Review Article

Aging with Hemophilia: The Challenge of Appropriate Drug Prescription

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Abstract. In high-income countries persons with severe hemophilia (PWH) A and B are aging, like their age-matched peers without hemophilia from the general population. Aging is associated not only with the comorbidities stemming from their inherited bleeding disorder (arthropathy, chronic viral infections such as hepatitis and AIDS) but also with the multiple chronic ailments associated with aging (cancer, cardiovascular disease, COPD). Multimorbidity is inevitably associated with polypharmacy, i.e., the chronic daily intake of at least five drugs, and with the related risk of severe adverse events associated with the use of inappropriate drugs and drug-drug interactions. Information on the pattern of drug prescription and usage by PWH is relatively scanty, but on the whole, the available data indicate that the rate of polypharmacy, as well as the risk of drug-drug interaction, is relatively low in PWH and better than that in their age peers without hemophilia followed by general practitioners. It is believed that this advantage results from the collaborative coordination on drug prescribing exerted, through their integration with practitioners and organ specialists, by specialized hemophilia treatment centers in the frame of comprehensive care programs. However, the available cross-sectional data were mainly obtained in relatively young PWH, so that there is a need to obtain more accurate data from the ongoing prospective studies that are being carried out in more and more progressively aging PWH.

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Introduction. In the last few decades, western societies have experienced dramatic improvements in life expectancy owing to the increased availability of efficacious drugs and vaccines, specialized medical care, higher standards of living and lifestyles. Indeed, population aging is accelerating not only in high income countries but also worldwide, from 461 million people aged over 65 years in 2009 to an estimated 2 billions by 2050.[1] Even some cohorts of patients with rare diseases, who previously had a short life expectancy due to inadequate treatments, recently witnessed miraculous progress in management, so that

their life expectancy has much increased. This is epitomized by patients with hemophilia (PWH), the most frequent inherited bleeding disorder.[2] Before the first significant progress in replacement therapy that took place in the early 1970s, PWH had a short life expectancy at birth (20-30 years), and many of them died young due to life-threatening bleeding episodes.[3-5] Those who survived did inevitably develop gross joint damage (arthropathy) with associated musculoskeletal handicaps and chronic pain as consequences of recurrent and poorly treated hemarthroses.[5] Moreover, throughout the 1980s the epidemic occurrence of

bloodborne infections was registered in many PWH following the transmission of the human immunodeficiency virus (HIV) and the hepatitis B and C viruses (HBV, HCV) by plasma-derived coagulation factors employed for replacement therapy. These infections caused not only high peaks of mortality in the 1980s-1990s[3,4] but also chronic infectious diseases (hepatitis and AIDS) with long-term morbidity in those PWH who survived.[2,4,5] Today the management of PWH has markedly progressed due to the wider availability and safety of plasma-derived and recombinant coagulation factor products, highly active antiviral drugs that eradicate or stabilize chronic infectious diseases and, most importantly, for the wider establishment starting from the 1970s of hemophilia treatment centers (HTC) offering specialized comprehensive care.[2] A direct consequence of the improvement in the clinical management of PWH is a current life expectancy similar to that of males in the general population, at least in high-income countries, and the parallel attainment of older ages much more often than before.[3-5] A current challenge is the novel presence of an expanding cohort of older PWH who carry not only the co-morbidities related to the natural history of their bleeding disorder (arthropathy and viral disease) but also the multiple chronic ailments associated with aging: chronic obstructive pulmonary disease, cancer, neurodegenerative diseases such as Parkinson and dementia, and cardiovascular diseases as myocardial infarction, atrial fibrillation and stroke.[6-8] Accordingly, more and more PWH need, besides specific factor replacement and antiviral therapies, other medications.[8] While there are cross-sectional data and review articles[6-8] on the multiple chronic diseases affecting the aging PWH, information on associated polypharmacy and related consequences is rather scanty.[9-12] Thus, there is a need to better understand whether or not the aging PWH are optimally handled with multiple drugs for their multiple concomitant illnesses, in order to avoid the deterioration of their bleeding tendency and of the existing comorbidities, as well as the adverse events due to the intake of potentially inappropriate medications and drug-drug interactions.

With this background and gaps of knowledge on the relatively new challenge of aging with hemophilia, this article has as first goal to update the patterns of chronic diseases associated with aging other than the congenital bleeding disorder, with special emphasis on cardiovascular disease and related risk factors. A subsequent goal is to evaluate to which extent older PWH take multiple medications, in addition to those specifically prescribed for the prevention and treatment of their hemorrhages and viral infections. Finally, a goal is to evaluate the appropriateness of multiple medication prescription (polypharmacy) in these older patients, who are likely to be particularly vulnerable to

drug-drug interactions and related adverse events: not only due to the baseline impairment of their hemostatic system but also to the often impaired function of organs as the liver and kidney, which play key roles in the kinetics and dynamics of commonly used drugs.

