parents performed the infusion correctly with 96% succeeding at the first attempt. In contrast, only half the patients/ parents washed their hands before infusing and completed the infusion diary.

For IV infusion, 147 procedures were performed by 122 patients/ parents in a median of 6.7 minutes (range 3-23.5 min). Parents needed slightly longer for the procedure (median 8 min) than patients who performed self-infusion (median 6.5 minutes), yet this difference did not reach statistical significance (p=0.23). At the start of the procedure, half of the patients/ parents (54%) washed their hands according to guidelines, which

took approximately 40 seconds. Verifying the correct product, expiry date and correct dose before administration was not actively done by 47% of the patients/ parents. In contrast, all patients performed the procedure of preparing the clotting factor concentrate correctly, which took a median of 2 minutes. Almost all patients/ parents (96%) succeed to inject the CFC correctly, taking a mean of 2.5 minutes. The majority of the patients/ parents (95%) disposed of the needle according to the protocol, yet registration in the infusion diary after infusion was forgotten by 60% of the patients/parents.

For CVAD infusion, 14 infusions performed by 10 parents were evaluated. The median total time needed CVAD infusion was 11.1 min (range 6.5-30 min). Before preparation of the materials, 69% of parents washed their hands and 77% checked the product name, date and dose. All parents dissolved the CFC correctly (3 min); this took slightly longer than for IV infusion, due to preparation of extra solvents (heparin, water). CVAD infusion according to the non-sterile approach (n=5) took a median of 2 minutes; and 3.5 minutes (n=8) according the sterile approach. All parents removed the needle and disposed it according to protocol. Registration of the infusion in a diary direct after the infusion was performed by 54%.

Some limitations of this study should be discussed. Convenience sampling led to selection of relatively younger patients (median 13.7 years), as young children visited the outpatient clinic more often than adult patients. In addition, the number of CVAD procedures assessed was limited (n=14) due to practical reasons; CVAD infusion procedures usually required the assistance of two nurses (one observer and one holding the child), which was difficult to combine with the study assessment. All assessments were performed in the outpatient clinic and not in the home setting: blood sampling was sometimes required. Nurses tried to emphasize to perform the procedure just the same as at home and stopped the stopwatch during blood withdrawal.

These findings were compared to a Dutch study assessing the effect of an e-learning program on self-infusion by Mulder et al. [7]. This study reported equal proportions of diary keeping (40% in both studies), but higher rates of hand washing (75% vs. 45% in this study). After following the e-learning programme, performance significantly improved to 75% (increase of 27%). We hypothesize that regular check-ups of the quality of the infusion procedure, including reminders for washing hands and completing the infusion diary, could help to maintain the quality of the procedure. Patients did not actively checked the product name, dose and date of expiry, before administration. Most patients check the whole batch after receiving this at the pharmacy. The time needed for the procedures was not studied before.

Table 2: Evaluation of quality and timing of infusion procedures

Activity	IV		CVAD	
	% Correct performance IV *(n=116*)*	**Median time IV** *(mm:ss/ n= 147)*	**% Correct performance CVAD** *(n=14)*	**Median time CVAD** *(mm:ss/ n=14)*
Preparing materials	89	00:37	100	01:03
Washing hands	54	00:40	69	00:42
Check product, date, dose	51	00:12	77	00:20
Dissolving product	100	02:15	100	03:05
IV: Correct injection of CFC Failure of infusion	96 4	02:29	-	-
CVAD: Non-sterile approach (n=5) Sterile approach (n=8)	-	-	100 100	02:00 03:29
Safe disposal of needle	95	00:38	100	01:00
Complete infusion diary after infusion	40	00:47	54	00:31
Total time (range)	-	06:40 (03:00-23:33)	-	11:07 (06:36-30:00)

Values are proportions and medians (minutes: seconds).
*During 31 infusions the checklist for self-infusion was not fully completed and excluded in this section.

In conclusion, self-infusion of prophylaxis takes only a little time: a median of 6.7 minutes for IV infusion or 11.1 minutes for CVAD infusion. Essential infusion activities (dissolving, injection of the factor concentrate) were generally performed correctly. Washing hands and completion of the infusion diary were often forgotten. Therefore, standard follow up every other year to check correct performance of self-infusion may improve these aspects of home treatment.

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CHAPTER 3

Achieving self-management of prophylactic treatment in adolescents with haemophilia

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Abstract

Introduction: Adolescence is characterized by significant changes in physical and psychosocial development. In addition, adolescents with a chronic disorder such as haemophilia need to attain responsibility for their disease. Adolescents with haemophilia need to learn how to self-infuse the prophylactic treatment. The aim of this study was to gain insight into how adolescents achieve self-management of prophylactic treatment.
Methods: In three Dutch Haemophilia Treatment Centres, adolescents (10-25 years) were interviewed during routine nursing consultation. Patients received structured questions on treatment responsibility and self-management. Endpoints of self-management were defined as independency in: 1) self-infusion; 2) bleeding management; 3) stock monitoring; and 4) communication with the haemophilia physician.
Results: In total, 155 interviews were performed in 100 patients with a median age of 14.4 years (Interquartile range (IQR): 12.5-18.1). Self-infusion was initiated at a median age of 12.3 years (IQR11.5-13.0), self-management was achieved 9.6 years later at a median age of 22.6 years. This process included three phases coinciding with known stages of adolescence. In early adolescence, patients acquired the technique of self-infusion (12.3 yrs) leading to independent self-infusion in middle adolescence (17.2 yrs). In late adolescence, patients demonstrated an increase in more complex skills, such as bleeding management and communication with the haemophilia physician (19.9-22.6 yrs).
Conclusion: Although, the first steps in self-management with regard to self-infusion are taken in early adolescence at a median age of 12.3 years, complete self-management was achieved in late adolescence at a median age of 22.6 years. Insight in this transitional process helps to provide individualized support and emphasizes the need for continued education with regard to self-management skills.

Introduction

In their teen years, adolescents experience physical, cognitive and psycho-social changes, including many aspects such as maturing of the body, an evolving identity, increasing independence and intimacy [1]. In addition, adolescents with chronic illnesses are also confronted with the challenges in attaining responsibility for their disease and its treatment. The desire to be as their peers often leads to non-adherence, with concomitant increased risk for complications and deterioration of the illness [2, 3]. Self-management skills have to be learned in this difficult age period, which is defined as 'the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition' [4].

Patients suffering from the inherited bleeding disorder haemophilia have a lifelong risk of bleeding and subsequent arthropathy [5, 6]. Standard therapy is intravenous clotting factor replacement therapy administered at established intervals per week, also referred to as prophylaxis [7, 8]. In the Netherlands, the majority of patients with severe haemophilia practice self-infusion of prophylaxis [9]. Prophylaxis in the home setting has greatly improved quality of life in haemophilia patients [10]. Adolescents with haemophilia mostly started learning self-infusion at the age of 13 years [11], this is a procedure involving complex self-management skills.

In current Dutch practice, young adolescents follow a short course to learn the technique of self-infusion and the theoretical background of their illness, symptoms and treatment [11, 12]. It remains unknown when patients obtain self-management skills. In a recent qualitative study it was identified that low self-management skills were an obstacle for optimal adherence to prophylaxis [13]. Little is known about the development of self-management skills in adolescents with haemophilia. The aim of this project was to gain insight in the process of achieving self-management in adolescents with haemophilia using prophylaxis.

Methods

This study comprised a cross-sectional, multicentre study in three Dutch haemophilia treatment centres (Utrecht, Amsterdam and Rotterdam). Adolescents (10-25 years) were interviewed about topics with regard to self-management and treatment responsibility. This structured interview was implemented in a routine nursing consultation. The research ethics committee of the University Medical Centre Utrecht, The Netherlands, approved this study (10/269).

Participants

All patients between the age of 10-25 years with a congenital clotting factor deficiency (moderate or severe haemophilia A or B and Von Willebrand disease type III) using prophylaxis with a minimum frequency of once per week, were eligible for inclusion. Convenience sampling was used: patients were interviewed during their regular clinic visit during the period September 2010 until December 2013.

Data collection

The following baseline characteristics were collected from patient files: age, diagnosis, the person performing the intravenous infusion, route of intravenous access (IV), and current treatment (start date of prophylaxis, prescribed regimen and when applicable, age certificate self-infusion). The structured interview included closed questions about aspects of the treatment and the individual who was responsible for performing the treatment (patient, parent or both). Treatment aspects involved: self-infusion (independent performance), treatment decisions (diagnosing bleedings and subsequent dosing), stock monitoring, use of infusion diary, and communication with the physician. The questions were based on the Dutch educational guideline for learning self-infusion [12] and were consistent with daily practice. Complete self-management of prophylactic treatment was defined as: a patients' ability to act independently concerning self-infusion, handling during bleeding episodes, monitoring of stock, and communication with the physician. To verify answers and assess validity, parents were asked the same questions in a separate room. Repeated interviews were allowed with a minimum interval of 1 year.

Analysis

Internal validity between answers of patients and parents was assessed by Cohen's kappa. To study the potential bias introduced by repeated interviews in some patients, the analyses were repeated after exclusion of the second or third interviews in these patients. The same trends were observed ($p=0.2$-0.9) and therefore ultimately all interviews were used in the analysis. Median values (Interquartile range) of age at which each activity was performed independently were calculated. In addition, proportions were calculated for three specific age groups: early adolescence (10-12.5 years), middle adolescence (12.5-17.5 years) and late adolescence (17.5-25 years) [19, 20]. Differences according to age groups were assessed using the Chi square test and were considered statistically significant at a $p<0.05$. All data processing and analyses were performed with SPSS® software, version 20 (SPSS Inc., Chicago, IL, USA).

Results

In total, 155 interviews were conducted in 100 Dutch patients (Utrecht n=70, Amsterdam n=22, and Rotterdam n=8). Overall, the response rate was 67% of the adolescents using prophylaxis were questioned. The patient characteristics are shown in Table 1. Median age was 14.4 years (Interquartile range (IQR):12.5-18.1), diagnosed with severe haemophilia (87% A, 10% B) and Von Willebrand type III (3%). Two patients (2%) had a central venous access device. The majority of patients infused three times per week the prophylactic treatment (64%) with a median dose of 1000 IU. As expected younger patients visited the clinic together with their parents; median age of 13 years in patients who visited with parents and 16 years of those who visited independently. Answers of the adolescent patients showed a strong consistency with the parental answers (n=38, kappa: 0.71), 94% of the answers were in agreement.

Table 1: Characteristics.

	Total interviews *N=155*
Interviews patients*	100
2nd interview	35
3rd interview	20
Interviews parents*	38
Age (med, IQR)	14.4 yrs (12.5-18.1)
Diagnosis	
A	135
B:	15
VWB	5
Type	
Severe	145
Moderate	5
Type III	5
Venous access	
Peripheral vein	153
CVAD	2
Frequency prophylaxis (med, range)	3.0 (2-7)
Dose prophylaxis (med, range)	1000 (500-2000)

Values are frequencies and medians.
*First and repeated interviews did not show systematic differences, therefore all interviews were used in further analyses (p=0.2-0.9).

The process of achieving self-management

The first step towards learning self-management skills was learning the technique of self-infusion. Patients achieved full self-management after a median of 9.6 years (range 4.5- 15 years). Details are reported in Table 2 and Figure 1. This process included three phases which occurred concomitant with the phases of physiological development in adolescents[14]. In early adolescence, patients learned the technique of self-infusion.

In middle adolescence patients learned: independent performance of self-infusion (including independent performance of self-infusion and remember to infuse). In late adolescence, patients learned complex self-management skills (including independent decisions concerning bleeding management and communication with the physician). Full self-management of haemophilia treatment was achieved at the age of 22.6 years (IQR: 20.6-24.5).

I: Start self-infusion (early adolescence)

Self-infusion training was initiated at a median age of 12.3 years (IQR: 11.5-13.0). After completion of the course patients were allowed to perform self-infusion independently, however only 25% (n=8) of the patients was able to do this at that age. Of this group, six patients still needed parental assistance.

II: Independent performance of self-infusion (middle adolescence)

In middle adolescence, most patients were able to independently perform tasks concerning self-infusion. Patients independently remembered to take prophylaxis at the prescribed time at a median age of 16.5 years (IQR: 14.2-21.5 years). Parents gradually transferred the responsibility for prophylactic treatment and eventually stopped reminding their sons of the necessity of prophylaxis. Most patients independently performed self-infusion, which included independent performance of self-infusion and remembering to infuse, at a median age of 17.2 years (IQR: 14.1-22.6 years). Patients independently completed their infusion diary by at a median age of 17.1 years. Completing the infusion diary seemed to have less priority at this age, as in total 20 patients (13%) stopped using the diary.

III: Complex skills (late adolescence)

The complex self-management skills were achieved only during the late adolescence. Patients independently diagnosed bleeds at a median age of 19.9 years (IQR: 15.4-22.6 yrs) and independently made dosing decisions at 20.2 years old (median 20.2, IQR 16.3-22.7 yrs). When patients reached the age of 21, most of them took the lead in communication with the haemophilia physician instead of their parents (median age: 21.5, IQR 17.7-23.4). Managing medication stock and materials was an activity that parents continued to perform longer than other activities. Patients took responsibility for this task at a median age of 21.9 years (IQR 17.5-24.0).

Discussion

This is the first paper describing and quantifying the process of achieving self-management in adolescents with haemophilia using prophylaxis. Achievement of self-management was a gradual process spanning a period of almost 9.6 years. In most patients, this

Table 2: Detailed overview of the process of self-management in the early, middle and late adolescence.

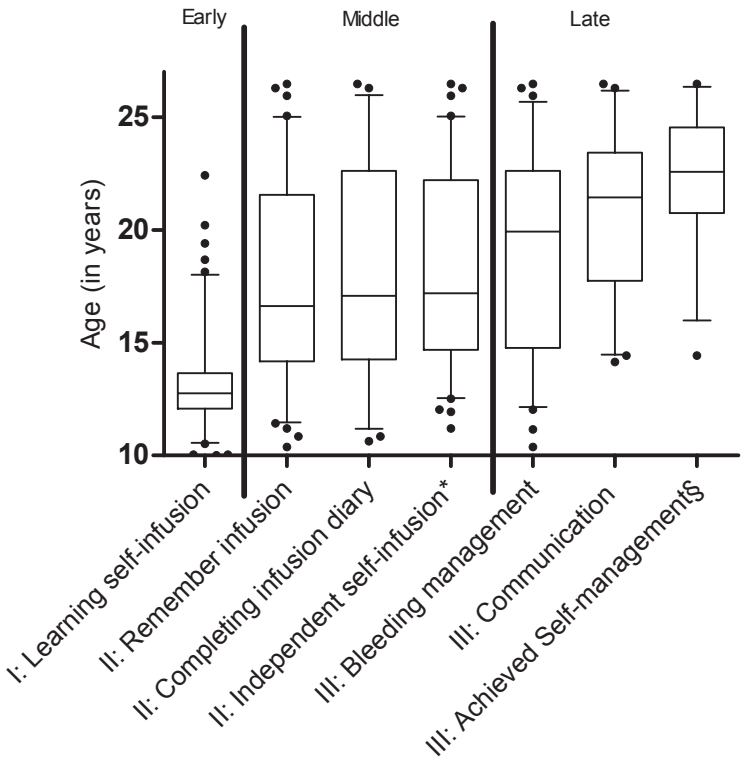
		Age *Median (IQR)*	**Early adolescence*** *(n=36)*	**Middle adolescence*** *(n=79)*	**Late adolescence*** *(n=40)*
I: Start self-infusion (early)	Age exam	12.3 (11.5-13.0)	NA	NA	NA
II: Independent performance of self-infusion (middle)	Remembering of infusion	16.5 (14.2-21.5)	22%	55%	90%
	Regular use of infusion diary Infusion diary completion	20 stopped 17.1 (14.1-22.6)	2 (5,6%) 15%	7 (8,7%) 38%	11 (27,5%) 90%
	Independent performing self-infusion	17.2 (12.6-20.6)	25%	55%	95%
III: Complex skills (late)	Diagnosing bleedings	19.9 (15.4-22.6)	6%	33%	93%
	Dosing decisions	20.2 (16.3-22.7)	3%	22%	95%
	Communication with hospital	21.5 (17.7-23.4)	0%	14%	88%
	Managing stock	21.9 (17.5-24.0)	0%	11%	78%
	Self-management acc to definition[§]	22.6 (20.6-24.5)	0%	5%	73%

*Per row, all values are statistical significant.

[§] Self-management: acting independently with regard to administration of clotting factor, with regard to handling a bleed, keeping stock and communication with the physician.

NA: not applicable

Figure 1: Activities for self-management process according to age.



Values are medians, Interquartile range and 10 and 90% percentile.
*Independent self-infusion: independent performance of self-infusion, including remembering to infusion.
§ Self-management: acting independently with regard to administration of clotting factor, with regard to handling a bleed, keeping stock and communication with the physician.

process consisted of three phases, which in general occurred simultaneously with the phases of adolescence. Patients started to learn to self-infuse during early adolescence and were able to perform this independently in middle adolescence (including remembering of infusion). During late adolescence patients learned the more complex skills, like bleeding management and communication with physician. Patients achieved complete self-management skills at a median age of 22.6 years.

Some limitations of this study should be discussed. First, the use of a cross sectional design with convenience sampling; this sampling method may have introduced selection bias. However, the risk of selection bias was reduced by sample size: in total, almost 70% of all adolescents between 10-25 years old were interviewed. Unfortunately, there was no validated self-management questionnaire available for haemophilia at the time of the study. Therefore, a self-designed questionnaire based on topics addressed during

the regular nursing consultations was used. The topics of this questionnaire are in accordance with recently developed questionnaires [15, 16]. Furthermore, adolescents with haemophilia were accustomed to these questions during outpatient clinic visits and the likelihood of giving socially-accepted answers was considered minimal. To assess validity, parents were asked the same questions in a separate room. The correlation between questionnaires of patients and parents was high. Full self-management of haemophilia treatment was achieved in a period spanning ten years. These results could be influenced by the fact that no follow-up course on self-management was offered to adolescents. Influential factors such as parental influences and upbringing styles as well as psychological aspects were not measured and therefore cannot be evaluated.

We could not identify any published reports regarding the age of achieving self management in adolescents with other chronic conditions. In diabetes, overall self-management levels for adolescents were studied [17-19] or the treatment responsibility was assessed from a parent perspective [20, 21]. However, these studies did not report on the age of achieving self-management skills. Overall, the study of Keough et al. [19] in diabetes was most comparable to our findings: it identified comparable patterns in learning across phases of adolescence (early, middle and late) and reported that problem-solving and communication skills were obtained in the late adolescence.
Better understanding could be obtained from studies performed in haemophilia. A qualitative study on self-management in adolescents with haemophilia showed that skills were acquired in a gradual learning process, through experiential learning and individualized education [22]. Patients have to learn to observe bodily functions and to diagnose bleeds [22]. Furthermore, Lindvall et al. observed similar results about the treatment responsibility [23]. Patients independently performed self-infusion at the median age of 17.2 years old versus 18 years old in Lindvalls' study. Furthermore, the Scandinavian patients stated that remembering of infusion of prophylaxis was one of the most difficult tasks. In this study we were able to quantify this aspect as 50% of the patients remembered to take their prophylaxis at the age of 16.5 years, with increase to 90% in late adolescence.

The present findings have both clinical and research implications. Adherence is lower in adolescents/ patients with low self-management skills [3, 13]; continuous education is of utmost relevance. These results could help to tailor (nursing) care and self-management education during the specific phases of adolescence. As chronically ill adolescents struggle with 'normal' developments, also known as *storm and stress* [24], they may be less receptive for information on their disease [25]. Providing tailored information at the time of a exacerbation (e.g. bleeding event in haemophilia) could help to create awareness and interest of the adolescent [1]. In addition, involving the adolescent perspective [25, 26], age-appropriate education [27] or peer teaching [28] could increase the likelihood

to be open for education. A recent Dutch study among adolescents with chronic diseases (including haemophilia) revealed that parents often took a leading role during the consultation, and that adolescents often felt 'bystanders' instead of 'partners'[29]. Currently, in the Dutch haemophilia practice patients receive a one-time course in the early adolescence only [11]. Possibly, education of self-management should be repeated in the middle and late adolescence. Kyngas et al. identified that adolescents preferred continuous support in parallel with one's life phase [25]. Therefore, we propose to introduce 'booster' sessions with stepwise learning objectives (e.g. beginner, intermediate and advanced) in the middle and late adolescence to develop advanced self-management skills and to increase treatment-success. We suggest that health care provider should invite only the adolescent into the consultation room.

From the research perspective, development and testing of an education program with stepwise learning objectives could help adolescents to easier learn the self-management skills and increase treatment-success [30, 31]. Furthermore, assessment of skills or self-efficacy could help to monitor the stage of independency with regard to the learning process. In this regard, an haemophilia specific self-efficacy questionnaire[16] or more general health education questionnaire [32] could be valuable to use in chronic care. These assessments could help the health care provider to tailor and individualize the care to the needs of the chronically ill adolescent.

Conclusion

In this paper the gradual process of achieving self-management in adolescents was quantified. This process included three phases which occurred simultaneously with the developmental adolescent stages. In haemophilia, patients started with learning the technique of self-infusion during early adolescence. During middle adolescence patients were able to perform the self-infusion independently (including remembering and completion of infusion diary). The more complex skills of bleeding management and communication with the physician were learned during late adolescence. Patients achieved full self-management at the age of 23 years.

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CHAPTER 4

Defining adherence to prophylaxis in haemophilia

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Submitted

Abstract

Introduction: Although most studies determine adherence as administration of 80% of prescribed medication. A more complete definition is lacking, the aim of this project was to develop consensus on what is regarded as adherence to prophylaxis in haemophilia by experts.

Method: Using the validated Delphi method, a systematic consensus procedure was performed in three rounds. Twenty three Dutch haemophilia professionals and patients participated in each round. Firstly, all aspects of adherence to prophylaxis were listed and clustered into domains. Secondly, the main domains were identified and prioritized. Thirdly, eight hypothetical cases and eight clinical cases were labelled as either adherent, sub-optimally adherent or non-adherent. Consensus was fixed at ≥80% agreement on a category.

Results: Consensus was reached (agreement > 84%) on the final definition of adherence to prophylaxis. Missed infusions, dose changes and deviations from the prescribed time were considered as the most important domains of non-adherence. This resulted in three adherence categories: *adherent:* missing <15% infusions, <10% dose changes (IU) and <30% deviation from prescribed time; *sub-optimally adherent:* missing 15-25% infusions, <25% dose changes or >30% deviation in time; *non-adherent*: missing > 25% infusions or >25% dose changes.

Conclusion: This study underlines that adherence as experienced by haemophilia professionals and patients is complex, yet can be described in more detail by using three domains: missed infusions, dose changes (IU) and deviation in timing. This formal definition is simple and can easily be applied to describe adherence to prophylaxis in research and clinical care.

