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REVIEW ARTICLE

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

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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.

Keywords: compliance, coping, nurse, prophylaxis, psycho-social, self-infusion

Introduction

Haemophilia is an X-linked bleeding disorder, characterized by a deficiency or absence of clotting factor VIII (FVIII) (haemophilia A) or (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: (i) the fact that it requires self-infusion [9] (ii) the short half-life of approximately 12 h requiring frequent infusions to maintain though levels needed

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for bleed prevention [10] and (iii) the fact that prophylaxis is continued lifelong [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 lifelong 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 Fig. 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 study, 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 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 feels comfortable, for example by a reassuring nurse who respected their insecurity. The development of a specific ritual, for example 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.

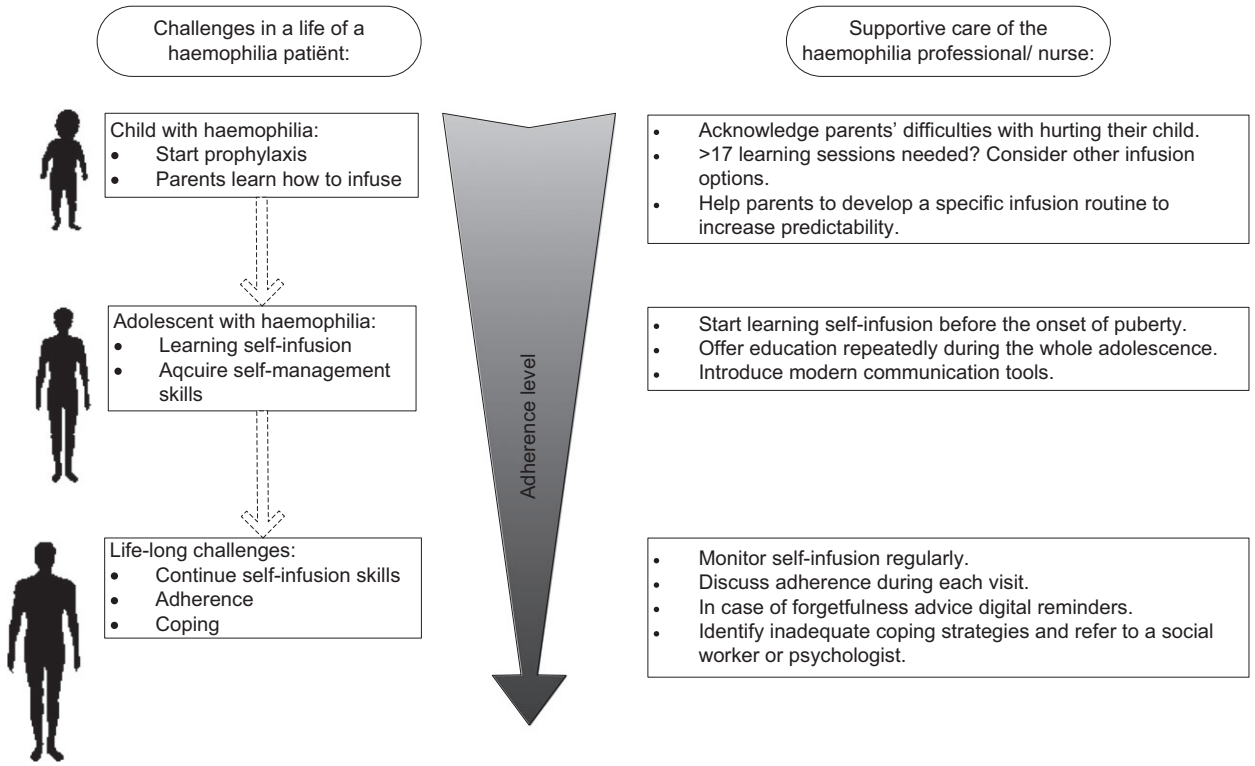

Fig. 1. Overview of challenges in the life of a haemophilia patient. Including suggestions for the haemophilia professional.

Recommendations for clinical practice.

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

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 [39] showed that adolescents preferred continuous support in accordance with the needs in different adolescence phases. Recently, a digital self-management programme for adolescents with haemophilia was developed [40–42]. Based on adolescents' opinion and needs [41] this programme 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 programmes for adolescents showed promising results on disease-specific outcomes.

Recommendations for clinical practice.

1. Start learning self-infusion before the onset of puberty.
2. Offer education continuously during the adolescence period.

3. Consider using modern communication tools, such as digital training, and social media.

Lifelong 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 5 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 2 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.