Introduction

Patients with severe haemophilia are at risk for spontaneous or trauma-related bleeds in joints or soft tissues [1]. Repeated joint bleeds eventually result in arthropathy [2, 3], limitations in activities and participation, and a substantial societal impact with reduced quality of life [4, 5]. Since the 1970s, prophylactic clotting factor replacement therapy is standard therapy for patients with severe haemophilia [6, 7]. Minimum clotting factor levels are maintained to prevent bleeding, achieved by intravenous injections usually 3 or 3.5 days per week [8]. Although the current prophylactic regimen has decreased mortality and morbidity and increased quality of life, prophylactic treatment is still considered invasive and has a major impact on the lives of patients with haemophilia [9, 10].

Adherence to prophylaxis is crucial for the treatment success [11]. Recent studies demonstrate that adherence is associated with less chronic pain scores, improved physical functioning and a reduced need for orthopaedic surgery [12-14]. In addition, adequate use of prescribed treatment is essential to improve cost-effectiveness of this expensive treatment at a mean cost of €0.83/IU (Dutch prices) [15]. Recent studies have reported adherence levels in haemophilia as proportions of infusions received (44 to 87% [9, 16, 17]) or points generated by a questionnaire (44-49 points [13, 18, 19]). This variation in criteria and definitions hampers interpretation of reports on adherence. Moreover, definitions of adherence for other chronic illnesses, with clinically applicable cut-off points, are not available.

As adherence is closely associated with treatment outcome, a clear definition is needed to monitor, discuss and promote adherence in clinical situations and research objectives. Most studies evaluating the effect of prophylaxis have used a cut-off of < 15% missed infusions [20, 21]. Recently, the 'Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis' questionnaire (VERITAS-Pro) for assessment of adherence was developed and validated [18, 19]. It involves domains of adherence like skipping, timing, stock management and communication. A threshold for adherence measured by this questionnaire was calculated based on the data obtained [18]. For clinical interpretation however, it is important to distinguish and prioritize different domains of prophylaxis. The aim of this project was to develop consensus on a set of definitions of adherence to prophylaxis in haemophilia from a clinical perspective.

Methods

In this study the Delphi methodology was used, which provides a systematic and validated strategy to achieve consensus regarding health care management [22, 23]. In the first round of the study, an item-list of significant aspects of adherence was generated by all professional and patient experts. These aspects were categorized and domains were developed. In the second round, experts were asked to prioritize these domains and to provide cut-offs for adherence. In the third round, different combinations of domains and eight clinical cases were labelled as adherent, sub-optimally adherent or non-adherent. The final version of the definition was discussed using a closed forum. Details of the Delphi method are explained below.

Participants

Experts working in three Dutch haemophilia treatment centres (HTC) from different disciplines (medical, nursing, social worker/ psychology and researchers in the field of adherence) and members of the Dutch Haemophilia Patient Society were invited to participate. Inclusion criteria were: at least one year of experience with haemophilia treatment or use of prophylaxis for more than one year. From May 2014 until September 2014, experts received a questionnaire by email for each study round. Experts were asked to return the answers to the researcher (LS) only, to ensure that experts were blinded for other responses. The following participant demographics were collected: treatment centre, type of centre (paediatric or adult care, or both), discipline, number of years of professional experience, experience in haemophilia and number of years using prophylaxis (expert patients only). Answers were anonymized before analysis. Frequencies, median values and (IQR) were calculated to describe characteristics of the participants.

The Delphi procedure

In round 1, experts were asked to mention items which play a role in adherence to prophylaxis, in preferably 1-3 words per item. The items generated were analysed and clustered into domains by two experts (LS and KF). Items mentioned less than seven times were not included in the second round.

In round 2, the indentified domains were returned to the experts to rank order each domain and to estimate a clinical cut-off for non-adherence. The cut-off could be a percentage or a multiple-choice answer, depending on the domain. Mean values were calculated to provide a ranking and the cut-offs. The three most highly ranked domains were used for a first version of the definition. After this second round the extreme limits of adherent and non-adherent became clear, yet the area in between was less obvious. Therefore, an additional category was added in round 3: sub-optimally adherent.

In round 3.1 and 3.2 the concept definition was tested and validated with hypothetical and real life scenarios. In 3.1, the hypothetical cases were provided in a scheme, for labelling as 'adherent', 'sub optimally adherent' or 'non-adherent'. For example: case 1: 0-15% missed infusions, 0-10% dosing deviation (IU) and 0-30% deviation from prescribed time of day assessed over a 4 week period. In addition, the experts and patients were asked whether these three categories were sufficient to describe adherence. A four week period was chosen because it is easy period use for calculation. In round 3.2, the concept definition was tested in eight patient case reports. These cases were based on real life data, collected for a prior study on adherence [24]. Consensus was considered reached when more than 80% of the experts agreed on each label. Discrepancies (<80%) were discussed with all experts on an online closed forum. All qualitative analysis (round 1) were support with the qualitative software program nVivo® (QSR International Pty Ltd, version 10, 2012). The quantitative data (round 2 and 3) was analyzed with SPSS® (software version 20, IBM SPSS Inc., Chicago, IL, USA).

Results

Details on the participants in the Delphi study are provided in Table 1. Overall, 23 of the 24 invited experts participated, including 20 clinical experts and 3 expert patients. One clinical expert agreed to participate but had to withdraw due to time considerations. The response rate per round varied from 88% (n=21/24) to 96% (n=23/24). The clinical experts had a median of 15 years' clinical experience (median, range 3-45 years) and 9 years of experience in haemophilia care (range 1-34 years). Clinical experts included physicians (43%), nurses (28%), a psychologist and a social worker (19%), and clinical researchers (10%). Most clinical experts treated both adults and children with haemophilia (62%), 28% treated only children and 10% only adults. The expert patients (n=3) had a median age of 26 years and were using prophylaxis for more than 23 years.

Round 1

The response rate in the first round was 96% (23/24 experts). The experts generated a total of 170 items, of which 120 items were classified into eight domains (Table 2). The domains: frequency of prophylaxis (23/23 experts), timing of prophylaxis (22/23), planning of risk events (18/23), HTC visits (16/23), managing stock (13/23), dose of prophylaxis (12/23), bleeding frequency (9/23) and completing the infusion diary (7/23). The remaining 50 items were classified as conditions or barriers for administration of prophylaxis (for example needle phobia, venous access issues, and difficulties with language) or were mentioned less than seven times.

Table 1. Characteristics of experts.

Clinical experts (n=20)	**Numbers**
Area of expertise:	
Medical	8
Nurse	6
Psychology	4
Research (adherence & haemophilia)	2
Medical experience (median years, IQR)	15 (6-27)
Experience in haemophilia treatment (med, IQR)	9 (3-16)
Experience with patient group:	
Paediatric	5
Adults	2
Both	13
Expert patients (n=3)	
Age (med)	26
Use of prophylaxis (med years)	23

Values are frequencies and medians (Interquartile range (IQR)).

Table 2. Results of Round 1 'Item-generation'.

Domains	**Times cited** (N=23 experts)
Frequency	23
Timing	22
Risk events	18
HTC visits	16
Managing stock	13
Dose	12
Bleeding frequency	9
Infusion diary	7

*120 items total, 50 items were classified as conditions

Round 2

The response rate in the second round was 92% (n=22/24). The eight domains of round 1 were ranked and cut-offs were produced (Table 3). The top-three domains were: frequency, dosing and timing of prophylaxis. The most important domain of adherence was the frequency of prophylaxis (mean rank 1.3) with an upper cut-off of 15% of skipped infusions per 4 weeks. The second most important domain was the dose (IU) of prophylaxis (rank 3.3), experts considered a maximum of 10% deviation of the prescribed dose as acceptable. The third most important domain was the timing of prophylaxis (rank 3.9), with an acceptable cut-off at maximum of 30% deviating from the prescribed time.

Table 3. Results of Round 2: Item-ranking and estimation of cut-offs.

Domains	Priority *(mean rank)*	Proposed cut-off	Experts' choice (%)
Frequency	1.3	Maximum missed infusions in 4 weeks (%)	12.9%
Dose	3.3	Maximum change in dose (%)	10.4%
Timing	3.9	Maximum infusions administered at hour other than prescribed in 4 weeks (%)	28.8%
Risk events	4.1	Handling and planning of a risk moment:	
		Extra dose & prophylaxis unaltered	15%
		Extra dose & prophylaxis postponed	30%
		No extra dose & prophylaxis unaltered	5%
		No extra dose & prophylaxis 1 day earlier/ later	50%
HTC visits	5.2	Attending planned hospital visits:	
		Always	60%
		75%	40%
		50%	0%
		No visits at all	0%
Bleeding frequency	5.6	Max number of spontaneous bleeds per year	mean 2.1
Managing stock	6.0	Ordering in advance:	
		1 month prior	20%
		2 weeks prior	60%
		1 week prior	20%
		Nothing in stock anymore	0%
Infusion diary	6.5	Completing the infusion diary:	
		100%	55%
		75%	45%
		50%	5%
		No log at all	0%

The domains above the dotted line were included in the final definition (highest ranking).

Table 4. Results of Round 3.1: Hypothetical cases.

	Domains of non-adherence to prophylaxis			
Hypothetical cases	**Missed infusions** (%)	**Dose changes** (%)	**Timing changes** (%)	**Label given:** (% of experts in accordance)
Case 1	0-15	0-10	0-30	**Adherent** 90
Case 2	0-15	0-10	>30	**Sub-optimally** 84
Case 3	0-15	10-25	0-30	**Sub-optimally** 89
		>25		**Non-adherent** 94
Case 4	15-25	0-10	0-30	**Sub-optimally** 89
	>25			**Non-adherent** 94
Case 5	0-15	10-25	>30	**Sub-optimally** 89
		>25		**Non-adherent** 94
Case 6	>15	0-10	>30	**Non-adherent** 85
Case 7*	>15	>10	0-30	**Non-adherent** 95
Case8	>15	>10	>30	**Non-adherent** 95

* The combination was less likely to occur.

Round 3 and final definition

The response rate in the third round was 88% (n=21/24). The three domains with cut-offs were presented in different variations (Table 4) and were labelled by the experts. On four categories experts disagreed (<80% agreement), these were further clarified and discussed with the experts using an online forum, leading to >80% agreement. The final version of the definition was approved by all co-authors. All experts agreed that the category 'sub-optimally adherent' was of added value. The final definition of adherence to prophylaxis in haemophilia is visualized in Figure 2 and described as followed (assessed over a 4 week period):

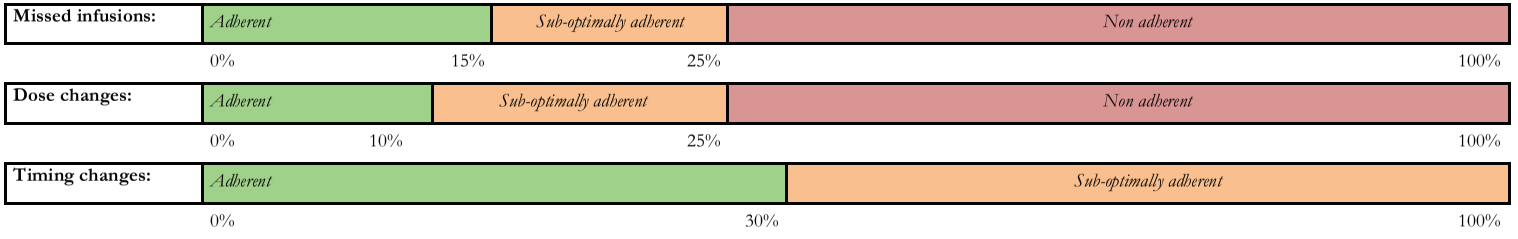
- *Adherent:* maximum 15% prophylactic infusions missed, maximum 10% deviation in dose (IU) and maximum 30% deviation in timing (hour).
- *Sub-optimally adherent:* 15 to 25% prophylactic infusions missed, maximum 25% deviation in dose (IU) or more than 30% deviation in timing.
- *Non-adherent*: more than 25% prophylactic infusions missed or more than 25% deviation in dose (IU), or a combination of both.

Discussion

This is the first study describing a formal definition of adherence to prophylaxis in haemophilia generated by a large group of professional and patient experts. The three most important domains of non-adherence to prophylaxis were: missed infusions, dose (IU) changes and timing of infusion. This led to three categories of adherence: *adherent:* <15% infusions missed, <10% dose changes and <30% deviation in timing; *sub-optimally adherent:* 15-25% infusions missing, <25% dose changes or >30% deviation in timing; *non-adherent*: >25% infusions missing or >25% dose changes. This definition can be used for research objectives as it is clear cut and easily utilized.

The study was conducted according to the guidelines of the Delphi procedure described by Hasson et al. in 2000 [22]. An additional validation strategy (the introduction of clinical cases in the third round) was added to increase reliability of the results and enable experts to test the definition in clinical situations. Inherent to the Delphi study, internal validity depends on the knowledge and experience of the experts [22]. In this study we asked experts with at least one year of experience in haemophilia. The majority of the experts however, had more than nine years of experience. A study-strength is that the expertise of patients and professionals were combined in the procedure. Due to the fact that the study was performed online, anonymity and independence was ensured, and experts could speak out freely. Furthermore, the response rates (92%) well above the minimum of 70% recommended [22].

Figure 2. Definition for adherence to prophylaxis in haemophilia.



Assessment over a period of 4 weeks: prescribed versus taken infusions, extracted from infusion diary.

Although the strategies of the Delphi procedure were taken in account, the fact remains that this procedure is based on expert opinion instead of validated with patient data.

The present definition was compared to other studies of adherence in haemophilia. Eight published definitions of adherence to prophylaxis were indentified, an overview is provided in Table 5 [9, 17, 18, 20, 25-28]. Only one of these published definitions described was derived from an (actual) dataset [18]. All published definitions included missed infusion [20, 28], dose changes [9, 25] or both [17, 26, 27]; these domains were also identified in our Delphi procedure, with the addition of the domain of timing of infusions. In 1994, a first definition of regular prophylaxis was provided as using prophylaxis for 45 weeks a year (87%) [20], since then this cut-off has been widely applied. The cut-off of 87% is comparable to our results: taking >85% of the prescribed infusions were ranked as the most important aspect of adherence. Llewellyn et al. used a mean deviation of 120 IU per dose as cut-off (over a 6 month period) for the definition of non-adherence [9]. This is comparable to our cut-off of 10% in dose; (10% of 1000IU= 100IU). The VERITAS-pro questionnaire includes six domains (Time, Dose, Plan, Remember, Skip and Communicate) [18], of which four were identified in the present study.

The present findings have both clinical and research implications. It is known that 88% of physicians and 82% of nurses routinely assess patients' adherence during the consultation [27]. As adherence is of such great importance for the efficacy of the treatment, this definition could help to standardize the assessment of adherence in clinical practice. The definition is easy to use by calculating the percentage of missed infusions (prescribed versus taken extracted from infusion logs). The (co-)authors propose a minimum assessment period of four weeks, however the definition is provided in proportions and therefore each period is possible. Dosing deviations can be assessed using information from the infusion diary; however, due to the use of entire vials a 10% dosing deviation is unlikely in clinical practice. A medication event monitoring system (MEMS) could provide more accurate data on adherence, unfortunately this system is currently unavailable for liquid medication [28].
In future therapeutic studies, this definition could help to identify non-adherent patients. In earlier therapeutic trails, for example of Manco-Johnson et al. [6, 29] and the ESPRIT-study [21], it was stated that non-adherent children were excluded from the trail; however no definition or cut-off for non-adherence was specified. To validate this definition it could be compared with long-term clinical outcomes, e.g. bleeds or arthropathy.

Table 5. Overview of definitions used in haemophilia literature.

Author, year	Study aim	Definition adherence provided:	Based on:	Remarks:
Aledort, 1994 [20]	Longitudinal study of haemophilia outcomes	Regular prophylaxis: >45/52 weeks per year (>87%).	Arbitrary cut-off.	
Duncan, 2009 [18]	Development of adherence questionnaire	≥57 point on VERITAS pro (possible total scores ranged from 24 (most adherent) to 120 (least adherent)).	Outcome VERITAS compared to: General adherence rating (7/10), 80% cut-off (prescribed vs taken) and sample mean + 1SD.	No weighting in domains.
Gringeri, 2011 [21]	RCT on prophylaxis	No cut-off was described.	Not described	In cases of apparently poor compliance, instructions were reinforced and checked at appropriate intervals.
García-Dasí, 2015 [28]	Assessment of adherence	Adherent: maximum of 25% missing or over treating Infra (non) adherent: more than 25% missing Over adherent: more than 25% over treating	Based on two general adherence definitions.	
Hay, 2012 [25]	RCT on ITI	FVIII dose compliance: a 20% variance from the total ITI dose was permitted.	Not described	N=12/134 were excluded due to poor compliance.
Ho, 2014 [17]	Assessment of adherence	100% adherence: exactly as prescribed 50% adherence: prescribed take ± 1 dose per week 0% adherence: any other.	Not described	The median adherence to frequency was 76% (IQR 67;85), and the median adherence to dose was 93% (IQR 73;97).
Llewellyn, 2003 [9]	Assessment of adherence	Adherent (score range from 0 to 120 IU), Non-adherence by over treating (scores 121 IU or above), Non-adherence by under treating (scores below 1 IU). (based on mean dose deviation per 6 months)	Not described.	
Manco-johnson, 2013 [29]	RCT on prophylaxis	No cut-off described.	Not described.	78% of the prescribed infusions were taken. N=4/42 were excluded due to poor compliance.
Sharipo, 2009 [26]	Evaluation of Advate®	Compliance with prophylaxis was defined as having received at least 80% of both the minimum prescribed dose and infusion frequency, and thus, subjects who did not comply received either lower doses or less frequent infusions.	Based on [27]	
Du Treil, 2007 [27]	Assessment of adherence	Based on prescribed dose & frequency vs. taken: High adherence: 67–100%, Moderate adherence: between 34% and 66%, Low adherence: <33%.	Not described	

Conclusion

This project was aimed at achieving a clinically relevant consensus definition for adherence to prophylaxis in haemophilia. It showed that defining adherence involves different aspects with different cut-off values. Three categories were established: adherent, sub-optimally adherent and non-adherent. The proposed definition can be used in clinical practice and for research on prophylaxis in haemophilia.

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CHAPTER 5

Adherence to prophylaxis and bleeding outcome in haemophilia: a multicentre study

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Submitted

Abstract

Introduction: Prevention of bleeding and joint damage in severe haemophilia is dependent on adherence to prophylactic replacement therapy. The aim of this study was to assess adherence to prophylaxis, including associations with age, bleeding and clotting factor consumption (CFC).

Methods: In three Dutch haemophilia treatment centres, pre-specified semi-structured interviews about adherence to prophylactic home-treatment over the past two weeks were administered to patients or parents of a child with haemophilia. Patients were classified according to pre-specified definitions as adherent, sub-optimally adherent or non-adherent based on missing, timing, and dose of infusions. Association of annual bleeding events, mean CFC, age (parents vs patients) and adherence categories were computed.

Results: Overall, 241 patients with haemophilia using prophylaxis were studied. Parents were more adherent (66%; n=48/73) than patients (43%; n=72/168). Sub-optimal adherence occurred in 29% of parents and 37% of patients and was characterized by changes in timing of infusion (mostly from morning to evening), while missing <6% of infusions. Non-adherence occurred less often: in 5% of parents and 20% of patients. Adherence levels were associated with CFC, but not with joint bleeding.

Conclusion: Non-adherence in haemophilia was relatively rare, yet 1/3 of the population struggled with prophylaxis.

Introduction

Since the introduction of prophylactic clotting factor replacement therapy, the lives of patients with haemophilia have completely changed. For forty years now, prophylaxis for severe haemophiliacs has made it possible to prevent most joint, muscle and soft tissue bleeds [1-3] and increase quality of life [4]. Current practice in the Netherlands is to initiate prophylaxis after the first joint bleed and continue throughout life [5-7], with the majority of the Dutch severe population practising self-infusion [2].

Maintaining high adherence levels of prophylaxis is crucial to prevent bleeding and to sustain well-being. In general, adherence is defined as the extent to which a person's behaviour - taking medication - corresponds with agreed recommendations [5] [6]. A meta-analysis in chronic diseases (heart failure, HIV, diabetes) showed that high adherence (75-90% of the medication taken) was associated with a lower mortality [7]. Reported levels of adherence to prophylaxis in severe haemophilia are inconsistent and vary from 44% to 87% [8-12]. In addition, little is known about the impact of non-adherence behaviour on bleeding. There is clinical evidence that even one (large) bleed can lead to irreversible damage to a joint [13] or the central nervous system, and may result in limitations in motor or cognitive dysfunction. There is however, little evidence in relation to the impact of non-adherence behaviour on bleeding.

As adherence is such a crucial factor to prevent bleeding, it is important to quantify the actual adherence to the prescribed treatment and its association with outcome. The aim of this study was to assess adherence to prophylactic treatment and its association with age, bleeding events, and clotting factor consumption.

Methods

This study comprised a prospective multi-centre study in the three largest haemophilia treatment centres of the Netherlands (Utrecht, Amsterdam and Rotterdam). Adherence was measured with a semi-structured questionnaire and patients were classified according to pre-specified definitions [14] as adherent, sub-optimally adherent and non-adherent. Age, bleeding events and the clotting factor consumption (CFC) according to adherence level were associated. The study was approved by the ethical committee of the University Medical Centre Utrecht, the Netherlands and registered in the Dutch Trial Register (NTR2686).

Participants

Patients affected with a severe or moderate congenital bleeding disorder using prophylaxis were eligible for inclusion. These patients had to practice regular infusions, by themselves or by a parent, for at least one year and at least once per week. Convenience sampling

was used: patients and parents visiting the clinic from September 2010 until January 2013 were eligible.

Adherence measurement

There is no gold standard for measurement of medication adherence [5]. During the development of this study there were no (Dutch) tools available to measure adherence in haemophilia patients. Evaluation of home treatment and subsequent adherence already was routinely performed by the Dutch haemophilia nurses. As no validated instrument for adherence was available at that time, a short questionnaire was developed by the participating nurses. This questionnaire consisted of routine questions on the different aspects of home-treatment (eight items). During the outpatient visit, nurses asked neutrally about a patients' prescribed regimen and adherence behaviour over the past two weeks [15]. Self reported questionnaires tend to have a good correlation with other measurement techniques of adherence [16] and recall period of two weeks is considered to be reliable [15]. In addition, the following baseline characteristics were collected from the patient medical records: year- and month of birth, person infusing, diagnosis, severity of haemophilia [17] and current treatment (date start prophylaxis, prescribed frequency and dose).

Bleeds and clotting factor consumption

Data on bleeding over the last three years was utilised from one of the participating centres, which had instituted electronic patient diaries [18]. These electronic diaries were completed by the patient or parent. The bleeding events were verified and updated during each clinic visit. Only bleeding events on regular prophylaxis were considered; events were excluded in case of surgery or when the prophylactic regimen was modified. Target joints were defined as any joint with three bleeds in three months [19]. Annual clotting factor consumption (CFC) over the last three years was extracted from pharmacy data.

Analysis

Data from parent and patient completed logs were analysed separately. Skipping prophylaxis and omitting morning infusion were expressed proportionally for each month Individuals within the two groups (parent and patient) were classified as adherent, sub-optimally adherent and non-adherent, based on a Delphi consensus procedure[14]. This classification was based on missed infusions, dose changes and deviation from prescribed time. This was defined as *adherent:* missing <15% infusions, <10% dose changes (IU) and <30% deviation in time; *sub-optimally adherent:* missing 15-25% infusions, <25% dose changes or >30% deviation in time; *non-adherent*: missing > 25% infusions or >25% dose changes. Bleeding events, target joints and CFC were

compared according to adherence categories using ANOVA (including post hoc tests). Differences were considered significant at a $P < 0.05$. All data processing and analyses were performed with SPSS® software, version 20 (IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA)).

Results

In total, 241 patients were included from three Dutch treatment centres (Utrecht n=184, Amsterdam n=43 and Rotterdam n=14), comprising 71% of the total population using prophylaxis in these centres. Seventy-three children (parent-reported) and 168 patients were included. Patient characteristics are shown in Table 1.

Table 1: Patient characteristics.

	Parent-reported *N=73*	**Patient-reported** *N=168*
Age (med)	8.4 (6.2-10.5)	29.9 (17.1-49.8)
Diagnosis		
Haemophilia A:	60 (82%)	147 (88%)
Haemophilia B:	11 (15%)	13 (8%)
Von Willebrands Disease:	-	4 (2%)
Other:	2 (3%)	4 (2%)
Severity		
<1%:	70 (96%)	160 (95%)
1-5%:	3 (4%)	4 (2.5%)
Type III:	-	4 (2.5%)
Venous access		
IV:	63 (86%)	168 (100%)
CVAD:	10 (14%)	-
Frequency prophylaxis (med)	3.0 (2.0-3.5)	3.0 (2.0-3.0)
Dose prophylaxis (med)	750 (500-1000)	1000 (1000-1000)
Joint bleeds (med)	1.3 (0.3-2.6)	1.4 (0.4-3.8)
Bleeds total (med)	3.7 (1.8-5.1)	3.0 (1.2-5.4)
Target joint (yes)	4 (7%)	26 (15%)

Values are frequencies (%) or medians (Interquartile ranges).

Characteristics of paediatric patients and parent adherence

The paediatric patients (parent-report, n=73) had with a median age of 8.4 years and the majority had haemophilia A (82%) and severe haemophilia (96%). The children mostly received infusions 3 times per week (45%) with a dose of 500 units (47%). Ten children (14%) had a central venous access device (CVAD). Children experienced a median of 1.3 joint bleeds per year, the total number of bleeds per year was 3.7 and four children had a target joint (6%).

Adherence levels, including details are shown in Table 2. Parents who infused their child were mostly adherent (66%, n=48). Sub-optimal adherence occurred in 29% of the

parents (n=21). This was characterised by changes in the timing of infusion: only 20% of the infusions was administered at the prescribed time. Non-adherence occurred less often (5%, n=4) and was characterised by 25% missed infusions per month. Almost all parents were aware of the need to infuse in the morning (96%) and used the prescribed dose (97%).

Characteristics patients and patient adherence

Patients who were able to self-infuse had a median age of 29.9 years old and were mostly diagnosed with haemophilia A (86%). The prophylactic regimen was mostly 3.0 infusions per week with 1000 units per infusion. Patients on prophylaxis experienced a median of 1.4 joint bleeds per year, and a total of 3.0 bleeds per year. Overall, 15% of patients (n=26) had a target joint.

In patients, 43% (n=72) was considered as adherent. One-third of the population (37%, n=62) was sub-optimally adherent, which resulted from rumbling with prophylaxis, mainly with timing. Non-adherence was lower (20%, n=34), yet included a mean of 41% of infusions missed per month. Although, the majority of patients were aware of the need to infuse in the morning (92%), only the adherent patients were able to maintain the morning infusions. Changing of the prescribed dose on a patients' initiative occurred infrequently (6.5%).

Parents vs. patients

Parents had a significant higher adherence than self-infusing patients ($p<0.01$). In Figure 1, the adherence levels according to age are shown; adherence levels were the highest in children and the lowest in patients aged 25 to 40 years. After the age of 50, the proportion classified as adherent increased again to 60%.

Bleeding episodes and CFC

The effects of non-adherence are shown in Table 3 and Figure 2. Although joint bleeding appeared increased in the non adherent patients, their number was too small to perform reliable statistical testing. Joint bleeding in adherent and sub-optimally adherent patients was similar (p=0.7). Target joints in children were rare and similar according to adherence level. Likewise, clotting factor consumption was similar across adherence levels (mean CFC 124-134 x 10^3 IU/ year).

In adults, bleeding frequencies showed no association with adherence levels. Adherent patients had a median of 1.7 joint bleeds per year, while sub-optimally adherent and non

Table 2: Overview of adherence to prophylaxis.

	Adherent‡	Sub-optimally adherent‡	Non-adherent‡	Total
Parent-reported	N=48 (66%)	N=21 (29%)	N=4 (5%)	N=73
Administered infusions§	99%	98%	75%	98.8%
Correct dose	100%	90%	100%	97.3%
Timing changes§	98%	20%	24%	72%
Knowledge correct time	96%	95%	100%	96%
Patient-reported	N=72 (43%)	N=62	N=34	N=168
Administered infusions§	99%	94%	59%	90.8%
Correct dose	100%	90%	85%	93.5%
Timing changes§	98%	25%	29%	57%
Knowledge correct time	97%	75%	85%	92%

‡Definition: *adherent:* missing <15% infusions, <10% dose changes (IU) and <30% deviation from prescribed time; *sub-optimally adherent:* missing 15-25% infusions, <25% dose changes or >30% deviation in time; *non-adherent*: missing > 25% infusions or >25% dose changes.
§ Values are mean percentages per month.
* Significant p<0.01.

Table 3: Outcome according to adherence (Utrecht patients only).

	Adherent	Sub-optimally adherent	Non-adherent
Parent-reported	N=37	N=19	N=3
Joint bleeds	0.8 (0.4-2.5)	1.3 (0-2.7)	2.3 (na)
Bleeds total	3.6 (2.1-5.5)	3.9 (1.5-5.2)	4.8 (na)
Target joint	3 (6%)	1 (5%)	-
CFC§	130	124	134
Patient-reported	N=59	N=56	N=30
Joint bleeds	1.7 (0.5-4.0)	1.2 (0.4-3.6)	1.0 (0.3-3.9)
Bleeds total	3.0 (1.2-5.1)	3.1 (1.2-5.4)	3.0 (1.1-5.8)
Target joint	9 (13%)	11 (18%)	6 (18%)
CFC§	212*	173*	150*

Joint bleeds and bleed total are medians (IQR), target joint are frequencies.
Na = not applicable.
§ CFC: mean x 10^3 IU/year clotting factor consumption.
* Significant p<0.01

adherent had a median of 1.2 and 1.0 joint bleeds per year (ns). In addition, the total number of bleeds per year was similar in all categories: about 3 bleeds per year. Nor were significant differences observed in the occurrence of target joints. Clotting factor consumption however, was significantly lower in patients with lower adherence: annual CFC decreased from 212 to 150 x 10^3 IU/ year (p<0.01).

Figure 1: Adherence (%) according to age.

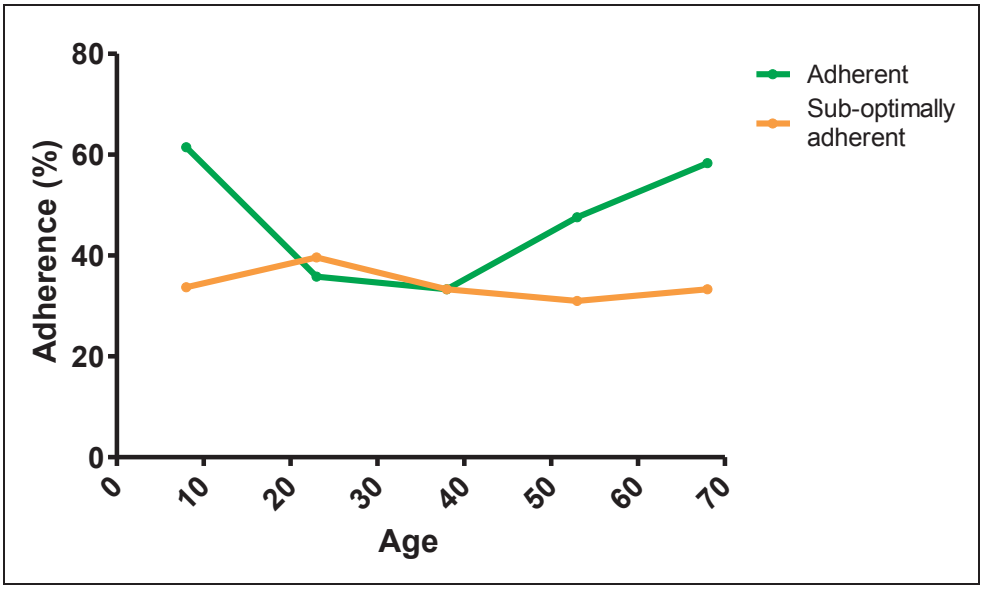
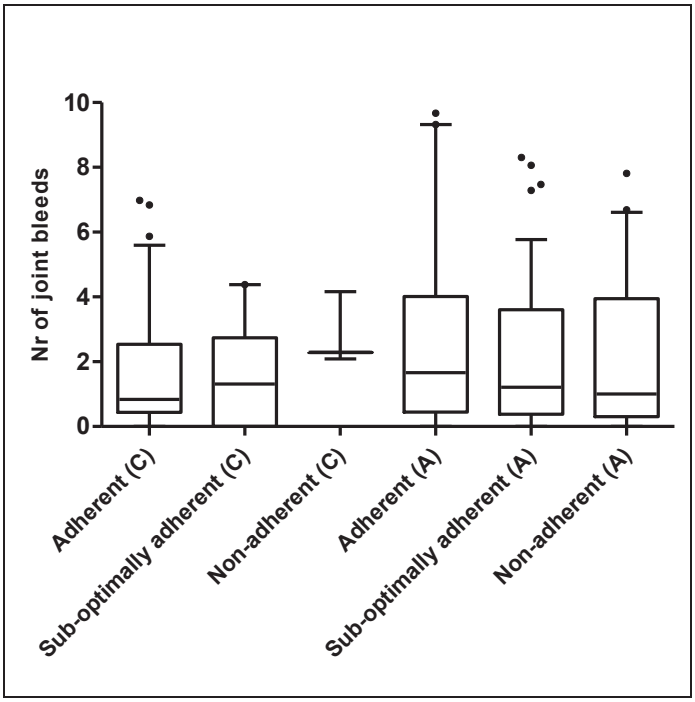


Figure 2: Number of joint bleeds according to adherence level.



Not significant (children p=0.7, adults p=0.6).Values are medians, interquartile ranges and 10-90 percentiles. C= children, A= adults.

Discussion

This study is quantifying adherence to prophylaxis in more than 200 haemophilia patients and across different ages. Non-adherence in haemophilia occurs relatively infrequently, yet one third of the population reported changing the timing of infusions, resulting in sub-optimal adherence. Parents infusing their child reported significantly less deviation from prescribed treatment than self-infusing patients. Adherence levels were lowest between 25 and 45 years. Almost all patients and parents were well informed of the necessity to infuse in the morning, yet many patients struggled with this. The group classified as non adherent skipped 25-41% of infusions each month, while adherent or sub-optimally adherent patients skipped only 1-6% of the infusions. Adherence showed no association with bleeding in children or adults. Clotting factor concentrate was similar across adherence levels in children, while non adherent adults used significantly less concentrate than more adherent patients.

To help interpret these findings, some aspects of the study need to be discussed. First, there is no gold standard for adherence measurement [5]. Options like plasma drug levels or a medication event monitoring systems are not available in haemophilia. Adherence questionnaires have a high correlation with objective measures of adherence (e.g. plasma drug concentrates) [15, 20]. In this study a non-validated adherence questionnaire was used, which could be easily implemented to obtain high response rates. At the start of the study no other validated instrument was available. Yet, validated adherence questionnaire developed shortly afterwards included similar domains and questions [21, 22]. The nurses tried to be non-judgmental while assessing the adherence behaviour. The authors considered the answers representative, because 57% of the patients reported issues with adherence, which is similar to other reports [9-12]. The definition of adherence was based on a national Delphi consensus procedure [14] which included the main aspects of adherence to prophylaxis. A limitation of the study is that fact that adherence was measured at one time point, while adherence levels could vary over time in patients' life. Overall, a recall period of two weeks is considered as optimal due to reliability [15]. Adherence could be influenced by number of symptoms [23], which could lead to variation within periods.
Regarding the external validity, it is important to consider that this study was performed in three Dutch centres with similar treatment strategies [24] and education [25]. There were no differences between the centres, except for the fact that Utrecht included more adult patients (n=114). The Netherlands has communicative social perspective with most patients who freely talk about their disease and their struggles. Therefore, we believe data to be quite reliable. However, non-adherent patients may attend the centres less frequently and may therefore be underrepresented.

Our findings are supported by previous reports. Two studies defined adherence as at least 67-75% of the infusions taken [11, 26], observed that 39-53% of the patients was defined as adherent [11, 26]. These percentages are comparable to adherence levels reported in other chronic diseases as it generally accepted that 50% of the patients adhere to the prescribed medication [5]. The observation that patients have lower adherence levels than parents has been reported by Duncan and Du Treil [26, 27]. Duncan et al. showed that changing the time of the infusion occurred more often than skipping infusions: 8.7 vs. 7.7 (range 4-20 points on VERITAS-pro questionnaire) [27]. Ho et al compared self-reported infusion dairies to physician prescription [10], they reported that adherence to prescribed frequency (76%) was lower than adherence to dose (93%). However, these findings could be biased as non-adherent patients usually do not maintain adequate infusion dairies.
The present study did not find an association of adherence with bleeding. The authors hypothesize that non-adherent patients reported less bleeding events or that they have no immediate feedback due to a milder phenotype (confounding by indication) [28].

Another explanation could be that the follow-up period was too short. Nijdam et al. followed a cohort from birth to 30 years, tapering and/or stopping prophylaxis resulted in more arthropathy while patient reported outcomes (e.g. bleeds) were similar [29]. While these differences in arthropathy were not detected in the same cohort with a follow-up of 20 years [30]. In contrast, in 78 Spanish children an association between adherence and joint bleeds was observed [11]. Furthermore, in 80 American adolescents adherence according to the VERITAS-pro questionnaire was associated with chronic pain [31].

The present findings have both clinical and research implications. From a clinical perspective, we can could conclude that adherence to prophylaxis in haemophilia includes more than taking infusions and may be improved in a substantial proportion of patients. Therefore, standard monitoring and supporting adherence is recommended to help patients to continue prophylaxis [32]. Discussing the infusion diary with the patient, providing positive feedback and discussing about difficult moments, provides insight into patients' behaviour and opens possibilities for intervention [32]. Experiencing a bleeding episode is probably the best motivator to adhere to prophylaxis [23]. Qualitative research has suggested that issues with acceptance or lack self-management skills are associated with non-adherence [28]. Selected patients could benefit from a tailored acceptance or education program to improve adherence. From a research perspective, a cohort study following patients for a long(er) period including repeated assessment of adherence could be an adequate approach to demonstrate associations between adherence levels and physical outcomes.

Conclusion

This is the first study quantifying adherence to prophylaxis in haemophilia on a large scale. Parents were more adherent than patients (66 vs. 43%). Sub-optimal adherence was observed in 29% of parents and 37% of patients and was characterized by changes in timing of infusions. Non-adherence occurred less often and was characterized mainly by missing infusions. Adherence levels were the lowest in the group aged 20 to 45 years. Adherence showed no association with bleeding, yet CFC use was significantly lower in non-adherent adults.

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CHAPTER 6:

Barriers and motivators of adherence to prophylactic treatment in haemophilia: a systematic review

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Abstract

Introduction: Long-term adherence to prophylactic therapy is the key to successful prevention of bleeds in severe haemophilia. The present study aims to provide a systematic review of the literature on the determinants of adherence to prophylaxis in haemophilia.

Methods: A literature search in the largest medical databases in Oct 2011. This search yielded 880 articles; reduced to 72 by further selection on title. 28 articles were excluded due to inclusion criteria. Full paper evaluation of 44 articles yielded five relevant articles that were critically appraised using the STROBE statement and items extracted from the critical appraisal criteria for cohort studies (Dutch Cochrane Centre).

Results: After critical appraisal, 2/5 studies were considered as the best evidence available. The results of these two studies were further used in the synthesis for description of the determinants of adherence. This concerned a total of 245 subjects in all age groups. Data was collected by using questionnaires and interviews. Motivators for a high adherence were: experience of symptoms, a positive belief of necessity of treatment and a good relationship with the health care provider. Important barriers were defined as: infrequent or absence of symptoms and increasing age.

Conclusion: Two high quality studies were identified. Reported determinants of adherence to prophylaxis were age, symptoms, beliefs, and the relation with the health care provider were. This information may provide a first step towards a strategy to promote adherence in haemophilia, with an important focus on age-specific interventions and patient education.

Introduction

Since 1965, the introduction of factor replacement therapy (cryoprecipitate and later clotting factor concentrates) has enabled the substitution of the missing clotting factor in haemophilia. for almost 40 years now, clotting factor replacement therapy has been administered to treat bleeds or as prophylactic replacement therapy to prevent bleeds [1,2]. Prophylaxis has improved therapy efficacy and consequentially enhanced quality of life by endorsing patient's autonomy [3,4]. In Europe, the majority of patients with severe and moderate haemophilia treat themselves at home, either prophylactically or on demand [5].

However, this intensive treatment requires lifelong dedication to prevent bleeding and maintain health. Adherence to this treatment is a crucial factor, defined as the extent to which a person's behaviour - taking medication - corresponds with agreed recommendations from a health care provider [6]. Yet, it has been reported that adult patients with chronic illnesses take only 50% of their medicine as prescribed [6]. This is observed in haemophilia too, and may affect treatment choices: a recent survey conducted across the US reported that one-third of all haemophilia physicians did not prescribe prophylaxis due to concerns about patients' adherence [7].

Nevertheless, the need for preventing bleeds is clear as it is known that repeated joint bleeds result in synovial hypertrophy, cartilage- and bone damage, and ultimately disabling arthritis [8]. Prophylaxis prevents bleeds and subsequent arthropathy [9]. In addition, taking prophylactic therapy is associated a significant risk reduction for intracranial haemorrhages [10] and less body pain [11]. In short, currently the most effective treatment approach to prevent bleeding and maintain joint function in severe haemophilia is achieved by upholding high adherence levels to the prophylactic regimen [12].
Because adherence is such an important factor for the prophylactic regimen, it is important to define the determinants of adherence. This allows the health care provider to support patients with haemophilia (and their parents) during this intensive treatment and anticipate on the barriers. The determinants were defined with a systematic search in the literature.

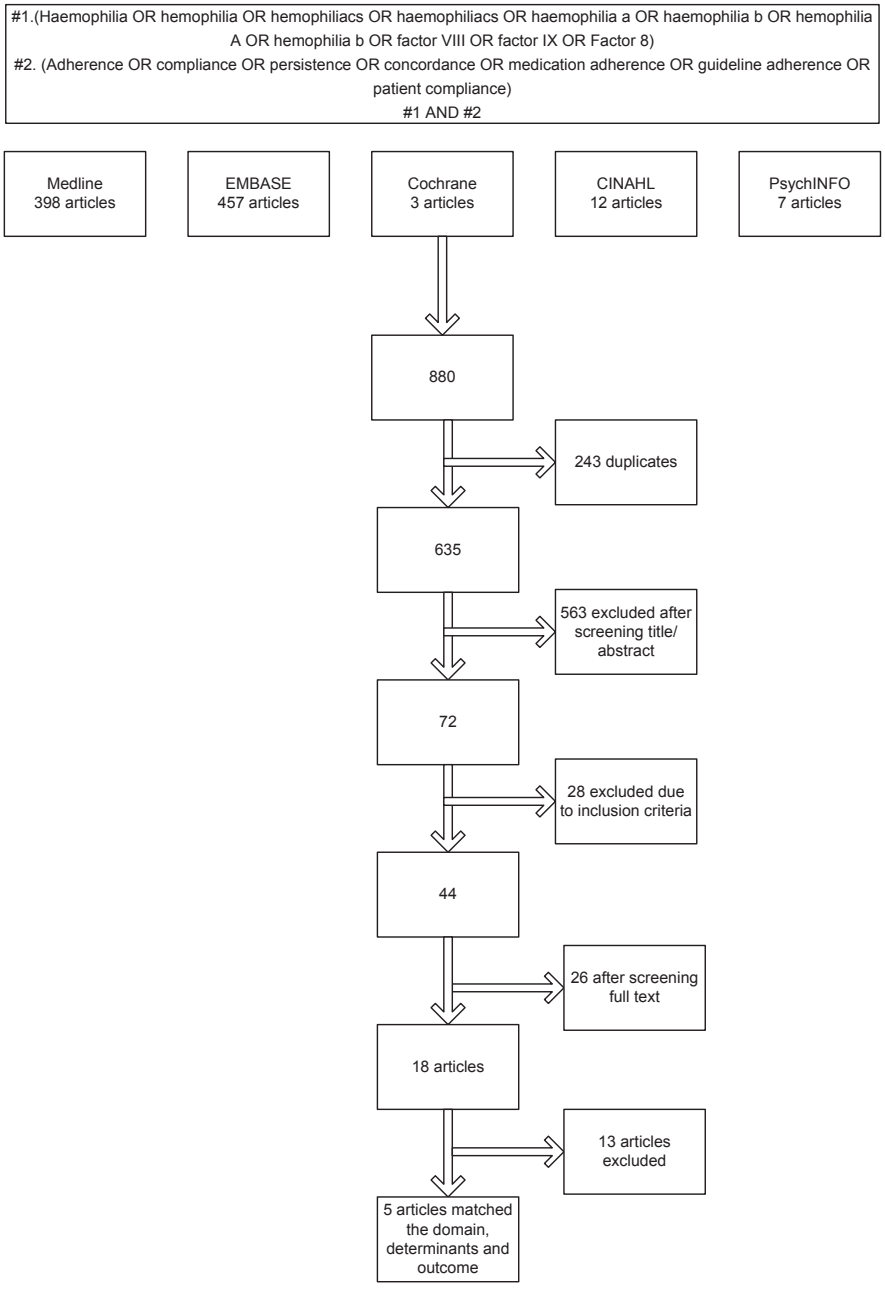
Methods

Search strategy

The electronic databases PubMed, EMBASE, Cochrane database, CINAHL and PsycINFO were searched for eligible studies. The search was run on October 31, 2011. After October 2011, additional studies were included by monthly updates until 15th of April 2012. The keywords included both: 1. terms concerning h(a)emophilia and 2.

terms concerning adherence (Figure 1). After selection of the eligible articles, reference tracking and related article searching was performed, to ensure no relevant studies were missed.