1. 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 (L. H. Schrijvers, M. H. Cnossen, M. Beijlevelt, M. Peters, M. Schuurmans and K. Fischer, unpublished data). 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 15–25% 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% , L. H. Schrijvers, M. H. Cnossen, M. Beijlevelt, M. Peters, M. Schuurmans and K. Fischer, unpublished data), and changes in dose (max 120 IU deviation , L. H. Schrijvers, M. H. Cnossen, M. Beijlevelt, M. Peters, M. Schuurmans and K. Fischer, unpublished data), yet timing of infusions was never considered in these trials [50–53]. The definition from the expert panel was used to analyse data from our multicentre study assessing adherence, (L. H. Schrijvers, M. der Beijlevelt-van Zande, M. Peters, J. Lock, M. H. Cnossen and K. Fischer, unpublished data). 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 (L. H. Schrijvers, M. der Beijlevelt-van Zande, M. Peters, J. Lock, M. H. Cnossen and K. Fischer, unpublished data) . 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% [51,54].

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 [51]. 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, L. H. Schrijvers, M. der Beijlevelt-van Zande, M. Peters, J. Lock, M. H. Cnossen and K. Fischer, unpublished data]. Other studies reported that non-adherence had a negative effect on long-term outcomes, including physical functioning [19,21,56], joint score on MRI [21] or more orthopaedic surgeries [21]. We observed no association of adherence levels with bleeding (L. H. Schrijvers, M. der Beijlevelt-van Zande, M. Peters, J. Lock, M. H. Cnossen and K. Fischer, unpublished data). 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 [57].

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 [57]. We identified that adherence is determined by the position of prophylaxis in life (Fig. 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 lifelong treatment [58]. The use of a digital reminder could support patients suffering from forgetfulness; this approach proved successful in patients with diabetes [59].

Recommendations for clinical practice.

1. Discuss adherence during each visit: discuss difficult moments, evaluate the infusion dairy and give positive feedback [58].
2. In case of forgetfulness advise digital reminders [59].

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 [60]. In our study adults frequently used the problem focussed (or task-oriented) coping approach rather than emotion-oriented or avoidance coping [61]. This problem-focussed strategy could be linked to high level of control over the disease because of the ability to perform self-treatment [62]. Patients who preferred the emotion-oriented coping strategy showed a lower socio-psychological health and reduced participation in daily life [61]. These patients could be referred to a social worker or psychologist (preferably dedicated to haemophilia) for counselling [63].

Recommendations for clinical practice.

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

Conclusion and implications for future research

Throughout life patients with haemophilia are facing many disease-related challenges. This study 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.

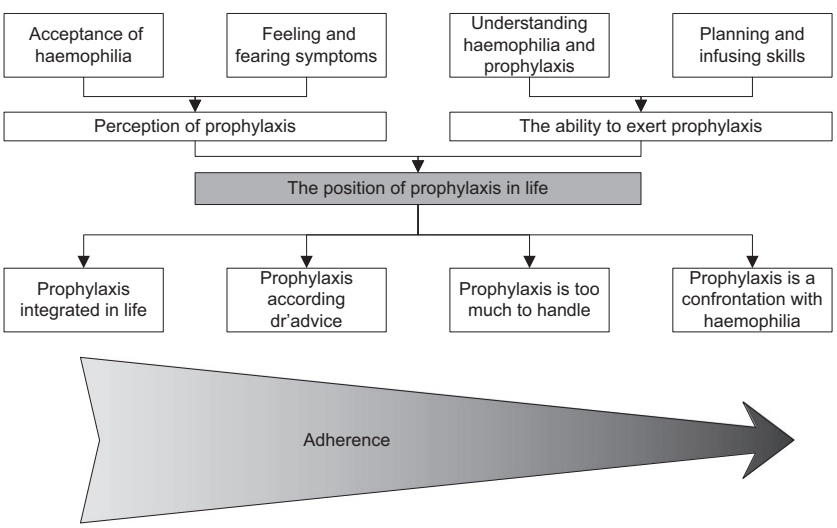

Fig. 2. Schematic model of adherence to prophylaxis in haemophilia [56]. Adherence is decreasing from left to right.

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 [64,65] 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 3 months is used, which is much longer than the period of 1 or 2 weeks generally considered as optimum for questionnaires [66]. 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) is unavailable for intravenous medication [58].

Association of adherence with clinical outcome

In our study, joint bleeding was not associated with adherence, (L. H. Schrijvers, M. der Beijlevelt-van Zande, M. Peters, J. Lock, M. H. Cnossen and K. Fischer, unpublished data). This may be expected as absence of symptoms [18] and feeling and fearing symptoms [57] 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, (L. H. Schrijvers, M. der Beijlevelt-van Zande, M. Peters, J. Lock, M. H. Cnossen and K. Fischer, unpublished data). For future studies, the use of objective outcome measures, like the Haemophilia Joint Health Score (HJHS [67]), X-ray or MRI data [68], 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 [69]) for self-management and the Illness Cognition Questionnaire (ICQ [70]) 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 programme, 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 [71]. 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 [57]. 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 [72,73]. A programme to improve adherence, including testing in an RCT, is currently being systematically developed [74].

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. To be able to offer all haemophilia patients the same high-quality care, European or (inter)national guidelines should be developed. Standardization 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 study can enhance evidence-based haemophilia care and should be incorporated in training of these professionals.

Disclosures

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