Figure 1: Flow diagram of study selection.



Study eligibility criteria

The selection was based on matching the full text with the domain, determinant and outcome of the current research question. These concepts were pre-specified; the domain concerned patients in all age groups, diagnosed with haemophilia A or B and using prophylactic treatment. The outcome was defined as adherence, according to the definition of the World Health Organisation [6]. Determinants affecting adherence (motivators, barriers, perceptions, facilitators or factors), were used as inclusion criteria during the study selection.

Study selection

The search strategy identified a potential set of relevant publications. Titles and abstracts were examined to identify relevant studies by one investigator (LS), because the eligibility criteria were apparent. All eligible studies were imported in an electronic data-file and duplicates were removed. When the title and abstract suggested a study that was potential for inclusion, a full paper copy of the article was obtained. LS examined the studies for correspondence with the inclusion criteria and this was discussed with a methodological expert (KF).

Assessment of methodological quality

All included articles were critically appraised by three independent reviewers (LS, NU, KF) using the STROBE statement (STrengthening the Reporting of OBservational studies in Epidemiology) [13] and the applicable criteria for quality of evidence developed by the Dutch Cochrane Centre [14]. The STROBE statement was used for assessing observational studies and consists of 22 items according to the reporting format. The Dutch Cochrane centre developed a checklist for critical appraisal for cohort studies, comprising of 12 items. The applicable items, concerning research domain, selection bias, determinants, information bias, outcome, results, generalizability, conclusion and ranking were used. The items concerning blinding, long follow-up, confounding, odds ratios and primary/ specialized care were not applicable for these studies included. The reviewers discussed and ranked the studies with pluses or minuses, these were later combined into a ranking score.

Data extraction and management

The following data items were extracted: author, year of publication, country, type of study cohort (single or multi centre), number of patients included in the study, study design, types of participants, measurement instruments used, statistical analysis done and the key results related to the research question (discussed by three reviewers, LS, NU and KF).

Summary measures

When available, P-values (α<0.05), Chi-square ($\chi 2$) or Pearson's correlations (r) were extracted from the publications. To summarize findings from studies with comparable subjects and methods, weighted averages were calculated from available data.

Results

Study selection

The full selection process is presented in a flow diagram (Figure 1). The initial search resulted in 880 articles. After removal of duplicates, 635 articles were screened on title. This yielded 72 articles which were screened on abstract, using the selection criteria for eligible studies. After exclusion of nineteen supplements, six reviews, letters and three studies of which full text was not retrievable (published before 1980); the full text of the remaining 44 studies was assessed. Ultimately, five studies were matched to domain, determinants and outcome and were considered to be relevant to the research question. Reference tracking and a search through related studies yielded no new studies.

Study characteristics

Table 1 presents a summary of the characteristics of the five studies. All studies were published in English in the period of 2001-2008. All studies had a cross sectional design; three studies used postal questionnaires [11,15,16], one used telephone-administered questionnaires [17] and one used personal structured interviews [18]. The questionnaires used; the Short Form-36 (SF-36) [11], Child Health Questionnaire (CHQ) [11], follow up of the Practice Patterns Survey (PPS) [16], the Illness Perceptions Questionnaire (IPQ) [15], the Beliefs in Medicine Questionnaire (BMQ) [15], and a questionnaire developed by the researchers [17]. Two studies were conducted in the United States [11,17], one in the United Kingdom [15], one in six European countries [18], and one had a global perspective [16]. The number of patients studied ranged from 38 to 208, with a total of 505 subjects included. In addition, two studies studied the perceptions of physicians and nurses, including in total 175 subjects [18,16]. The total population varied in age; there were 97 children/ parents, 45 adolescents and 188 adults.

Risk of bias

The risk of bias was assessed with the Dutch Cochrane Checklist and STROBE statement, and the results are shown in Table 2. The study of Llewellyn et al. [15] and De Moerloose et al. [18] scored high on most items, and were considered as providing the best evidence on the determinants of adherence. The study of Hacker et al. [17], had a small sample size (n=38) with mostly children or parents of the child with haemophilia. Furthermore, the questionnaire was not validated with other data and the outcome

(adherence) was not measured. In the study of Du Treil et al. [11] only 47/192 patients were studied due to refusal (n=113) or incomplete logs (n=32), suggesting a high risk of selection bias. In addition, 18/ 47 included patients used prophylaxis; this number was too low to produce reliable outcomes on potential determinants of adherence to prophylaxis. In the last study, Geragthy et al. [16] measured opinions of haemophilia nurses and adherence to prophylaxis was not measured. Due to the large gap in quality of the studies, only the studies of Llewellyn et al. and De Moerloose et al. were included and analyzed.

Motivators

Positive motivators for adherence were the experience of symptoms, good relationship with the health care provider and positive belief in necessity of treatment. Belief in the treatment influenced adherence slightly more than experience of symptoms (r= -0.44 vs. r= -0.37), however both correlations showed a low to moderate relationship. Patients who experienced more symptoms (defined as; 'illness identity', including eight symptoms, e.g. joint bleeds, pain, aching joints) were higher adherers (P <0.05) [15]. Furthermore, patients' beliefs concerning the necessity of the treatment (defined as; beliefs about the need for- and efficacy of clotting factor) were also identified as an important factor influencing adherence [15]. Higher levels of adherence were associated with stronger perception of necessity of treatment (P <0.01). The importance of the relationship with the HTC was shown in the study of De Moerloose et al. [18]. A good relationship with the haematologist ($\chi 2$ = 23.07, P < 0.001) was the most strongly associated with high adherence, followed by a good relation with the haemophilia nurse ($\chi 2$ = 13.76, P = 0.001) and a longer time spent in the HTC ($\chi 2$ = 10.57, P = 0.005).

Barriers

Patients reported absence of- or infrequent symptoms as the most important barrier to regular prophylactic therapy. In the study of De Moerloose et al. [18], 36% of 180 patients considered reduction, fluctuation or disappearance of the symptoms as the most important barrier. The barrier was even more frequently cited in adult patients (51% of all adults) [18]. Furthermore, an increasing age seemed an important barrier for a higher adherence: in older patients the adherence levels were lower ($\chi 2$= 12.59, P = 0.002) [18]. In the study of Llewellyn et al. [15], only patients of 12 years and older were included, age was not identified as a significant barrier.

Discussion

This is the first systematic review of the literature on determinants of adherence in haemophilia. Although the quality of the literature was limited, several consistent determinants could be identified. Patients reported experience of symptoms, good

Table 1: Characteristics and results of the included studies.

Study Year	*Country (single or multi centre)*	*Design*	*N Response rate (%)*	*Participants Age groups*	*Instruments*	*Analysis*	*Motivator*	*Barrier*	*Influencing determinant*	*P Quantitative information*	*χ2/ R*	*%*
Llewellyn [15] 2003	UK (single)	CS, questionnaire	65/104 (63%)	65 patients >12 yrs old	IPQ and BMQ and adherence (based on logs and prescribed treatment)	Descriptive analysis, chi-square test, t-test, Pearson's correlation, linear regression and ANOVA.	x x		○ Frequency of symptoms ○ Belief in necessity of treatment	0.05 0.01	-0.37 -0.44	
De Moerloose [18] 2008	Six European countries (multi)	CS, Interviews	180 (100%)	180 patients 28 physicians/ nurses 93 adults 45 13-19 yrs 42 2-12 yrs	Open-ended questions primarily as a structured interview	Descriptive analysis, multivariate logistic regression	 x x x	x	○ Age ○ Time spent in with the HTC member ○ Relationship with haematologist ○ Relationship with the nurse ○ Reduction/ disappearance of the symptoms	0.002 0.005 0.001 0.001	12.59 10.57 23.07 13.68	 38%
Hacker [17] 2001	USA (single)	CS, Telephone administered questionnaire	38/52 (73%)	38 patients 2 adults 36 children	Nine-multiple choice questions	Descriptive analysis	x		○ Knowledge			45%
Du Treil [11] 2007	USA (single)	CS, questionnaire	47/192 (24%)	47 patients 28 adults 19 children	SF-36 and the CHQ and adherence (based on logs and prescribed treatment)	Descriptive analysis, chi-square test, two-way ANOVA		x	○ Mental health	0.02		
Geraghty [16] 2006	Global (multi)	CS, questionnaire	147/274 (60%)	147 HTC's	Follow up on the PPS 2000 questionnaire	Descriptive analysis		x	○ Infrequent bleeds			80%

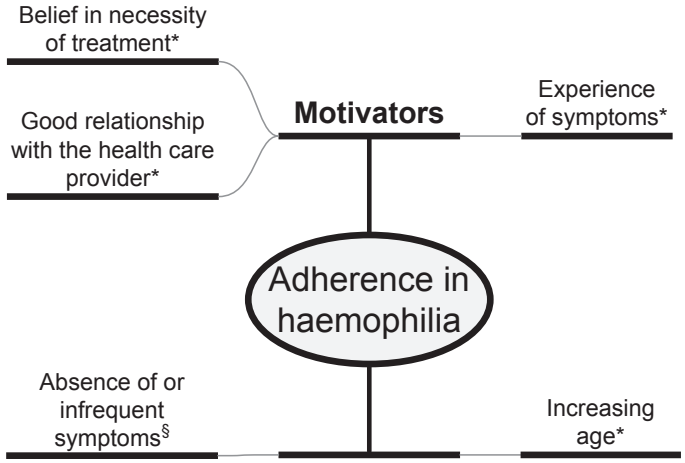
CS= cross sectional, P= P value, $\chi 2$= chi square, R = pearson correlation coefficient, % = percentage of citations.

Table 1: Summary of the critical appraisal of the studies included.

Studies included	Domain	Selection bias absent	Determinants well written	Information bias absent	Outcome clearly defined	Valid results	Generalizibility	Score
Llewellyn [15]	++	+/-	++	+	+	++	+	++
De Moerloose [18]	++	+/-	+	+/-	+	++	+	+
Hacker [17]	++	+/-	+	-	+	+/-	-	-
Du Treil [11]	+/-	- -	+	+/-	+	+/-	-	--
Geraghty [16]	-	-	+/-	-	+/-	-	+	--

Results of included studies
A model representing the results of the two included studies is shown in Figure 2.

Figure 2: Factors influencing adherence in patients with haemophilia, using prophylactic therapy.



* Significant association § Most frequent cited

relationship with the health care provider and belief in the necessity of treatment as the most important motivators for a high adherence. Absence of- or infrequent of symptoms were identified as the most important reasons for non-adherence. In addition, adherence was lower with increasing age.

Several limitations of this systematic review should be discussed. First, the number of studies reporting on the determinants of (non) adherence behaviour in haemophilia

was limited. Many of the available studies had a poor quality; three out of five did not satisfy the methodological criteria and were therefore not used for further synthesis. This resulted in a simple model with significant determinants of correct performed studies. Second, data collection was based on pre-specified questions rather than on patient initiated information. Therefore, it is likely that not all possible determinants influencing adherence were measured in these two studies. This emphasizes the need for further research on this subject. Third, the determinants of adherence were often only reported as a motivator or a barrier, rather than both sides of the effect. Only age and experience of symptoms were found both, as a motivator and a barrier. Finally, patient characteristics were not fully reported, this is limiting generalization to other populations. Moreover, it is clear that the generalizability of the results is limited to Western countries where prophylaxis is the standard of haemophilia care [19].

Greater understanding of adherence could be obtained from other chronic conditions using lifelong self-medication, such as diabetes mellitus. A meta-analysis on determinants of adherence in diabetes treatment by Nagasawa et al. [20], This study defined internal and external motivation (according to the Health belief model [21]), emotional stability, experience of benefits and age a supportive structure as important determinants to adherence in diabetes. Most of these determinants are in accordance with the findings of our study: age, experience of benefits, and internal and external motivation. The supportive structure may correspond with the relationship with the health care provider. The experienced benefit, and internal and external motivation appeared to be associated with the frequency of symptoms: the studies reviewed suggested that patients who experienced more symptoms were more likely 'to stay on course' and a reduction of symptoms was associated with a lower adherence. This emphasizes the continuing need for patient education on the risks of under treatment and bleeding.
"Although, there are no formal studies on the relationship between age and adherence in haemophilia, it appears an important factor which can be defined as both a barrier and a motivator. It is known phenomenon in chronic illnesses that children/ parents reported a higher adherence compared to the adolescent or adult group [20,22]. Kyngas et al. [22] demonstrated in different chronic illnesses that this phenomenon can be explained by treatment responsibility. Therefore, it is hypothesised that patients with haemophilia infused by a family member showed a higher adherence than patients practising self infusion. A downward trend in adherence is seen in the adolescent/ young adulthood [23]. Puberty is associated with different behaviour and exploring boundaries, also in the use of prophylactic treatment. It is important to develop a strategy focussing on the transition period, by supporting self-management in adolescents when parental supervision is weaning [24]. Adherence levels in elderly patients (65+) nor the apparent contradictory effects of symptoms and age on adherence in older patients are studied yet.

The present findings have both clinical and research implications. From a clinical perspective, these identified determinants can be directly influenced in daily practice. An important suggestion for clinical practice is to invest more in education techniques or -programs. The determinants symptoms and beliefs, are closely related to knowledge of the disease, reliance on the treatment and the healthcare provider [25]. With an important focus on this relationship and increasing patients' knowledge, adherence could be stimulated. In fact, adherence could and should be replaced by concordance - an agreement between a patient and a healthcare provider about whether, when, and how medicines need to be taken [26] - to emphasize the practice of joint decision making between patient and healthcare provider in chronic treatment. In the present study however, 'concordance' in combination with 'haemophilia' yielded no results.

From the research perspective, future research should be more focused on a representative sample of both adherent and non adherent patients with haemophilia. Furthermore, it is important to elucidate patient initiated information, rather than using pre-specified questions from a caregivers' perspective. A qualitative study should be performed to generate insights in patients' perspectives on adherence.

Conclusion

Non adherence of prophylactic therapy in patients with haemophilia is a complex problem. There is a lack of well-performed studies in the field of adherence and haemophilia. After critical appraisal, there were two studies with a high quality. These studies found that motivating factors for treatment adherence were experience of symptoms, a positive belief in necessity of treatment and a good relationship with the health care provider. Important barriers were absence of or infrequent symptoms and increasing age. It is crucial for health providers to be conscious the barriers and motivators influencing to adherence to promote adherence to long-term prophylactic replacement therapy.

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CHAPTER 7

Unravelling adherence to prophylaxis in haemophilia: a patients' perspective

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Abstract

Introduction: Given the lifelong therapy in haemophilia patients, insight in (non) adherence behaviour from a patient perspective is important to understand patients' difficulties with following treatment recommendations. The aim of this study was to clarify the process underlying adherence (behaviour) to prophylactic treatment, from a patients' perspective.

Method: To develop a grounded theory, a qualitative study using individual in-depth interviews was performed to understand experiences, perceptions and beliefs concerning adherence to prophylaxis. From two Dutch treatment centres, 21 adults with haemophilia using prophylaxis were interviewed. Patients were asked how they experience their task to administer prophylaxis and how they adhere to this. The interviews were transcribed, coded and analysed in an iterative process, leading to the development of the grounded theory.

Results and conclusion: Adherence was determined by the position of prophylaxis in life. The position of prophylaxis was determined by the perception of prophylaxis and the ability to exert prophylaxis. Patients' perception was influenced by two main factors: acceptance of haemophilia and feeling/fearing symptoms. The ability to exert prophylaxis was influenced by understanding haemophilia and prophylaxis and planning/infusion skills. The combination of different perceptions and skills led to four main positions of prophylaxis in life: 1) prophylaxis integrated in life, 2) prophylaxis according doctors' advice, struggling with irregular situations, 3) prophylaxis is too much to handle, 4) prophylaxis is a confrontation with illness. The adherence level gradually decreased from position 1 to 4. This information can be used to design tailored interventions to promote adherence.

Introduction

Patients with severe haemophilia are at risk of spontaneous and trauma related bleeds in muscles and joints. Repeated joint bleeds eventually result in arthropathy, leading to severe disabilities in daily life [1]. Since 45 years, the missing clotting factor can be injected intravenously to treat or prevent bleeding. Preventive replacement therapy (prophylaxis) usually consists of injections thrice weekly or every other day to prevent bleeds [2,3]. For this treatment, parents and patients learn the technique of intravenous infusion [4]. Prevention of bleeds and the ability to perform self-infusion significantly improved quality of life and autonomy in patients with severe haemophilia [5,6]. In Europe, the majority of patients with severe haemophilia uses prophylaxis [7].

Adherence is a crucial factor for the effectiveness of prophylaxis. One (large) bleed can lead to irreversible damage, especially in a joint or central nervous system. In order to reduce bleeding risk, treatment should be continued without interruption [8,9]. Discontinuation leads to physical damage, and affects socio-economic aspects of life. Hospital admissions, joint surgery, and/ or permanent joint damage limit social participation [10]. Adherence is defined as the extent to which a person's behaviour corresponds with agreed recommendations from a healthcare provider [11]. Reported levels of adherence to prophylaxis in severe haemophilia range from 44 to 87% [12,13,14].

A recent study identified independent factors associated with adherence: age, symptoms and belief in the necessity of treatment [15]. However, insight in non-adherence behaviour from a patient's perspective is still lacking. More fundamental research is needed to understand patients' difficulties with following treatment recommendations [16]. The aim of this study was to clarify the process underlying adherence to prophylaxis in severe haemophilia from a patients' perspective.

Methods

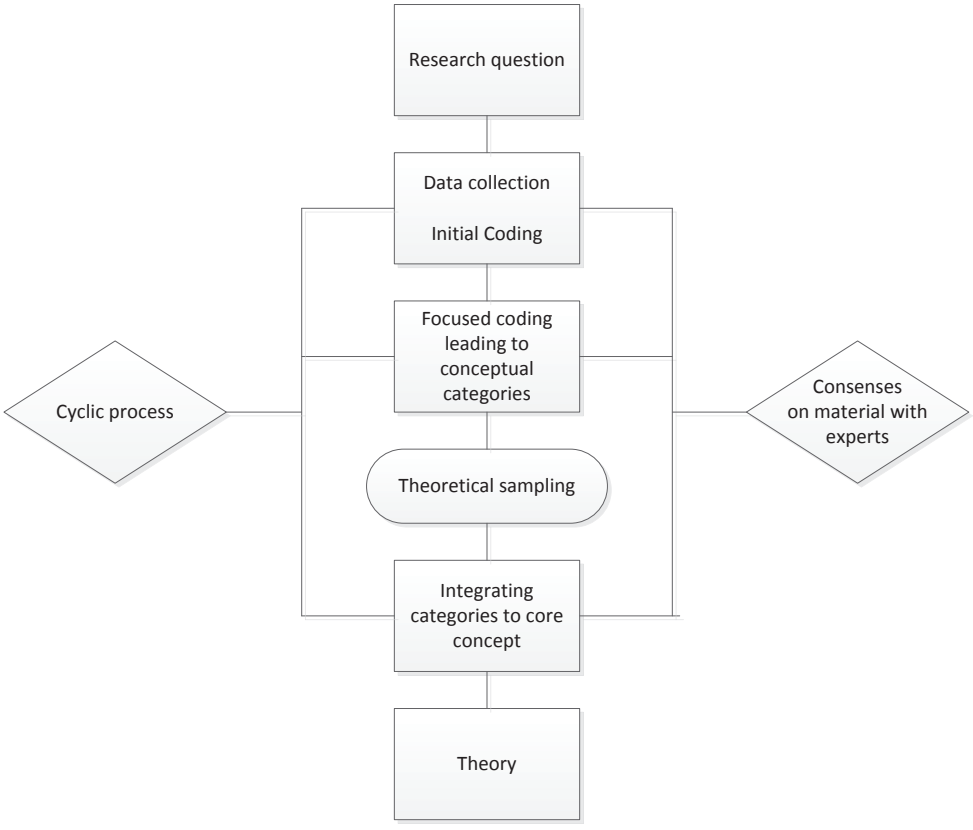
A qualitative study design allows in-depth exploration of adherence from the patients' perspective [17,18]. A grounded theory approach is suitable for developing theoretical understanding of subjective processes [17] (Figure 1). The research ethics committee of the University Medical Centre Utrecht, The Netherlands, approved this study (12-643).

Sampling

During the period of February-November 2013, adult patients (≥18 years) were selected from two Dutch haemophilia treatment centres (Amsterdam and Utrecht). Patients were selected from a previous study which quantified adherence in n=241 patients (convenience sampling, comprising 71% of total population [19]). Patients were eligible

when they had been prescribed prophylaxis with a minimum frequency of two infusions per week, for a minimum duration of two consecutive years. No patients participated in long acting trails. In line with qualitative sampling strategies, maximum variation with respect to adherence level, bleeding frequency and age was sought for the initial sample [20]. Pre-specified definitions of adherence (adherent, non-adherent and over treating), bleeding frequency (low, moderate, high) and level of education (low, middle, high) were used (Box 1). Other patient characteristics were obtained from the medical records and were verified with the patient during the interview. Data collection and data analysis were alternated in rounds. This allowed for constant comparison and purposeful selection of new cases to deepen the preliminary analysis.

Figure 1: The grounded theory process according to Charmaz [17].



Box 1. Definitions used to create a purposeful sample.

Adherence level	Adherent: followed the prescribed regimen for at least 80%-100% of the time; Non adherent: following the prescribed regimen for <80% of the time; Over treating: using >100% of the prescribed dose, specifically during bleeding episodes.
Bleeding frequency	Low: <5 bleeds per year; Moderate: between 5-15 bleeds per year; High: >15 bleeds per year.
Level of education	Low: primary school, lower secondary general; Middle: higher secondary general education, intermediate vocational education; High: higher vocational education, university.

Data collection

The researcher approached eligible patients to explain the study and to gauge their interest in participation. Written informed consent from all participating patients was obtained prior to the interviews. Individual face-to-face in-depth interviews were performed, based on topics (Box 2) that were converted to open questions. The interviews were held by two haemophilia nurses (LS and MB) and took place at the respondents' home. To improve the openness and quality of the interviews, both interviewers received specific interview training and did not interview patients recruited from their own centre. The interviews were performed in a non-judgemental atmosphere and emphasizing the interviewers' need to learn from the respondent. Interviews were audiotaped and transcribed verbatim. All information that could be used to identify patients was removed from the transcript prior to analysis.

Box 2. Topic list

- *Experiences with prophylaxis (and haemophilia)*
  - *Integration of treatment in daily life*
  - *Impact of prophylaxis and symptoms*
  - *Personal and medical history*
- *Beliefs and perceptions of prophylaxis*
- *Acceptance*
- *Adherence - current*
  - *Barriers*
  - *Facilitators*
  - *Self-monitoring and treatment of symptoms*
- *Social influences*
  - *Disclosure*
  - *Family relations*
  - *Relationship with health care provider*
- *Knowledge and understanding (indirect)*
- *Patient characteristics*

Data analysis

In accordance with the methods of the grounded theory approach [17], new data was compared to the established concepts in a constant comparative iterative process [21]. This included open (labelling meaningful sentences), axial (comparing, splitting, or clustering the codes, to verify content with the label) and selective coding (establish relationships between labels) [22]. The coding process was supported by qualitative software nVivo 10® (QSR International Pty Ltd 2012). The first researcher (LS) coded the interviews and developed a code-tree after each round of four interviews [23]. The research team (LS, MK, MB, MP and KF) individually read the first four interviews and checked coding results. After each round of 4-5 interviews, aspects from the codes and emerging categories were analysed. Explanations considered were verified with existing data and ambiguities were further explored during next interviews. These strategies increased reliability and enabled researcher triangulation. Saturation was reached on the main concepts after 21 interviews, i.e. no new information adding to the already constructed theory could be identified [17,24].

Results

Twenty-one of the twenty-three patients invited participated in the study; two patients indicated that they did not have time for an interview. Characteristics of respondents are shown in Table 1. All patients had severe haemophilia. Detailed diagnosis was not provided (haemophilia B, n=2) to ensure patients anonymity. The age of the respondents varied from 19 to 64 years (mean: 38.7 years). Ten patients were classified (Box 1 for definitions) as adherent, 11 as non-adherent (2 over treating). Almost half of the included patients had a low bleeding frequency (n=11), 29% had a moderate bleeding frequency (n=6) and 19% had a high bleeding frequency (n=4).

Table 1. Demographic and background characteristics (N=21).

Respondent	Adherence level*	Age	Bleeding frequency*	Marital Status‡	Education*
1	Adherent	63	Moderate	F	High
2	Adherent	27	Low	M	High
3	Adherent	56	Moderate	A	Middle
4	Over treating	40	High	M	Low
5	Adherent	64	Moderate	F	Middle
6	Adherent	27	Low	P	High
7	Non adherent	30	Low	P	Middle
8	Non adherent	22	High	P	Low
9	Non adherent	34	Moderate	F	High
10	Non adherent	33	Low	P	Low
11	Non adherent	52	Low	M	High
12	Non adherent	53	Low	F	Middle
13	Non adherent	54	High	F	Low
14	Adherent	20	Low	A	High
15	Over treating	35	Low	A	High
16	Adherent	39	High	F	High
17	Adherent	31	Moderate	A	Low
18	Adherent	30	Moderate	A	High
19	Non adherent	35	Low	F	Low
20	Non adherent	49	Low	F	Middle
21	Adherent	19	Low	P	Middle

* Definitions of the categories, can be found in Box 1.
‡ Living with parents (P), Alone (A), Married or cohabiting (M), Family with Children (F).

Adherence: determined by the position of prophylaxis in life

We identified four different positions towards prophylaxis determined by four main factors. Two factors influenced patients' perception of prophylaxis and two factors influenced the ability to exert prophylaxis. The positions towards prophylaxis represented different adherence levels. Details are described in the subsequent paragraphs (Table 2) and visualised in a model (Figure 2).

Factors influencing the perception of prophylaxis

Acceptance of haemophilia

Acceptance of haemophilia was identified as an important factor influencing the perception of prophylaxis. A wide variation in acceptance of the illness was seen ranging from not accepting at all ('...but I never accepted it' *(haemophilia)*) to full acceptation ('It is a part of me and my life'). The level of acceptance of the illness determined the perception of prophylaxis. Patients who expressed difficulty with accepting haemophilia mentioned that prophylaxis reminded them of being ill and that activities needed for management of haemophilia were experienced as a burden. Consequently, these patients

were more reluctant to adhere to the therapy in contrast to patients who accepted haemophilia. Patients who accepted haemophilia showed to adapt their life goals to haemophilia and developed a routine of prophylactic administration. These patients did not question the necessity of prophylaxis and were likely to adhere to the prescribed regimen.

Feeling and fearing symptoms

Feeling and fearing symptoms was identified as a factor that influenced the respondents' perception of prophylaxis. Symptoms which were frequently mentioned were those of (joint) bleeds and haemophilic arthropathy. Different patient categories were observed: patients with limited bleeding experiences, patients who had experienced (large) bleeds in the past, and patients who were still suffering from the consequences of former bleeds. Some patients with limited bleeding experiences mentioned: 'I don't have many bleeds anyway, so I don't need to take so much prophylaxis'. These patients played down their symptoms and consequently gave less priority to adhere to the prophylactic regimen. Most patients who had experienced bleeds in the past were well aware of their current bleeding risk and the necessity of prophylaxis. Patients stated: 'Bleeds are so annoying and, more important, cause damage to my joints and prophylaxis can prevent that'. Patients who were still suffering from the consequences of bleeds in the past and had joint damage, told us that they often treated with a higher dose or more frequently then prescribed by their doctor. Many patients mentioned that they found it difficult to distinguish between joint bleeds and arthropathic joint pain. They told us that they feared joint deterioration and tended to over treat themselves to prevent risks. Finally, some patients only became aware of the necessity of prophylaxis when they experienced a bleed as a consequence of inadequately planned or skipped prophylactic infusions.

Factors influencing the exertion of prophylaxis

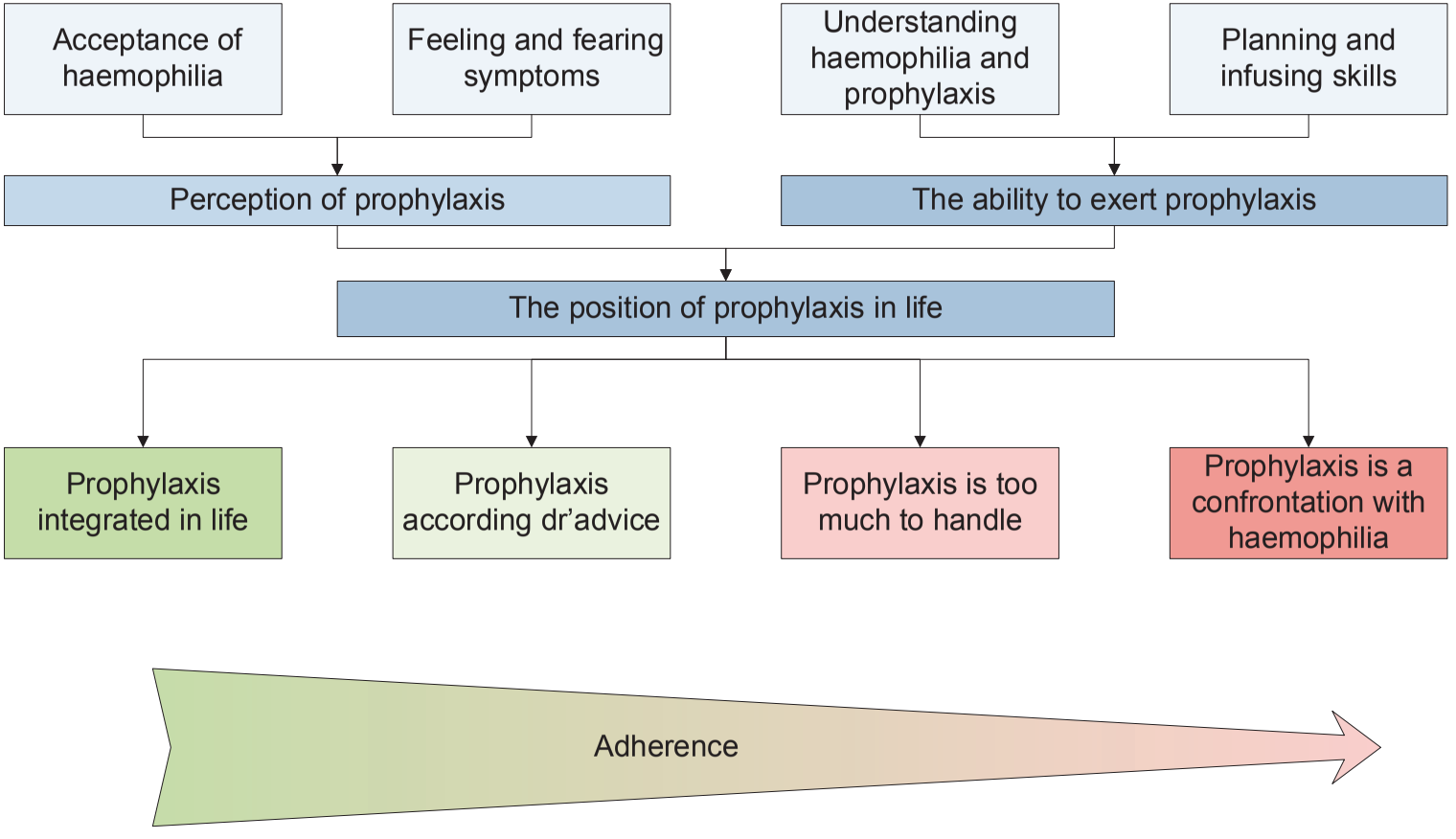
Understanding haemophilia and prophylaxis

Understanding haemophilia and prophylaxis was identified as an important factor influencing the ability to exert prophylaxis. From the patients' stories it became clear that their ability to understand health care information influenced their ability to make appropriate decisions concerning prophylaxis. We encountered a substantial number of patients who showed adequate understanding of haemophilia and the working mechanisms of prophylaxis. Patients who showed adequate understanding were able to make adequate decisions regarding their prophylaxis: 'I work in shifts and adapt my prophylaxis to the shifts'. A remarkable finding was that some patients who clearly showed adequate understanding of their illness and prophylaxis, sometimes consciously deviated from their regimen, despite the risks. These patients made a willingly choice for non-adherence, explained that they did not want to adapt their activities to haemophilia

Table 2. Model explaining adherence to prophylactic treatment in haemophilia.

Positions / *Factors*	**Prophylaxis integrated in life**	**Prophylaxis according to doctors' advice, struggling with irregular situations**	**Prophylaxis is too much to handle**	**Prophylaxis is a confrontation with illness**
Acceptance of haemophilia	Acceptance of haemophilia and prophylaxis is part of life	Acceptance of haemophilia and prophylaxis is something that has to be done	Acceptance of haemophilia and prophylaxis is too much to handle	Non acceptance of haemophilia and aversion of prophylaxis
Feeling and fearing symptoms	Feeling and fearing symptoms due to prior experiences	Awareness often related to inadequate treatment of irregular situations	Feeling symptoms related to difficulties with managing prophylaxis	Limited feeling and fearing symptoms
Understanding haemophilia and prophylaxis	Adequate understanding of haemophilia resulting in adequate prophylaxis	Less understanding following professional advice resulting in inadequate decision-making	Less understanding resulting in inadequate decision-making	Adequate understanding resulting in a conscious choice for non-adherence
Planning and infusion skills	Adequate routine skills and pro-active handling in complex situations	Adequate routine skills, struggling with complex situations	Limited routine skills and difficulties with integration of skills in life	Adequate skills, but choose not to use them
Perception of prophylaxis	Prophylaxis is a part of life	Prophylaxis according to doctors' advice	Other things in life have more priority than prophylaxis	Prophylaxis reminds me of having haemophilia
Adherence behaviour	Regular administration and adapted the prophylaxis to activities in life	Regular prophylaxis, struggling with situations requiring extra treatment	Overall difficulty with managing prophylaxis and integration in life	Stopping, significantly reducing dose or frequency of infusions, not treating minor bleeds and no follow-up treatment

Figure 2: Schematic model of adherence to prophylaxis in haemophilia.



Adherence is decreasing from left to right.

and were prepared to accept the consequences of their decision. In contrast, some patients failed to understand their illness and the working mechanisms of their regimen. Adherence behaviour in these patients was characterized by inadequate decision-making and the development of wrong routines: 'Respondent (R): I like skateboarding, Interviewer (I): With protection? R: Uhm, no I never thought about that'.

Planning and infusing skills

Planning and infusions skills were identified as a factor associated with the ability to exert prophylaxis. From the patients' stories we learned that both routine as well as complex (self-management) skills are needed to manage the prophylactic treatment accurately. Routine skills were described by patients as practical skills needed for self-infusion (infusing) and administration of prophylaxis on a regular basis (planning). The complex skills were described as anticipating on the demands of daily life with adequate treatment, identifying risk moments, and bleeding management. This required a pro-active attitude. Variation in the individuals' skills was seen: patients who fully integrated both routine and complex skills in life and who handled pro-actively, patients who experienced difficulties with the complex skills only, and patients who had difficulties with both. Patients who handled pro-active tried to prevent bleeding and the necessary skills were fully integrated in daily activities. Patients who struggled with the complex self-management skills mostly reacted passively to a bleed, e.g. immobilizing, under-treating or postponing treatment. Patients, who struggled with both routine and complex skills, struggled with the infusion technique and integration of prophylaxis in daily life. These patients struggled also with forgetfulness and postponing prophylaxis, which reduced adherence.

The positions of prophylaxis in life

The combination of factors led to different positions of prophylaxis in life. Four main positions of prophylaxis were identified from the interviews; patients who had fully integrated the prophylaxis in life, patients who administered prophylaxis according doctors' prescription, but struggled with irregular situations patients who found prophylaxis too much to handle and patients who found prophylaxis a confrontation with haemophilia. Illustrating quotes are shown in Table 3.

I. Prophylaxis integrated in life

Patients accepted the fact that prophylaxis affects their life and that they had to integrate treatment in daily life and adapt their standard of living. These patients mentioned that it was a conscious choice to administer the prophylaxis regularly. Routine strategies were developed and postponing prophylaxis was rare; it occurred sometimes due to time pressure or forgetfulness. A positive perception towards prophylaxis dominated, patients

stated that prophylaxis was a prerequisite for a normal life. Patients were motivated by previous experiences of (joint) bleeds or joint limitations. Some patients experienced a 'natural reminder' (symptoms occurred when the prophylactic effect had worn off) as a motivator for taking the treatment. During a bleeding episode patients treated immediately and took rest when needed. A notable finding was that patients who integrated prophylaxis in life, sometimes took a carefully considered risk for a 'once in a life time experience' (like bungy-jumping) using an extra prophylactic infusion.

II. Prophylaxis according doctors' advice, struggling with irregular situations

Part of the patients administered prophylaxis regularly ('as the doctor said') and thus were adherent, but told us that they struggled with irregular situations. Patients showed inadequate self-management skills in these deviant situations. This was expressed by e.g. infusing after the risk activity rather than before, or postponing treatment during a bleed until it was unbearable. Therefore, symptoms occurred more often or lasted longer. Patients who were struggling with symptoms of arthropathy showed that they followed doctors' advice, however treated often higher or more than prescribed in case of joint damage or joint bleed.

III. Prophylaxis is too much to handle

This position is comparable to position II, however these patients were also non-adherent to routine prophylaxis and struggled with the integration of prophylaxis in life. The patients told us that they failed to administer prophylaxis, due to inadequate routine and the complexity of the needed self-management skills. Planning prophylaxis and managing treatment of bleeds were considered difficult and other things in life easily overruled the treatment. Forgetfulness, skipping and inability to manage other activities concerning prophylaxis (planning, stock management and completing the log) were frequently mentioned. Bleeding occurred when patients forgot the prophylaxis and following the proper dosing schedules for treatment of a bleed was difficult.

IV. Prophylaxis is a confrontation with haemophilia

These patients gave haemophilia less priority in life: a negative perception of haemophilia and prophylaxis dominated. Patients felt prophylaxis restricted their life and therefore considered it to be a burden. Most patients told us that they consciously choose to skip prophylaxis and patients stated that not accepting their illness was an important element for making this choice. Quotes like 'taking prophylaxis is admitting to a weakness' and 'I always resisted prophylaxis' supported this element. Behaviour like stopping prophylaxis, significantly reducing dose or frequency of infusions, not treating minor bleeds and refraining from follow-up treatment after a bleed, was frequently mentioned. Patients related experiencing less bleeding episodes to the presence of haemophilia and

Table 3. Illustrating quotes of the different positions towards prophylaxis.*

Position I: Prophylaxis integrated in life R 2: 'Prophylaxis has a very positive influence on my life. I don't think I could manage without it, knowing from my own experience that it's impossible.' R18: 'It gives you a normal life. Normally I don't give that much about 'being normal', but I don't want to worry about my haemophilia and the risk for bleeds. Therefore, I always administer prophylaxis, because you minimize the chance that you get a bleed.'	Position II: Prophylaxis according to doctors' advice, struggling with irregular situations R 3: 'Depending on the severity of the bleed, I just sit still, or I am very careful. I: When will you treat the bleed? R: The next day, or day after, that's the point that I say, well it might be wise to give some treatment today. The idea of prophylaxis is that you use it when you have an increased risk.' R10: 'I administer the prophylaxis at a moment which its comfortable for me. It happens sometimes that it is in the morning, but usually after work' (performs physical heavy work activities)
Position III: Prophylaxis is too much to handle R 8: 'It's not that I think I need to take prophylaxis… I just forget it. I feel a kind of stiffness, and I think o no… too late… Then I have a look in my logbook, I did it again, I forgot the prophylaxis.' R 13: 'When I take treatment regularly, it goes better. And then I forget the treatment for a while and then I feel pain in my elbow, mostly it is a bleed.'	Position IV: Prophylaxis is a confrontation with illness R 9: 'When I have a bleed, I think: 'I don't have haemophilia'. And when I think it's not there and I keep it from myself, then it's not there. Only when I can't barely hold it anymore, I will do it.' R 19: 'Haemophilia is admitting to a weakness, I do not want it. To admit to the fact that you constantly, neatly three times per week, standard prophylaxis administer, that I find a weakness.'

* All quotes are direct translated quotes of the patients.
R: respondent (corresponds with Table 1) and I: interviewer.

therefore they considered it legitimate to delay or avoid the treatment. These patients administered treatment only in case of severe bleeding with pain.

Discussion

As to our knowledge this is the first qualitative study identifying the factors underlying (non) adherence behaviour to prophylaxis in haemophilia. Adherence was determined by the position of prophylaxis in life. This position was determined by the patients' perception of prophylaxis, influenced by acceptance and symptoms, and their ability to exert prophylaxis, influenced by understanding and skills. Eventually four different positions towards prophylaxis were identified: 1) patients who integrated prophylaxis in life, accepted their illness and had a high level of self-management skills, 2) patients who administered prophylaxis according to doctors' advice, but struggled with irregular situations, 3) patients who found prophylaxis too much to handle, who struggled with routine and complex (self-management) skills resulting in decreased adherence , and 4) patients who considered prophylaxis was a confrontation with haemophilia and consciously deviated from the prescribed regimen.

This study was performed in accordance with qualitative research methods [17,25]. A rigorous qualitative study was performed based on the patients' perspective. Internal validity was increased by maximum variation sampling in prophylaxis-users, and the use of independent trained interviewers experienced in haemophilia. Data saturation was reached after 18 of 21 interviews: the three last interviews added no new information to the model. The present findings are limited by the characteristics of selected patients and treatment setting. In patient stories treatment of bleeds was mentioned frequently, despite the interview-focus on prophylaxis, therefore we involved this aspect in our model. Moreover, in this study we included Dutch only adult patients, where prophylaxis is the standard for haemophilia [26] and were disclosure of illness is no major issue [27], which limited the generalizability to other countries.

The literature about adherence in haemophilia supports several aspects of the present model. A systematic review about barriers and motivators towards adherence in haemophilia defined significant factors influencing adherence [15]. The current study identified patterns in the previously identified barriers and motivators of adherence, which led to a consistent model. A qualitative study on treatment-decision-making in adolescents with severe haemophilia, three of the four patterns identified were similar (lifestyle routine prophylaxis, strict routine prophylaxis and no prophylaxis) [28]. 'Lifestyle routine prophylaxis' corresponds with position 'prophylaxis integrated in life'. The 'no prophylaxis' group corresponds with position 'prophylaxis is a confrontation with illness. 'Strict routine prophylaxis corresponds with position 'prophylaxis according to doctor's advice'. Only situational prophylaxis did not corresponds with any of the

positions identified in this study. In the absence of other qualitative studies on adherence in haemophilia, these findings were compared to reports on other conditions requiring life-long treatment. In patients with HIV, Vervoort et al. [29] performed a qualitative study. In patients with HIV, acceptance and disclosure were identified as key elements of adherence behaviour. Whilst acceptance was an important factor in haemophilia too, disclosure was not mentioned by Dutch haemophilia patients.
In patients with Diabetes Mellitus (DM) requiring insulin treatment, self-monitoring of blood glucose was perceived as a 'friend or a foe' [30]. In respondents with a positive perception of self-monitoring, it was integrated in life and adherence was high. The respondents who experienced difficulties with the procedure and never felt 'free' were more non-adherent. These findings correspond very well to the positions of 'prophylaxis integrated in life' and 'prophylaxis is a confrontation with illness' which are both dominated by acceptance.
The developed model is in accordance with the health belief model explaining health behaviour [31,32]. The health belief model states that individual perception influences the perceived severity of the disease. These individual perceptions are modified by different factors, such as perceived severity and knowledge. 'Perceived severity' corresponds to feeling/ fearing symptoms and ' knowledge' with understanding/ planning prophylaxis as identified in this study. The individual perception and the modifying factors determine the likelihood of health behavioural change; patients weighted the perceived benefits and barriers to decide whether they would like to perform health behaviour. This was also observed in the present study: the patients' position of prophylaxis in life influenced medication taking behaviour.

From the present results it is clear that self-management and acceptance are two aspects that can be addressed. Identifying the underlying position towards prophylaxis in non-adherent patients is a first step for designing an intervention. A recent qualitative study in adolescents with severe haemophilia defined the self-management skills necessary for adequate treatment (bleed recognition, self-infusion, self/ medicine management, pain/ risk management and conceptualizing preventative therapy) and observed that these were developed through experiential learning and individualized education [33]. Young patients struggling with self-management skills could benefit from recent developed self-management program [34,35]. In haemophilia, e- learning and peer-to-peer support have recently been established as helpful tools to improve knowledge [36,37]. For acceptance issues, there is experience in other chronic conditions with psychological interventions focussed on illness-acceptance with short- and long-term favourable effects [38,39]. Development of a set of interventions tailored to the main issue causing non-adherence could help to improve adherence in patients with haemophilia.
Future research should focus on the development and evaluation of cost-effectiveness of interventions designed to improve self-management and acceptance, preferably using a

randomised design to avoid selection bias and confounding. Another issue is improving adherence in the most difficult group: the adolescents. Both from clinical practice and research in haemophilia and other chronic conditions [40] it is clear that adherence is generally lower in adolescence. However, it is expected that different or additional factors may affect the position of haemophilia in life in this age group. Therefore, a separate qualitative study, leading to the development of a theoretical model, should be performed for this age group.

Conclusion

This study explored the underlying factors of (non-) adherence behaviour to prophylaxis in patients with haemophilia. Adherence was determined by to four different positions of prophylaxis in life. These positions represented different adherence levels. This model can serve as a baseline for intervention development to improve adherence to prophylaxis in haemophilia.

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Appendix 1: Overview of interview questions and modifications

Starting questions Round 1:

How do you experience your haemophilia in life?
Do you have to do anything for your haemophilia in daily life, and if yes, what? Do you integrate the treatment in your daily life and if yes, how?
What is the effect of prophylaxis on your (daily) life?

- Can you describe your feelings about this?
- How would you describe the impact on daily life?
- Can you explain why you have an aversion/no aversion to prophylaxis?
    - If aversion, when did this start?

We know that for some it is quite difficult to follow the treatment and for others it is very easy, how is that for you?

- Can you explain that?
- Can you give an example of a situation?
- Are you experiencing benefits when you stop taking prophylaxis?
- And you also experiencing disadvantages when you do this?
- Do you experience also advantages / disadvantages when you take the prophylaxis at the correct time?

How do you manage prophylaxis during holidays?
What equipment do you use for prophylaxis?

- Does this play a role in following the regimen? If yes, how?
  What are your expectations of prophylaxis?
- Does the prophylaxis fulfil your expectations?
    - (Yes / No) Why?

How do you deal with your prophylaxis for your environment / family / household?
Are there any previous events with haemophilia that still have impact on you or the prophylaxis?
What would you make it easier for you to perform prophylaxis?

Additional questions round 2:

When patients forgot or skip prophylaxis: ask for nuances and details.

- What happened when you're busy?
- When you postpone the treatment, does it happen that you won't take it at all?
- Self-initiated treatment changes; how did they emerge? and why were they continued?
- What are the experiences with the current prescribed prophylactic regimen?
- What skills are developed over time?

- When did you experience stability and how was it maintained in the prophylactic treatment?
  Self-monitoring of the own body
- How do you 'listen' to your own body?
- How do you decide whether you should treat or not?
- What is it, that makes you feel that you can/cannot skip the treatment?
- Do you feel vulnerable when you do not use/do use prophylaxis?

Additional questions round 3:

What supports you to take the prophylaxis?

- What do you experience as benefits of taking prophylaxis?
- Which benefit is most important for you?
- What do you experience as barriers for taking prophylaxis?
- Which barrier is most important for you?

Appendix 2: Schematic display of the code tree (more detailed labels on request)

Round 1 *Description patients' perspectives:*	**Round 2** *Input new material:*	**Round 3** *Topics further explored:*	**Round 4** *Topics verified and deepened:*
Experiences haemophilia	**Perception of haemophilia** • Illness-perception - Adherent - Non-adherent • Self-monitoring • Symptoms - Experiences from past	Acceptance of haemophilia determines the perception of prophylaxis Feeling/ fearing symptoms influences adherence	
Experiences prophylaxis	**Perception of prophylaxis** • Perception of prophylaxis - Adherent - Non-adherent • Performing treatment - Tasks involved to exert prophylaxis - Self-management skills	Self-management skills Two patterns observed; relationship between adequate routine skills, but struggling with complex situations and limited routine skills and difficulties with integration of skills in life	Self-management skills further clarified: - Understanding haemophilia and prophylaxis - Planning and infusing skills
Experiences adherence	**Adherence to prophylaxis** • Types of adherence behaviour and variations • Perception/ position of prophylaxis plays important role in decision-making of adherence behaviour • Self-initiated treatment changes • Risks and symptoms - Intentionally taking risks - Unintentionally taking risks • Costs of treatment • Relationship with health care provider	**Perception of prophylaxis** Different types of adherence behaviour were observed and linked to the perceptions of prophylaxis.	**Adherence is determined by the position of prophylaxis in life:** Factors influencing the perception of prophylaxis: - Acceptance of haemophilia - Feeling and fearing symptoms Factors influencing the exertion of prophylaxis - Understanding haemophilia and prophylaxis - Planning and infusing skills **Resulting in 4 main typologies:** - Prophylaxis integrated in life - Prophylaxis acc to dr' advice, struggling with irregular situations - Prophylaxis too much to handle - Prophylaxis is a confrontation with illness

In round 5 the model was verified and established, no new information adding to the already constructed theory could be identified.

CHAPTER 8:

Coping in adult patients with severe haemophilia

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Abstract

Introduction: An adequate use of coping strategies could help patients to deal with disease-related stress. The study aim was to explore coping behaviour in adult patients with severe haemophilia and its possible determinants.

Methods: Coping was assessed through three basic dimensions (task-oriented, emotion-oriented and avoidance coping), using the short version of the Coping Inventory for Stressful Situations (CISS-21). Patients' scores were compared with Dutch working men (N=374), according to three categories: low use(<P25 of normal), average use (P25-P75) and high use (>P75). Determinants were measured using questionnaires on activities (HAL), participation (IPA), physical functioning (physical component of the D-AIMS2) and socio-psychological health (psychological component of the D-AIMS2).

Results: In total, 86 adults with severe haemophilia (FVIII/ IX<1%) were included. The median age was 38 years (range: 18-68) with 85% affected with haemophilia A and 75% using prophylaxis. Patients with haemophilia used task-oriented coping as frequently as the control group (p=0.13); but used significantly less emotion-oriented coping (57% vs. 25%, p<0.05) and avoidance coping (p<0.05). Emotion-oriented coping showed a strong correlation with socio-psychological health (*r* 0.67) and weak correlations with participation (*r* 0.32) and social interaction (*r* 0.29). Other associations of coping strategies with patient characteristics of health status could not be demonstrated

Conclusion: Overall, patients predominantly used the task-oriented approach to deal with their disease; the use of this strategy was comparable to the control group. Having a poor psychological health, less social interaction and/or less participation in daily life was associated with an increased use of emotion-oriented coping.

Introduction

In daily life, patients with haemophilia are confronted with the consequences of their disease. Especially adult patients with severe haemophilia need to deal with frequent spontaneous and trauma related bleeding [1], potentially resulting in irreversible joint damage [2,3]. Substitution of the missing clotting factor with factor replacement therapy is available since 1965, to prevent bleeds and subsequent consequences. In spite of adequate treatment, many patients with haemophilia are still concerned about the occurrence of a bleed [4,5] and elderly patients have to deal with the consequences of years of sub-optimal treatment [6].

The way patients with haemophilia deal with disease-related stress, largely depends on their coping strategies [7,8]. Coping is defined as the cognitive and behavioural efforts which regulate emotions and tackle problems [9,10]. Many conceptual models tried to describe how individuals cope with stressful events. Most models suggested two fundamental ways of coping: 1) making efforts to control the situation, including problem solving, cognitive restructuring and 2) trying to change the situation (known as: problem-focused/ task-oriented) and trying to manage the negative emotions related with the stressful events (known as: emotion-oriented) [10,11]. Generally, problem-focused coping is considered as the most effective approach in chronic diseases [11]. While, emotion-focused coping could be more effective to deal with acute stressful situations, like being diagnosed with a progressive or terminal illness [10,11]. Avoidance coping is a maladaptive coping strategy characterized by the effort to avoid or denial the illness and mostly seen as a sub- strategy of emotion-oriented coping. Avoidance or denial of the illness could lead to a patient-related delay to proper health care and is a risk factor for psychopathology [12,13]. It is important to define patients with inadequate coping behaviour, to prevent unmanageable health situations and identify individuals who require support.

Inadequate coping can negatively affect health outcomes and eventually diminish quality of life [5,7,14]. Until now, it is unknown which coping strategy patients with haemophilia use and little is known about determinants influencing coping in haemophilia. In addition, there is no standardized care to support adequate coping skills for Dutch patients with haemophilia. Therefore, the aim of this study is to explore coping strategies and its determinants in adult patients with severe haemophilia.

Methods

Secondary analysis of data from a cross sectional study in patients with haemophilia were combined with data from a population of Dutch working men [15]. In 2003-2005, adult patients with severe haemophilia A or B (FVIII/ IX <1%), visiting the clinic for their regular check-up, were invited to complete the questionnaires. The study

was approved by the Medical Ethical Committee and written informed consent was obtained. The original study aim was to validate the Haemophilia Activities List [16,17] and the findings of the coping questionnaire (Coping Inventory for Stressful Situations (CISS-21)) were not included in the analyses. These results were compared to a control group of Dutch working men. This control group has been studied in context of an epidemiological study of work and fatigue among 374 working men in 2002 (mean age 41.0, SD 9.2) [15]. Furthermore, these 374 working men were used as a 'norm' during the development of the CISS-questionnaire.

Measurements

The data collection of patient characteristics comprised: date of birth, diagnosis, treatment modality (prophylaxis or on demand therapy) and history of orthopaedic surgery. The Coping Inventory for Stressful Situations (CISS-21) questionnaire was developed by De ridder et al. [18,19]. The CISS is available in two versions, 21 and 48 items and is frequently used to assess coping in different populations. The CISS 48 items was tested with good psychometric properties (α=0.76-0.88) [20]. However, due to large number of questionnaires administered, the shorter version was chosen. The questionnaire had three subdomains: problem-focused coping (task-oriented, TOC according to CISS-21), emotion-focused coping (emotion-oriented, EOC according to CISS-21) and avoidance coping (AC according to CISS-21). Each item was scored on a five-point Likert scale and scoring ranges varied per strategy: EOC: 8-40, TOC: 6-30 and AC: 7-35. A high score indicates a frequent use of the particular coping strategy.

Questionnaires used to identify health status and associating determinants were: the Haemophilia Activities List (HAL) [16,17], the Impact on Participation and Autonomy questionnaire (IPA) [21,22,23] and the Dutch Arthritis Impact Measurement Scales-2 (D-AIMS2) [24]. The HAL questionnaire was used to assess the self-reported functional abilities in patients with haemophilia (domains: upper extremity, basic lower extremity and complex lower extremity activities) and is widely validated in haemophilia [16,17]. The total score ranged from 100-0, where a high score represents better functional abilities.

Participation was measured using the IPA, distributed over 5 domains: autonomy indoors, family role, autonomy outdoors, social relations and work and educational opportunities [21,22,23]. The internal consistency of the IPA was evaluated with a high reliability in severe haemophilia (α = 0.91) [21]. The scores of different domains were added to yield a total score ranging from 0-120 points, with a higher score representing more restrictions in participation.

D-AIMS2 was originally designed to evaluate physical, psychological and social aspects of health in patients with rheumatoid arthritis [25]. Yet, the use in patients with haemophilia is well established [24,26]. Components of the questionnaire used in the present study are physical function (physical health and pain) and socio-psychological health (psychological health and social interaction). The scoring of each component ranged from 0-10, where a high score represent a greater impact on physical, psychological and social aspects of the illness in daily life.

Data analysis

Patients who did not fully complete the CISS-21 and patients who were unemployed or retired were excluded, due to missing values on the IPA. Frequencies, medians and interquartile ranges (IQR) were calculated for descriptive analyses. To enable a comparison with the control group, the coping scores of Dutch working men [15,19] measured by the original CISS (48 items) were proportionally converted to 21-item CISS scores by multiplication (Table 1). Based on the scores of this control group, three categories were assigned for each coping strategy: low use (below the 25th , percentile P25 of normal), average use (P25-P75) and high use (above the P75). Assuming a normal distribution of the scores, mean, standard deviation (SD) and Z-score were used to calculate the percentiles (P25, P50, and P75) for all three coping strategies according to the equation: mean + (SD*-0.647) for P25, and mean + (SD*0.647) for P75. Coping strategies of patients were compared to the coping strategies in controls by performing the Chi-square goodness-of-fit test, and by comparing 95% confidence intervals (95% CI). Correlations between coping strategies and health status were assessed using Pearson's correlation coefficient for each coping strategy (differences considered significant $p < 0.05$). SPSS® version 20.0 was used for statistical analysis (IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA)).

Table 1. Reference values of coping scores in control group of Dutch working men (N=374).

	Reference *Mean (SD)*	**Low** *Lowest-p25*	**Average** *p25-p75*	**High** *p75-Highest*
Task-oriented coping	22.4 (3.1)	6-20	21-24	25-30
Emotion-oriented coping	18.4 (5.1)	8-15	16-21	22-40
Avoidance coping	20.4 (4.3)	7-18	19-22	23-35

The mean and standard deviation (SD) of the control group were calculated for the CISS-21.

Results

In total, 86 patients with severe haemophilia were analysed, 41 of the original 127 patients were excluded; 22 patients who did not fully complete the CISS-21 and 19 patients who did not work or were retired. Patient characteristics and results from the questionnaires are provided in Table 2. The majority of patients were diagnosed with severe haemophilia A (n=73, 85%). The median age was 38 years (range 18-68). At the time of evaluation the majority (76%) of the population used prophylaxis with a median frequency of three times per week and the remaining 24% used on demand treatment. Twenty-eight patients (28%) had a history of orthopaedic surgery.

Health Status

The self-reported ability to perform activities and functional ability (HAL) showed some restrictions at a median score of 71.6 (range: 100-23.4, optimum score 100). Six patients (7%) experienced no restrictions at all and 15 patients (17%) had poor functional abilities (score ≤ 50). The self-reported restrictions in participation (IPA) were relatively low at a median score was 27.0 (range: 0-67, optimum 0 and maximum 120). The majority (58%) scored in the lower quadrant (score ≤ 30).

The impact of the haemophilia on physical function and measured by the D-AIMS2 was relatively low with a median score of 0.75 (range: 0-5.7, maximum score 10). The median score on pain was high: 3.0 (range: 0-9 out of a maximum of 10 points). Only eight patients (9%) experienced no pain at all, in contrast, 19 patients (22%) reported serious (chronic) pain issues (score ≥ 5.0). All patients experienced some impact of haemophilia on their socio-psychological health as measured by the D-AIMS-2; a median score of 2.5 (range: 0.3-6.8, out of a maximum of 10 points). Only three patients had a high score (5-7 points). Scores on the domain of social interaction varied strongly with a median score of 2.8 and a wide range of 0 to 8.2 (maximum score 10 points), including ten patients with a high score (> 5.0 points).

Table 2. Patient characteristics and health status.

Patient characteristics	**Range**	**N** *(%)*	**Median** *(IQR)*
Age (years)	18-68		38.0 (30.0-46.0)
Haemophilia A		73 (85%)	
Prophylactic treatment		65 (76%)	
History of orthopaedic surgery		28 (33%)	
Health status			
Activities (HAL)*	100-0		71.6 (59.0-91.7)
Participation (IPA§)	0-120		27.0 (10.5-37.5)
*Physical function (D-AIMS2**)*			
- Physical health	0-10		0.8 (0.3-1.9)
- Pain	0-10		3.0 (1.5-4.5)
*Socio-psychological factors (D-AIMS2**)*			
- Psychological health	0-10		2.5 (1.8-3.5)
- Social interaction	0-10		2.8 (2.0-3.7)

Values are ranges, number (proportions) and medians (IQR).
Lower is values give better health care outcomes, except the HAL.
*HAL: Haemophilia Activities List
§ IPA: Impact on participation and autonomy questionnaire.
**D-AIMS2: Dutch Arthritis Impact Measurement Scale 2.

Coping strategies

The use for each coping strategy in patients with severe haemophilia is shown in Table 3 and Figure 1. The use of task oriented coping was similar to the male control group. The median overall score was 22.0 (IQR: 19.0-25.0) in haemophilia, comparing to mean scores of 22.4 (SD 3.1) in controls. Low use was reported by 34% of the patients, 41% average use, and 25% a high use of task oriented coping and this was similar to the control group ($p=0.13$). Patients with severe haemophilia had a median overall score of 15.0 on emotion-oriented coping (IQR: 12.0-18.0). EOC was used significantly less frequent than in controls ($p<0.05$); 57% low and 27% average use in haemophilia versus 25% low and 50% average use in the control group. The median overall score for avoidance coping in patients with haemophilia was 17.0 (IQR: 14.0-22.0). The use of AC was less frequent than in controls; the majority (51%) had a low use, 30% had an average use, and 19% used it frequently ($p<0.05$).

Patient characteristics associated with coping behaviour

For better understanding the process underlying coping behaviour, potential associations with physical function, activities, participation, socio-psychological factors were investigated (Table 4). High use of EOC showed a strong correlation with a poor

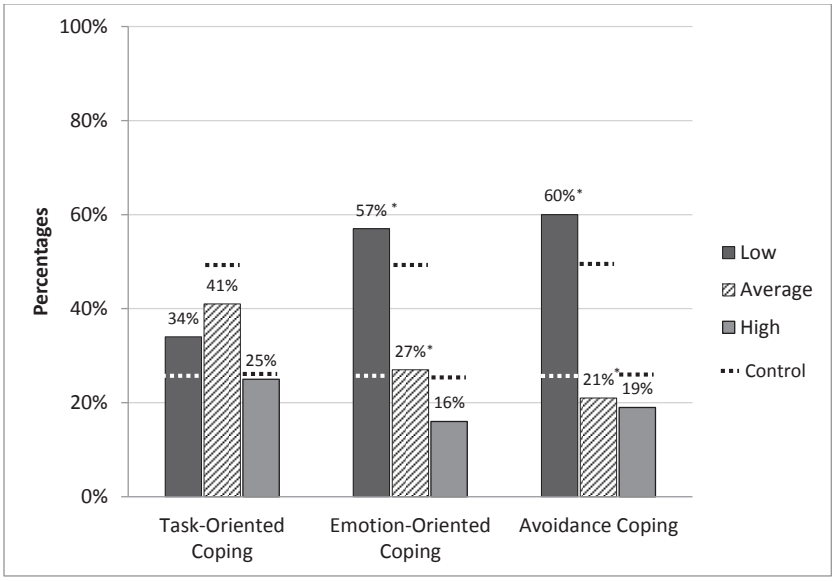
psychological health (*r* 0.67), as well as a good psychological health was correlated with a low use of EOC. Furthermore, a high use of EOC showed weak correlations with low participation (*r* 0.32) and lack of social interaction (*r* 0.29). Other associations of coping strategies with patient characteristics of health status could not be demonstrated (data could be provided on request).

Table 3. Distribution of the use of coping strategies in patients with severe haemophilia, compared to control group.

	TOC *Task oriented*	**EOC** *Emotion oriented*	**AC** *Avoidance*
Low use *N (%)*	29 (34)	49 (57)*	52 (60)*
Average use *N (%)*	35 (41)	23 (27)*	18 (21)*
High use *N (%)*	22 (25)	14 (16)	16 (19)

Values are numbers, percentages * Significantly different from the control group of Dutch working men, P<0.05.
Interpretation: 57% of haemophilia patients reported a low use of EOC and 27% an average use of EOC, compared to 25% low use and 50% average use in the control population.

Figure 1. Distribution of the use of coping strategies in patients with severe haemophilia.



The dotted lines represent the control group (N=374).
*Significant difference compared to the control group of Dutch working men, P<0.05.

Table 4. Correlation of coping strategies with health status

Health status	TOC	EOC	AC
	r	*r*	*r*
Activities (HAL)	-0.06	-0.20	-0.06
Participation (IPA)	-0.05	**0.32***	-0.01
Physical function (D-AIMS2)			
- Physical health	0.05	0.11	0.09
- Pain	0.02	0.16	0.03
Socio-psychological health (D-AIMS2)			
- Psychological health	0.03	**0.67***	0.20
- Social interaction	-0.09	**0.29***	-0.16

r = Pearson's correlation coefficient. * p <0.01

Discussion

To our knowledge, this is the first study assessing the three basic dimensions of coping in adult patients with severe haemophilia. Overall, patients with severe haemophilia most frequently used problem focused coping to deal with issues of their illness. Emotion oriented coping and avoidance coping were used less frequently. Patients with a poor psychological health, less social interaction and less participation in daily life, showed an increased use of emotion-oriented coping.

No formal studies on coping in adults patients with haemophilia were performed and this study will contribute to the knowledge in haemophilia. However, a few limitations of this study should be considered in the interpretation of these results. First, this study was a secondary analysis of data collected earlier in 2003-2005. There were no major treatment changes in the past ten years for adults [27,28], new treatment opportunities (long-acting FVIII and gene therapy) are not available yet [29]. Therefore, we think this information on coping skills is still valid. Second, in the present study the CISS-21 was used, however reference values were only available for the original CISS questionnaire (48 items). Values of the original CISS were recalculated to accommodate the shortened version used in the present study. Third, selecting only working men limited external validity, but allowed comparison between patients and Dutch working men. As expected, the 19 excluded patients who were retired or unemployed and therefore did not complete the domain 'Work and Education' of the IPA questionnaire, were significantly older and differed in health status [30]. Finally, coping is dynamic process which changes over time. The CISS questionnaire was measured at one-time point; no coping patterns over time could be presented.

The limited studies available in haemophilia, have focused on coping in children and their parents [5,31,32] or pain coping [33] or had a small sample size. Therefore, the

present outcomes of the CISS were compared to those obtained in three other chronic conditions requiring life-long treatment; Diabetes Mellitus type 1 (DM-I), Rheumatoid Arthritis (RA) and Multiple Sclerosis (MS) [34]. Patients with DM-I used significant more TOC in contrast with patients affected with RA or MS. In our study patients with haemophilia showed comparable results as patients with DM-I. In the study of the DM-I patients it was hypothesised that the high use of TOC by patients with DM-I was associated with the higher controllability of the disease by self-care; RA and MS are both less controllable and less predictable. Our findings confirm this hypothesis; patients with haemophilia predominantly use TOC and are able to control their disease for a large extent by self-administered treatment too. In chronic diseases with less controllability, patients tend to use more EOC [11]. The level of control over the disease seems to influence coping behaviour [34,35,36].

The fact that patients with haemophilia predominantly used TOC is very positive. TOC is designated as an effective approach in haemophilia, because the disease is controllable with prophylactic replacement therapy to prevent bleeding as well as direct self-treatment in case of a bleed. Therefore, negative emotions and unpleasant feelings and subsequent use of EOC, could be minimized. In clinical practice, these data may be used as a 'benchmark' to identify inadequate or adequate coping behaviour as well as identify patients with increased use of EOC. This underlines the importance of a comprehensive care team in haemophilia and emphasizes the need for a health care worker who has the abilities to support and promote the use adequate coping skills. This health care worker can help identify inadequate coping behaviour and apply strategies to modify this behaviour, even during childhood. Detection of this group, may enable timely initiation of psychosocial support. Furthermore, as psychological problems seem to influence coping, it is important to identify these problems and support the patients in dealing with them.

To improve our understanding of adequate coping and enable its support, we need more information on the processes underlying coping behaviour, preferably by using a qualitative study approach. In addition, more information is needed concerning the relationship between coping, locus of control and illness-acceptance, this may also affect aspects like adherence to treatment. Further research is needed to identify associations with other (psychological) determinants and coping strategies.

Conclusion

The present study showed that patients with severe haemophilia generally used an adequate problem focused approach to deal with their disease. Compared to the control group, patients with severe haemophilia used less emotion-oriented coping or avoidance coping. Having a poor psychological health, less social interaction and/or less participation in daily life were associated with a high use of emotion-oriented coping. A comprehensive care team in haemophilia can identify patients with inadequate coping behaviour and support them.

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GENERAL DISCUSSION

Promoting self-management and adherence during prophylaxis: evidence based recommendations for haemophilia professionals

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Abstract

Introduction: Throughout life, a patient with severe haemophilia is confronted with many treatment-related challenges. Insight into self-management and non-adherence could improve the quality of care for these patients. The aim of this study was to provide an overview of the current evidence on self-management and adherence to prophylaxis in haemophilia.

Method: Based on series of studies and published literature, aspects of treatment were explored: learning and performing self-infusion, achieving self-management skills in adolescence, adherence issues and coping with haemophilia. Evidence based and age-group specific recommendations for haemophilia professionals were formulated.

Results: Nearly all severe haemophilia patients and parents were able to perform self-infusion and the quality level of infusion skills was acceptable. Learning self-infusion was generally initiated before the onset of puberty and full self-management was obtained 10 years later. Adherence was defined using a Delphi consensus procedure and was determined by skipping, dosing and timing of infusions. Adherence levels varied according to age, with highest levels in children (1-12 years) and the lowest among 25-40 years. Adherence to prophylaxis was acceptable (43%), yet 57% of the population struggled with prophylaxis. Qualitative research showed that the position of prophylaxis in life is the main driver of adherence. This position is influenced by acceptance and self-management skills. Regarding coping with haemophilia, the majority of patients used a problem-focused approach.

Conclusion: Self-management and adherence to prophylaxis vary during the life span. Acceptance of the disease and self-management skills were important aspects that may require tailored professional support.

Introduction

Haemophilia is an X-linked bleeding disorder, characterized by a deficiency or absence of clotting factor eight (FVIII, haemophilia A) or factor nine (FIX, haemophilia B). The severity of haemophilia defined according to the level of clotting factor present; 0% as severe haemophilia, 1-5% as moderate haemophilia and 6-40% as mild haemophilia [1, 2]. Especially patients with severe haemophilia are at risk for spontaneous bleeds in the joints or soft tissues. Repeated joint bleeds eventually result in haemophilic arthropathy [3]. For 45 years, patients with severe and some with moderate haemophilia have been treated with prophylactic replacement therapy (prophylaxis) with the aim to prevent bleeding by maintaining minimum FVIII/IX levels. Patients intravenously infuse clotting factor concentrate FVIII/FIX approximately three times weekly or every other day [4, 5]. This treatment has greatly improved the life of a patient with haemophilia [6, 7], yet has also created new challenges [8]. Three aspects of this prophylactic treatment are very demanding: 1) the fact that it requires self-infusion [9] 2) the short half-life of approximately 12 hours requiring frequent infusions to maintain though levels needed for bleed prevention [10] and 3) the fact that prophylaxis is continued life-long [11].

Throughout life, patients have to deal with different treatment related challenges, which vary according to age. In the Netherlands, prophylaxis is initiated after the first joint bleed. This is mostly around the age of 1.7 years old [12]. The haemophilia nurse teaches the parent(s) to infuse their child, which is a demanding and complex task. Sometimes peripheral injections of prophylaxis fail, especially in children before age of 3 years, and a central venous access device (CVAD) is required [12]. Accessing a CVAD requires learning of a second infusion technique. In the Netherlands, parents follow a course to learn the infusion technique, theoretical background of child's illness, symptoms and treatment [13]. In other European countries, there is no formal course: individualized education is given. The haemophilia nurse has a guiding role in this learning process.

When the child becomes an adolescent, he will go through the 'normal' physiological, cognitive and psycho-social developments. In this period patients need to learn to perform self-infusion independently and learn subsequent complex self-management skills, including bleeding management, stock management and communication with the health care providers [14]. During adolescence and young adulthood, the desire to be like others often leads to non-adherence. This increases the bleeding risk and the risk for arthropathy [15-18].

Adherence to prophylaxis is a life-long challenge. One bleed can already lead to irreversible damage in a joint, soft tissue or the central nervous system. Recent studies showed that non-adherence or stopping of prophylaxis is associated with a worse physical status [19], more chronic pain [20] and more orthopaedic surgery [21]. When bleeding

does occur, direct adequate treatment is of great importance [22] to avoid damage, pain and prolonged treatment. Patients have to deal with these haemophilia-related consequences, and therefore adequate coping skills are of great importance.

Comprehensive care [23], with different disciplines supporting the haemophilia patient throughout life, has further revolutionized haemophilia care [24, 25]. One of these disciplines is the haemophilia nurse: highly skilled nurses provide specialized care adapted to the need of the haemophilia patient [26]. During different European surveys it was noticed that there was a great of variety of haemophilia care within countries, centres and even within professionals [26-28]. Most nursing activities in haemophilia are experience based, rather than evidence based. Evidence based practice is defined as: 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research' [29]. In the absence of evidence and guidelines, haemophilia professionals are struggling to reach, support and educate patients about self-management and adherence issues. Recently, we conducted a series of studies on self-management and adherence in haemophilia. Based on our findings and published evidence, recommendations were formulated on how haemophilia professionals, especially haemophilia nurses can deal with (age-related) challenges in haemophilia. These recommendations include topics on learning self-infusion, self-management, adherence and coping. In Figure 1, a schematic overview is provided on the challenges in each phase of life, including evidence based recommendations for the health care provider. In this paper, these recommendations will be described per life phase (child, adolescent and lifelong), followed by conclusions and suggestions for further research.

The child with haemophilia

Learning to perform prophylaxis

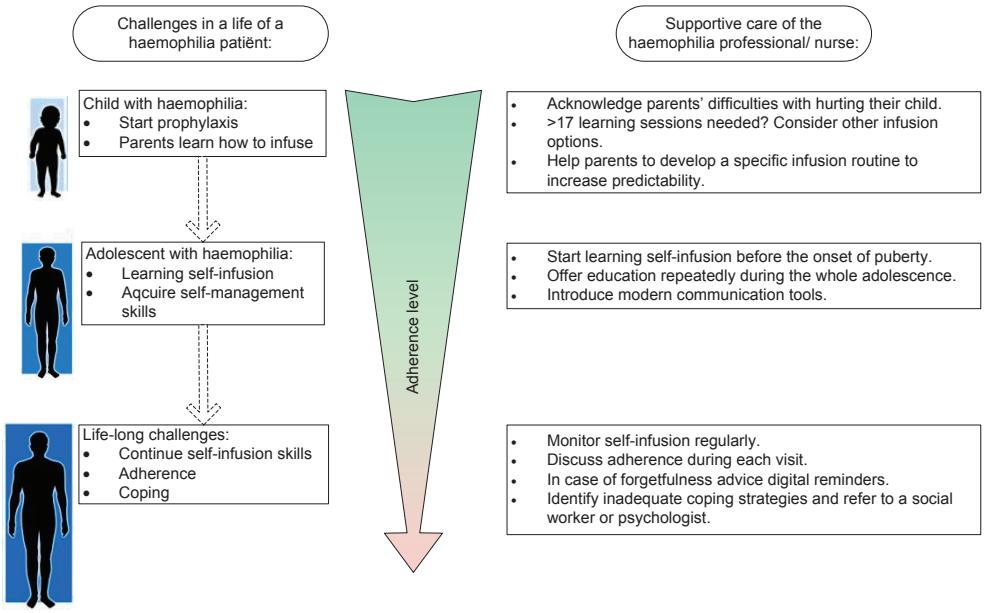
Our study showed that almost all parents (99%) of a child with haemophilia learned how to perform infusion of prophylaxis [30]. The learning process started mostly around child's age of 2. Parents took an average of 12 sessions to learn peripheral infusion or to learn how to access a central venous access device (CVAD), with 75% succeeding within 17 sessions [30]. This number could be used as a 'benchmark. When the learning process requires more sessions, other infusions options (e.g. CVAD or home care services) should be considered. Parents who learned to infuse their child needed significant more time to learn the technique than patients who infused themselves (12 vs. 5 visits). This may be explained by the fact that for parents the diagnosis and treatment of haemophilia is relatively new and that they have to overcome the physiological burden of 'hurting' their child [31]. Qualitative research revealed that a supportive environment and developing a specific ritual was crucial to reduce the fear and anxiety of both parents and their child

[31]. Creating a supportive environment helped the parent and child feel comfortable, for example by a reassuring nurse who respected their insecerity. The development of a specific ritual, e.g. sitting on the same place, counting to three, helped both the parent and child to experience control over the situation. In addition, this 'ritual' increased the predictability for the child, which led to a reduced anxiety [31]. In contrast, factors such as the presence of an inhibitor, use of a CVAD or lack of experience with haemophilia could increase stress for parents and their child [32, 33]. These factors must be taken in account during the instruction process.

Recommendations for clinical practice

- Acknowledge parents' difficulties with hurting their child.
- When parents need longer than 17 sessions to learn, consider other infusion options (e.g. CVAD, home care services).
- Help parents to develop a specific infusion routine to increase predictability.

Figure 1: Overview of challenges in the life of a haemophilia patient.



Including suggestions for the haemophilia professional.

The adolescent with haemophilia

Achieving self-management

Adolescents experience changes of the maturing body, establishing identity, growing independence and intimacy [34]. On top of this youngsters with haemophilia are confronted with the need to take responsibility for their disease and treatment. Adolescents often experiment with reducing treatment, which increases the bleeding risk [16, 18]. Learning self-infusion was usually initiated between 12 and 13 years of age, with the aim to start before the onset of puberty [30, 35]. Our study showed that although adolescents needed less time to learn self-infusion, they needed on average 10 years to become independent in their treatment and self-management skills [36]. This process developed simultaneously with the generally accepted phases of adolescence (early, middle and late [37, 38]). In early adolescence (10-12.5 years) patients learned self-infusion, yet it took until middle adolescence (12.5-17.5 years) to infuse independently. In late adolescence (17.5-25 years) patients learned the more complex self-management skills, such as communication with the physician and diagnosing bleeds, and making subsequent dosing decisions. A similar process was observed in an UK qualitative study: self-management skills were developed over time, mostly through experience [14]. Skills could be improved by repeatedly offering education, preferably during middle and late adolescence. Kyngas et al. showed that adolescents preferred continuous support in accordance with the needs in different adolescence phases [39]. Recently, a digital self-management program for adolescents with haemophilia was developed [40-42]. Based on adolescents' opinion and needs [41] this program led to a successful improvement of disease specific knowledge and self-efficacy [42]. In patients with juvenile arthritis [43] and diabetes mellitus [44, 45], such programs for adolescents showed promising results on disease-specific outcomes.

Recommendations for clinical practice

- Start learning self-infusion before the onset of puberty.
- Offer education continuously during the adolescence period.
- Consider using modern communication tools, such as digital training, and social media.

Life-long challenges

Evaluation of self-infusion skills

After the (self-) infusion course patients and parents are qualified to perform the infusion at home. We assessed the quality of self-infusion skills five years after qualification [46]. Most patients and parents still had adequate infusion skills, although some lacking due to routine was observed. Washing hands before administration, and completing the

infusion dairy were forgotten or skipped in 50% of cases. Checking the product name, dose, or date of expiry before the administration was not done actively either, although most patients check the whole batch after receiving at it. We recommend to regularly (e.g. once per year or every two years) check the patients' self-infusion skills, and continuously remind patients to wash their hands and complete the infusion dairy [47].

Recommendations for clinical practice

- Monitor self-infusion regularly and remind patients to wash their hands and complete the infusion dairy.

Adherence

In chronic illnesses (HIV, COPD, diabetes, heart failure), approximately 50% of the patients adhere to their prescribed medication regimen [48]. In haemophilia, bleeding usually does not occur immediately after missing an infusion; this makes it more challenging to adhere to prophylaxis [49]. Yet, what do experts and patients consider adherent or non-adherent? A definition of adherence to prophylaxis did not exist. We conducted a Delphi consensus procedure, which showed that missing of infusions, changes in dosing and timing were considered the most important aspects of non-adherence [50]. The experts considered patients adherent when they missed <15% of prophylactic infusions and/ or deviated <10% in dosage (IU) and/ or deviated <30% in timing (hour). Sub-optimal adherence was defined as missing 15 to 25% of prophylactic infusions or <25% deviation in dose (IU) or >30% deviation in timing. Non-adherence was defined as missing >25% prophylactic infusions or >25% deviation in dose (IU), or a combination of both. This definition was in accordance with other definitions used in clinical trials regarding the proportion of missed infusions (range 15-33% [50]), and changes in dose (max 120 IU deviation [50]), yet timing of infusions was never considered in these trials [51-54]. The definition from the expert panel was used to analyse data from our multicentre study assessing adherence [55]. Adherence varied across age groups: parents infusing their child showed the highest adherence; while patients between 25 and 40 years old showed the lowest adherence. In 73 parents studied, 66% were adherent, 29% were sub optimally adherent and 5% were non adherent. In 168 self-infusing patients, adherence was significantly lower: 43% adherent, 37% sub-optimally adherent and 20% non-adherent. These numbers are comparable to other chronic diseases [49]. Overall, there was a large group of the patients who were adherent to prophylaxis, yet 57% of the population tampered with prophylaxis [55]. Two other recent adherence studies in haemophilia used less stringent criteria (adherent if at least 67 and 75% of the infusions taken) and reported comparable adherence rates at observed that 39 and 53% [52, 56].

Yet, if so many patients do not take prophylaxis as prescribed, what are the consequences? Spanish non adherent patients (6-20 years) showed more joint bleeds, more target joints and a lower quality of life [52]. Non adherence was associated with increased chronic pain and missed days from school in 80 American adolescents [20]. In adults, the short-term health outcomes of non-adherence were less obvious; it remained unclear if non-adherence is directly associated to more self-reported bleeding [55, 57]. Other studies reported that non-adherence had a negative effect on long-term outcomes, including physical functioning [19, 21, 58], joint score on MRI [21] or more orthopaedic surgeries [21]. We observed no association of adherence levels with bleeding [55]. We hypothesize that non-adherent patients experience less bleeding due to a milder bleeding pattern (confounding by indication) or have a different perception of bleeding [59].

Why are patients non-adherent to prophylaxis? Our literature review on determinants of non-adherence showed that a low adherence was associated with a higher age, absence of symptoms and lack of belief in the necessity of treatment [18]. In a subsequent qualitative study, a consistent model regarding the underlying process of non-adherence from the patients' perspective was established [59]. We identified that adherence is determined by the position of prophylaxis in life (Figure 2). The position is influenced by two main aspects: self-management skills (ability to exert prophylaxis) and acceptance of haemophilia (perception of haemophilia). Patients with self-management issues showed non-adherence in forms as overtreatment and inadequate treatment of bleeds. Patients struggling with acceptance of haemophilia and prophylaxis often stopped or decreased the prophylactic treatment and were at risk of serious bleeding and synovitis, eventually resulting in arthropathy. A standard assessment of adherence, including discussion of difficult moments, assessment of the infusion diary and providing positive feedback, could help patient to persist to this life-long treatment [60]. The use of a digital reminder could support patients suffering from forgetfulness; this approach proved successful in patients with diabetes [61].

Recommendations for clinical practice

- Discuss adherence during each visit: discuss difficult moments, evaluate the infusion dairy and give positive feedback [60].
- In case of forgetfulness advise digital reminders [61].

Coping

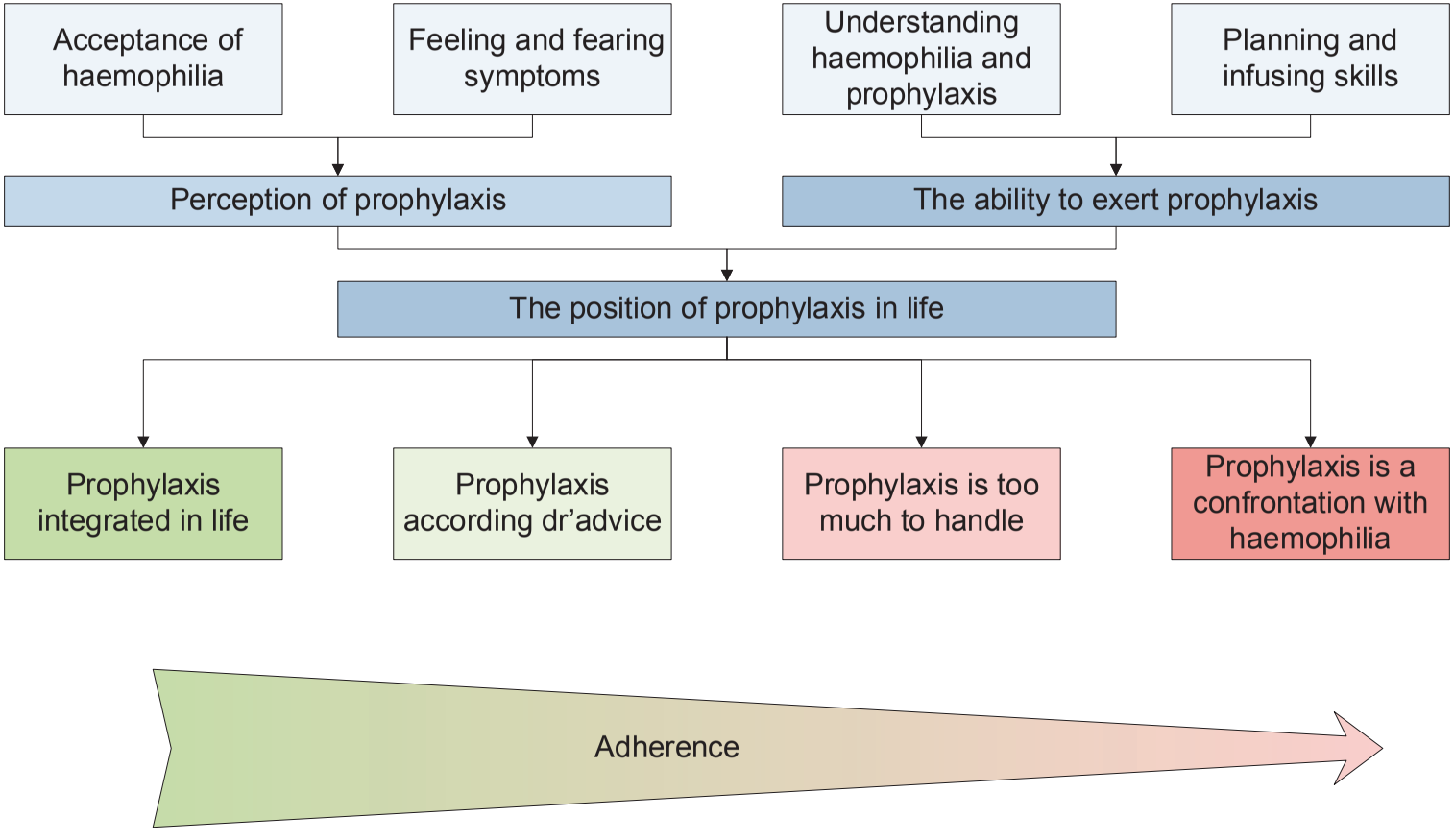
Patients with haemophilia have to cope with the fact that they are affected with a chronic illness. They are concerned about the occurrence of a bleed and many adult patients have to deal with the consequences of joint-damage. The way patients with haemophilia deal with disease-related stress depends on their coping strategies [62]. In our study adults frequently used the problem focussed (or task-oriented) coping approach rather

than emotion-oriented or avoidance coping [63]. This problem-focussed strategy could be linked to high level of control over the disease because of the ability to perform self-treatment [64]. Patients who preferred the emotion-oriented coping strategy showed a lower socio-psychological health and reduced participation in daily life [63]. These patients could be referred to a social worker or psychologist (preferably dedicated to haemophilia) for counselling [65].

Recommendations for clinical practice

- Identify inadequate coping strategies and if necessary refer patients to a social worker or psychologist.

Figure 2: Schematic model of adherence to prophylaxis in haemophilia [59].



Adherence is decreasing from left to right.

Conclusion and implications for future research

Throughout life patients with haemophilia are facing many disease related challenges. This paper provides an overview of practical recommendations for haemophilia professionals. In childhood, almost all parents are able to infuse their child. Acknowledging the fact that is difficult to hurt your own child and working towards a routine performance could help the parents to successfully acquire and perform the infusion technique. For patients practicing self-infusion, education in self-management skills should be offered repeatedly to promote development and maintenance of more advanced skills. Adherence is generally high, except for the period from adolescence to age 40 years. Qualitative research revealed that non-adherence was determined by the position of prophylaxis in life, with acceptance and self-management issues as the main drivers of the position. Standard assessment of adherence behaviour, self-infusion skills and coping strategies provide insight in behaviour and helps to open the discussion and facilitate provision of education and support to patients. The recommendations provided can be directly applied in clinical practice, resulting in evidence based support for the patient with haemophilia.

Measurement of adherence

Some comments for future studies should be made. Starting with the fact that measuring adherence is extremely difficult. There is no gold standard and many different measurements are being used in adherence studies. The VERITAS-Pro [66, 67] is a recently developed validated instrument aimed to assess adherence to prophylaxis. Although this questionnaire was validated, no priorities in different aspects of adherence were made. The sub-domains Time, Dose, Plan, Remember, Skip and Communicate are weighted equally in the calculation of a total score. Therefore, it is difficult to interpret the actual adherence behaviour from the total score. Furthermore, a recall-period of three months is used, which is much longer than the period of 1 or 2 weeks generally considered as optimum for questionnaires [68]. To facilitate interpretation of results in research and identify problematic aspects of adherence in clinical care, we propose to present the results of the VERITAS-Pro in domain scores and study the effects of a shorter recall period. Prioritizing sub-domains, proposing cut-offs per domain and a shorter recall period would be necessary to fully align this questionnaire with our results and the definition generated by the Delphi procedure. Unfortunately, more objective assessment of medication behaviour such as medication event monitoring systems (MEMS) are unavailable for intravenous medication [60].

Association of adherence with clinical outcome

In our study, joint bleeding was not associated with adherence [55]. This may be expected as absence of symptoms [18] and feeling and fearing symptoms [59] have

been identified as important barriers for adherence to prophylaxis. Therefore, patients experiencing bleeds are motivated to adhere to prophylaxis while patients who experience less or no bleeding are not. Therefore, one can question the relevance of self-reported (joint) bleeds as outcome-measure for adherence [55]. For future studies, the use of objective outcome measures, like the Haemophilia Joint Health Score (HJHS [69]), X-ray or MRI data ([70]), may give a more reliable impression of the effect of long-term non-adherence. Furthermore, adherence may vary over time, and this may show a stronger association with outcome. Following the recent developments in assessment of adherence, it is expected that future studies will include this parameter when studying the effects of treatment.

Improving adherence and self-management

There are currently no formal interventions focussed on promoting adherence to prophylaxis in haemophilia. From previous studies it is known that it is difficult to change behaviour, especially concerning adherence [48]. Therefore, the authors suggest that addressing the source of the problem should be the first step. The main reasons for non-adherence are acceptance and/or self-management problems. These may be measured by the Health Education Impact Questionnaire (HeiQ [71]) for self-management and the Illness Cognition Questionnaire (ICQ [72]) for assessment of acceptance. Having established this together with the patient, the next step is to initiate an intervention tailored to the specific needs of the patient. Patients struggling with self-management could benefit from a self-management program, focussed on integrating prophylaxis in life, diagnosing bleeds and sharing experiences with peers. These strategies were recently successfully used in patients with a rheumatic disease [43] and in other chronic diseases [73]. In our qualitative study, it was noticed that patients struggling with acceptance are well aware of the fact that they needed to change this, because they experienced burden in daily life but did not know how to deal with this [59]. Although it might be difficult to convince patients to participate, patients definitely benefit from guidance on how to cope with haemophilia. Acceptance and commitment therapy has proven to be effective in other chronic illnesses (HIV, DM, chronic pain, psychological disorders) and could serve as a starting point for acceptance interventions [74, 75]. A program to improve adherence, including testing in an RCT, is currently being systematically developed [76].

Next steps in haemophilia nursing care

An overall recommendation for haemophilia (nursing) professionals is to continue standardizing care, as many health care activities are based on experience only. Due to the rarity of haemophilia, there is a risk for lack of expertise. In order to be able to offer all haemophilia patients the same high quality care, European or (inter)national guidelines should be developed. Standardisation of haemophilia care leads to a structured approach of the consultation. Currently, there is no formal education training for haemophilia

nurses and in general most nurses are dependent on experienced colleagues [26]. Development of a formal haemophilia nursing curriculum and (European) principles of haemophilia nursing care [23] could help to establish and strengthen the role of the haemophilia nurse. The recommendations provided in this paper can enhance evidence based haemophilia care and should be incorporated in training of these professionals.

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Summary

To avoid bleeds in joints, central nervous system and muscles, patients with haemophilia require a lifelong treatment of clotting factor concentrate. Three aspects of this prophylactic treatment are challenging: 1) the fact that the treatment requires self-infusion and 2) the short half-life of approximately 12 hours requiring frequent infusions to prevent spontaneous bleeding and 3) the fact that prophylaxis is continued life-long. Self-management skills and upholding high adherence levels are essential to perform and maintain this demanding treatment throughout life. In this thesis self-management skills and adherence in haemophilia are studied. The first part provides insight in how to learn and practice these self-management skills needed for prophylaxis. The second part assesses the extent and underlying reason for of non-adherence to prophylaxis.

Part I: How to practice prophylaxis?

The first part starts with a retrospective assessment of the learning process of self-infusion (**Chapter 1**). This paper was aimed to provide information to patients/ parents about the time-investment and burden to acquire the technique of self-infusion. Data from 154 patient files (Amsterdam and Utrecht) were analysed, which resulted in 168 learning processes. The great majority had severe haemophilia and started prophylaxis at a median age of 2.7 years. Almost all patients (99%) successfully learned intravenous infusion, this included 9 patients who needed a 'break' during the process and succeeded later. In total, parents or patients needed a median of 8 visits in a median of 7 weeks to learn self-infusion of prophylaxis. Parents started with CVAD infusion at a median child's age of 1.9 years and succeeded within 12 visits. Parents who performed IV infusion started at a median child's age of 4 years and needed 11 visits. Young adolescents started learning to infuse themselves at the age of 12.9 years and needed just 5 visits. We conclude from this study that nearly all parents and patients were able to learn and perform self-infusion within a reasonable time period (7 weeks).

In **Chapter 2** the aim was to quantify adherence to the Dutch (self) infusion guideline as well as the time to administer prophylaxis. This paper comprised an observational assessment of the procedure of self-infusion and the time needed was recorded with a stopwatch. In total, 161 infusion procedures in 132 patients or parents were evaluated in the three Dutch centres. Patients and parents had a mean experience with self-infusion of 4.9 years. The great majority of patients and parents performed the infusion correctly, 96% succeeded within the first attempt. Other essential infusion activities were performed according to the guideline, yet washing hands and completion of the infusion dairy were in 50% of the cases forgotten. The total procedure took a little time: a median of 6.7 minutes for IV infusion or 11.1 minutes for CVAD infusion. A standard follow up every one or two years to check correct performance of self-infusion may improve these aspects of home treatment.

Chapter 3 describes the process of achievement of self-management skills in adolescents with haemophilia. Adolescents between the age of 10 to 25 years were interviewed (10 questions) about treatment responsibility and self-management. Achievement of self-management was defined as: being independent in self-infusion, bleeding management, stock monitoring, and communication with the haemophilia physician. Overall, 155 interviews were performed in 100 patients (median age of 14.4 years). Most patients started to learn self-infusion at a median age of 12.3 years, resulting in achievement of self-management after 9.6 years (at the median age of 22.6 years). This growing process proceeded simultaneously with the three phases of adolescence. In early adolescence, patients acquired the technique of self-infusion and in the middle adolescence, patients were able to independent perform self-infusion (17.2 years). In late adolescence, patients developed the more complex skills, like bleeding management and communication with the haemophilia physician (21.5 years). In conclusion, the first steps with regard to self-management were taken in the early adolescence, complete self-management was achieved in the late adolescence.

Part II: How to adhere to prophylaxis?

The second part in this thesis describes the extent and underlying reason for non-adherence. In **Chapter 4** a definition of adherence to prophylaxis was developed. Previous general studies defined adherence as administration of 80% of the prescribed medication. Haemophilia specific definitions are lacking, therefore a systematic consensus procedure was performed to develop a definition. Twenty three Dutch haemophilia professionals and patients participated in three Delphi rounds. Consensus was achieved when there was ≥80% agreement on the definition. The three most important aspects of (non-) adherence to prophylaxis were: 1) missed infusions 2) dose changes and 3) deviations from the prescribed time. This led to three adherence categories: *adherent*: missing <15% infusions, <10% dose changes (IU) and <30% deviation from prescribed time; *sub-optimally adherent*: missing 15-25% infusions, <25% dose changes or >30% deviation in time; *non-adherent*: missing > 25% infusions or >25% dose changes.

The definition developed in chapter 4 was used to assess adherence to prophylaxis in haemophilia (**Chapter 5**). Pre-specified semi-structured interviews about adherence to prophylaxis over the past two weeks were administered to patients or parents of children with haemophilia. Patients were classified as adherent, sub-optimally adherent or non-adherent based on missing, timing, and dose of infusions (Ch 4). Associations of adherence and annual bleeding events, mean CFC, age (parents vs patients) were calculated. In total, 168 patients with haemophilia using prophylaxis and 73 parents of children with haemophilia were included. Parents were more adherent (66%) than patients (43%). Sub-optimal adherence occurred in 29% of parents and 37% of patients, characterized by changes in timing of infusion. Non-adherence occurred less frequently:

5% of parents and 20% of patients was non-adherent. Adherence levels were associated with CFC, but not with joint bleeding.

Chapter 6 and Chapter 7 both address the underlying reason for non-adherence. **Chapter 6** describes a systematic review of the literature on the determinants of adherence to prophylaxis in haemophilia. After full paper evaluation of 44 articles, five relevant articles were critically appraised. Two of the five studies were considered as the best evidence available. Motivators for a high adherence were: experience of symptoms, a positive belief of necessity of treatment and a good relationship with the health care provider. Important barriers were defined as: infrequent or absence of symptoms and increasing age.
In **Chapter 7**, the underlying reasons of non-adherence are further unravelled in a qualitative study. To develop a grounded theory, 21 individual in-depth interviews were performed to understand experiences, perceptions and beliefs concerning adherence to prophylaxis. Interviews were transcribed, coded (in three steps) and analysed in an iterative process, leading to the underlying reasons of non-adherence.
Adherence was determined by the position of prophylaxis in life. This position in life was determined by the perception of prophylaxis and the ability to exert prophylaxis. Patients' perception was influenced by two main factors: acceptance of haemophilia and feeling/ fearing symptoms. The ability to exert prophylaxis was influenced by to other main factors: understanding haemophilia and prophylaxis and planning/ infusion skills. The combination of different perceptions and skills led to four main positions of prophylaxis in life: 1) prophylaxis integrated in life, 2) prophylaxis according doctors' advice, struggling with irregular situations, 3) prophylaxis is too much to handle, 4) prophylaxis is a confrontation with illness. The adherence level gradually decreased from position 1 to 4.

In **Chapter 8** the coping skills of patients with severe haemophilia were described. The coping skills were assessed with the Coping Inventory for Stressful Situations (CISS-21) and classified in three basic coping strategies (task-oriented, emotion-oriented and avoidance coping). Determinants of coping were measured using three questionnaires: activities (HAL), participation (IPA), physical functioning and socio-psychological health (D-AIMS2). In total, 86 adults with severe haemophilia were included and compared with coping skills of 374 healthy Dutch men. Patients with haemophilia used task-oriented coping in a comparable amount as the control group, yet used significantly less emotion-oriented coping (57% vs. 25%, $p<0.05$) and avoidance coping ($p<0.05$). In haemophilia, emotion-oriented coping showed a strong correlation with socio-psychological health (r 0.67) and weak correlations with participation (r 0.32) and social interaction (r 0.29). Other associations of coping strategies with patient characteristics

of health status could not be demonstrated. In conclusion, patients with haemophilia predominantly used the task-oriented approach to deal with their disease.

The thesis ends with a **general discussion** and practical recommendations for the haemophilia professional on self-management and adherence to prophylaxis in haemophilia. Based on studies described in this thesis and other published literature, evidence based recommendations for haemophilia professionals were formulated.
To conclude, self-management and adherence to prophylaxis vary during the life span. Acceptance of the disease and high self-management skills were the important aspects that may require tailored professional support.

Samenvatting

Om bloedingen in gewrichten, centraal zenuwstelsel en spieren te voorkomen, behandelen patiënten met hemofilie zichzelf levenslang met stollingsfactor concentraat. Drie aspecten van deze behandeling maken het moeilijk voor de patiënt: 1) het feit dat de patiënt de behandeling zelf intraveneus moet toedienen, 2) dat deze profylaxe zo'n drie keer per week toegediend moet worden om voldoende beschermd te blijven en 3) dat profylaxe het hele leven lang volgehouden moet worden. Therapietrouw en zelfmanagement vaardigheden zijn cruciaal om deze profylactische behandeling uit te voeren. In dit proefschrift worden de zelfmanagement vaardigheden en therapietrouw bij hemofilie onderzocht. In het eerste deel wordt inzicht gegeven in het aanleren en volhouden van de zelfmanagement vaardigheden. Daarnaast wordt in het tweede deel de omvang van therapie-ontrouw onderzocht en onderliggende reden geëxploreerd.

Deel I: Handelen omtrent profylaxe

Het eerste deel start met een retrospectieve evaluatie van het leerproces om zelf-infusie te leren (**Hoofdstuk 1**). Deze studie had als doel om informatie te geven aan patiënten/ ouders over de belasting en tijdsinvestering die nodig is om zelf-infusie te leren. Data uit 154 patiëntendossiers (Amsterdam en Utrecht) werden geanalyseerd, waarin 168 leerprocessen werden beschreven. De grote meerderheid van de patiënten had ernstige hemofilie en startte met profylaxe op een mediane leeftijd van 2.7 jaar. Vrijwel alle patiënten/ ouders (99%) leerde zichzelf of hun kind profylaxe intraveneus toe te dienen. Er waren 9 patiënten tijdelijk gestopt, maar zijn uiteindelijk toch later 'geslaagd'. In totaal hadden patiënten en ouders acht bezoeken nodig in zeven weken om de techniek eigen te maken. Ouders die hun kind via een port-a-cath behandelden begonnen hier mee op een mediane leeftijd van het kind van 1.9 jaar en deze ouders hadden 12 bezoeken nodig. Ouders die de perifere techniek aanleerden startte hiermee als het kind 4 jaar oud was en hadden ook ongeveer 11 bezoeken nodig. Jongeren starten met leren rond 12.9 jaar en hadden 'maar' vijf bezoeken nodig om zich zelf te leren prikken. We kunnen dus concluderen dat vrijwel alle ouders en patiënten in staat waren om (zelf-) infusie te leren in een redelijke tijdsperiode.

De studie in **Hoofdstuk 2** had tot doel om te observeren of patiënten de zelf-infusie volgens de Nederlandse richtlijn uitvoerden en de tijd te meten die nodig was voor de zelf-infusie. In totaal, werden er 132 patiënten geobserveerd tijdens 161 toedieningen. Patiënten en ouders hadden gemiddeld 4.9 jaar ervaring met het toedienen van profylaxe. De grote meerderheid voerde essentiële activiteiten van de procedure correct uit: 96% slaagde in één prikpoging. Echter, het wassen van de handen en het logboek invullen werd door 50% vergeten of niet uitgevoerd. De totale handeling vraagt weinig tijd: een mediaan van 6.7 minuten voor perifere toediening en 11.1 minuten voor een toediening via de port-a-cath. Op basis van deze resultaten werd geconcludeerd dat een

standaard controle van de handeling elk jaar of elke twee jaar, zou de kwaliteit van de thuisbehandeling kunnen verhogen.

Hoofdstuk 3 beschrijft het proces aanleren van zelfmanagement vaardigheden in jongeren met hemofilie. Jongeren tussen de 10-25 jaar werden geïnterviewd (10 vragen) over de verantwoordelijkheid met betrekking tot de behandeling en zelfmanagement. Zelfstandig uitoefenen van de zelfmanagement vaardigheden was gedefinieerd als: zelfstandig uitvoeren van zelf-infusie, omgaan met bloedingen, voorraadbeheer en communicatie met de hemofilie arts. In totaal werden er 155 interviews uitgevoerd onder 100 patiënten (mediane leeftijd 14.4 jaar). De meeste patiënten begonnen met het leren van zelf-infusie op 12.3 jaar, echter uiteindelijk duurde het 9.6 jaar om tot volledig zelfstandigheid van de zelfmanagement vaardigheden te komen. Dit groeiproces liep gelijk met de drie fasen van adolescentie. In vroege adolescentie leerden patiënten de techniek van zelf-infusie en in de midden adolescentie waren patiënten in staat om dit zelfstandig uit te voeren (17.2 jaar). In de late adolescentie ontwikkelden patiënten de meer complexe vaardigheden, zoals het leren omgaan met bloedingen en communicatie met de hemofilie arts (21.5 jaar). Concluderend werd vastgesteld dat de eerste stappen met betrekking tot zelfmanagement al worden genomen in de vroege adolescentie, terwijl volledige zelfmanagement word bereikt in de late adolescentie.

Deel II: Volhouden van profylaxe

Het tweede deel van dit proefschrift beschrijft de omvang en onderliggende reden van therapieontrouw. Een definitie voor therapietrouw bij profylaxe is ontwikkeld in **Hoofdstuk 4**. Eerdere algemene studies definiëren therapietrouw als toediening van 80% van de voorgeschreven medicatie. Hemofilie specifieke definities ontbreken, daarom is er definitie ontwikkeld via een systematische consensus procedure. Drieëntwintig Nederlandse hemofilie professionals en patiënten namen deel aan een Delphi procedure (totaal drie rondes). Consensus was bereikt bij ≥80% overeenstemming onder de experts. De drie meest belangrijkste aspecten van therapie(on)trouw waren: 1) gemiste infusies, 2) dosis wijzigingen, en 3) schuiven met het voorgeschreven tijdstip van toediening. Dit heeft geleid tot drie categorieën van therapietrouw: *therapietrouw:* missen van <15% van de infusies, <10% wijzigen van de dosis en <30% afwijken van het voorgeschreven tijdstip; *suboptimale therapietrouw*: missen van 15-25% van de infusies, <25% wijzigen van de dosis of >30% afwijken in tijdstip; *therapieontrouw*: missen van > 25% van de infusies of >25% wijzigen van de dosis.

De definitie die ontwikkeld is in hoofdstuk 4, werd in **Hoofdstuk 5** toegepast om de omvang van therapieontrouw bij profylaxe te bestuderen. Semi- gestructureerde interviews over het therapietrouw-gedrag werden afgenomen bij patiënten of ouders van kinderen met hemofilie. Patiënten werden vervolgens ingedeeld volgens de classificatie zoals beschreven in hoofdstuk 4. Er werd onderzocht of therapietrouw geassocieerd was

met het aantal bloedingen (per jaar), stollingsfactor verbruik, leeftijd. In totaal werden er 168 patiënten met hemofilie die profylaxe gebruikten en 73 ouders van kinderen met hemofilie geïncludeerd. Ouders waren meer therapietrouw (66%) dan patiënten (43%). Suboptimale therapietrouw kwam voor bij 29% van de ouders en 37% van de patiënten, vooral gekenmerkt door wijzingen in het voorgeschreven tijdstip. Therapieontrouw kwam veel minder vaak voor: 5% van alle ouders en 20% van alle patiënten was ontrouw. Er was een relatie tussen therapietrouw en stollingsfactor verbruik, maar niet met het aantal bloedingen.

Hoofdstuk 6 en Hoofdstuk 7 richten zich beiden op de onderliggende reden voor therapieontrouw. **Hoofdstuk 6** beschrijft een systematische review van de literatuur over determinanten van therapietrouw bij profylaxe in hemofilie. Na evaluatie van 44 artikelen, werden vijf relevante artikelen kritisch beoordeeld. Twee van de vijf studies werden beschouwd als de best beschikbare kennis op dit moment. Motiverende factoren voor therapietrouw waren: het ervaren van symptomen, geloof in de noodzaak van de behandeling en een goede relatie met de zorgverlener. Belangrijke barrières voor therapietrouw waren: onregelmatige of afwezigheid van klachten en een toenemende leeftijd.
In **Hoofdstuk 7** is de onderliggende reden voor therapieontrouw verder ontrafeld in een kwalitatieve studie. Bij 21 patiënten zijn diepte interviews uitgevoerd, waarbij gevraagd werd naar ervaringen, percepties en overtuigingen over therapietrouw bij profylaxe. Deze interviews werden getranscribeerd, gecodeerd (in drie stappen) en geanalyseerd in een iteratief proces. Therapietrouw werd bepaald door de positie van profylaxe in het leven. Deze positie werd weer bepaald door twee aspecten: de perceptie van profylaxe en bekwaamheid in het uitvoeren van profylaxe. De perceptie over profylaxe werd beïnvloed door de mate van het accepteren van de hemofilie en ervaren/ vrezen voor symptomen. De bekwaamheid van het uitvoeren werd beïnvloed door het begrijpen van de hemofilie en de behandeling en door de daadwerkelijke planning en infusie vaardigheden. De combinatie van verschillende percepties en vaardigheden leidde tot vier hoofd posities van profylaxe in het leven: 1) profylaxe geïntegreerd in het leven, 2) profylaxe volgens dokters' advies, maar moeite met situaties anders dan normaal, 3) profylaxe is te veeleisend, 4) profylaxe is een confrontatie met ziekte. De therapietrouw niveaus verminderden geleidelijk van positie 1 tot 4.

In **Hoofdstuk 8** zijn de coping vaardigheden van patiënten met ernstige hemofilie beschreven. De coping vaardigheden werden gemeten met de coping vragenlijst voor stressvolle situaties (CISS-21) en geclassificeerd in drie basis coping strategieën (taak-georiënteerd, emotioneel-georiënteerd en vermijdend). Determinanten van coping werden gemeten met drie vragenlijsten: de activiteiten (HAL), participatie (IPA), fysiek en psychosociaal functioneren (D-AIMS2). In totaal werden er 86 volwassenen met

ernstige hemofilie geïncludeerd en deze werden vergeleken met 374 gezonde Nederlandse mannen. Patiënten met hemofilie gebruikte de taak-georiënteerde coping strategieën in vergelijkbare mate als de controle groep, echter gebruikte significant minder emotioneel-georiënteerde coping (57% vs. 25%, $p<0.05$) of vermijdende coping ($p<0.05$). In hemofilie, emotioneel-georiënteerde coping liet een sterke correlatie zien met de mate van psychosociale gezondheid (r 0.67) en zwakke correlaties met participatie (r 0.32) en sociale interactie (r 0.29). Andere associaties tussen coping en patiënt karakteristieken konden niet worden aangetoond. Samenvattend, patiënten met hemofilie gebruiken overwegend de taak-georiënteerde coping strategie om om te gaan met de hemofilie.

Dit proefschrift eindigt met een **algemene discussie** en bevat praktische aanbevelingen voor de hemofilie professional over zelfmanagement en therapietrouw bij patiënten met hemofilie. Gebaseerd op de studies uit dit proefschrift en overige gepubliceerde studies, zijn evidence based aanbevelingen geformuleerd. In conclusie, zelfmanagement en therapietrouw bij profylaxe variëren gedurende het leven. Acceptatie van de hemofilie en hogere zelfmanagement vaardigheden zijn belangrijke aspecten van het succesvolle profylaxe, die een individuele professionele aanpak vragen.

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Curriculum Vitae

Liesbeth Hélène (Marlies) Schrijvers was born January 13, 1987 in Nieuwegein, The Netherlands. After graduating secondary school at Cals College, Nieuwegein (2005), she obtained her Bachelor degree (Dual), in Nursing in 2009 at the University of Applied Sciences, Utrecht and University Medical Center, Utrecht. As part of this working/ learning study, Marlies performed different yearly internships at traumatology (2005/ 2006), oncology (2006/2007), vascular surgery/ urology (2007/2008) and obstetrics (2008/ 2009). After her graduation she continued working on obstetrics.

In 2010, Marlies started with the PhD project which resulted in this thesis, under supervision of Prof. M.J. Schuurmans and Dr. K. Fischer. During her PhD project, she obtained her Masters' degree in Nursing Science in 2013 (University Utrecht) and obtained clinical experience as a haemophilia nurse in the Van Creveldkliniek (University Medical Center, Utrecht). Since 2013, Marlies participated in different European committees in the field of haemophilia. Currently, she is the chair of the nurses committee of the European Association for Haemophilia and Allied Disorders (EAHAD). In the summer of 2014, Marlies received a grant from the Dutch Government (ZonMw) for development of an intervention focused on improvement of adherence to prophylaxis in haemophilia. Furthermore, she is working as a lecturer at the department of Nursing Science, Utrecht University. Marlies has the ambition to contribute to the quality of nursing care through evidence based research.

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