Patterns of Chronic Diseases in the Aging PWH. As a preamble, we offer definitions on the differences between comorbidity and multimorbidity. Comorbidity is the concomitant presence of one or more clinical conditions co-occurring in an individual as a consequence of a primary disease: in PWH typical comorbidities are arthropathy and chronic liver disease.[13] Multimorbidity is not only the coexistence but also the complex interactions of two or more chronic conditions, which have no overt relationship with the primary disease but make more challenging its management.[13]

Barring the comorbidities typical of hemophilia, have the main diseases prevalent in older people without hemophilia have the same prevalence in PWH? This question applies not only to such frequent cardiovascular diseases as coronary artery and cerebrovascular atherothrombotic disease, atrial fibrillation and heart failure but also to cancer, chronic kidney disease, degenerative arthritis and diabetes. Because aging with hemophilia is a relatively recent picture, data are relatively scanty and published reports mainly stem from cross-sectional observational studies or case series that obviously have inherent limitations in design and case selection.[9-12] In most of them, the age limit to define older PWH is as early as 40-50 years. Even though these patients would not be defined old according to the commonly used criteria, this early threshold is meaningful in PWH, because those who have currently reached at least this or older ages were born at a time when regular replacement therapy with coagulation factors, and particularly their prophylactic use, was far from being largely available. In addition, the majority of them became infected with HCV and HIV in the 1970s and 1980. Thus, owing to the inevitable effects of associated chronic comorbidities (liver and kidney disease) these patients are aging earlier and are more frail and vulnerable at relatively younger ages than their age peers without hemophilia.

The great majority of the published reports are quite concordant to indicate that older PWH have a lower prevalence of morbidity and mortality from atherothrombotic cardiovascular diseases than age-matched peers from the general population.[9-12] Lower morbidity and mortality are usually attributed to the protective effect on thrombus formation by the lifelong deficiency of coagulation factors, particularly cogent in older PWH poorly treated until recently, considering that in them there is no lower prevalence of atherosclerosis[14,15] nor of the general cardiovascular risk factors,[9,12,16,17] except for lower serum

cholesterol.[10,17] An important CVD risk factor as hypertension has a higher prevalence than in the populations taken for comparison,[9,10,17,18] even though the underlying reasons are partially elusive.[19] Pertaining to such other ailments frequently associated with aging as diabetes, cancer[20,21] and osteoporosis, PWH are not spared from them but evidence of substantial differences in morbidity rates from the general population is scanty. Arthritis is a very common and precocious consequence of the hemophilic arthropathy and the related chronic pain is looming large in PWH. Atrial fibrillation, a disease typical of aging, is less frequent, perhaps because the investigated cohorts included very few patients above the age of 80, when this cardiac arrhythmia reaches the very high rates of 10% or more. On the whole, there is a need for prospective cohorts studies or registries to accrue more data on the incident burden of cardiovascular disease and other ailments typical of aging in PWH. Some of these cohort studies are indeed ongoing in the frame of a joint UK-Dutch effort,[17] in the USA[18] and in Italy[22,23] (**Table 1**), and the clinical picture of older PWH at enrolment is published.[17,18,22,23] The prospective follow-up of these cases and the acquisition of the corresponding data on incident events should help to develop guidelines on management, that are currently lacking, particularly for coronary artery disease and atrial fibrillation,[24] or are based on the local experiences of a few large HTC.[25,26]

Patterns of Drug Use in PWH. Polypharmacy, defined as the chronic daily intake of 5 or more different medications,[27] is very frequent in older patients with multiple chronic diseases, being the consequence of the application to these patients of the findings of randomized clinical trials, which in turn are the basis of the guidelines for evidence-based medicine.[27,28] Thus, multiple diseases are often handled by adding to the same multimorbid individual all the drugs that are recommended by guidelines for every single disease.[29] The snag is that randomized clinical trials are based on the enrolment and inclusion of patients widely different from the multimorbid older patients treated in real-life situations: younger, with a single disease chosen as the target of the investigated drugs, and with general clinical features that minimize the risk of drug-related adverse events. This explains why polypharmacy rather than helping older people

with multiple disease has become a disease itself, with consequences more ominous than those of the single diseases for which those drugs were prescribed:[29-31] higher mortality, more hospital admissions and re-hospitalizations, the cause of up to 30% of unexpected adverse events, a higher risk of drug-drug interactions, poor treatment adherence and frequent drug intake errors.[29-32]

With this knowledge on the noxious effects of polypharmacy in older people, the peculiar cohort of older PWH is likely, as mentioned above, to be particularly liable to the consequences of polypharmacy, owing to underlying comorbidities and related dysfunction of key organs such as the liver and kidney. Despite these concerns, until recently there have been few reports on the prescription pattern of drugs other than those specific for hemophilia in the aging persons with this disease. In their cross-sectional analysis of older PWH conducted in the frame of a multicenter cohort study promoted by the American Hemostasis and Thrombosis Network (ATHN) Sood et al[18] compared 200 patients with a mean age at enrolment of 61 years with age-matched controls selected from two large ongoing US population studies (ARIC and NHANES). Pertaining to the usage of medications for cardiovascular disease, aspirin was used much more seldom in PWH than in the comparison ARIC and NHANES cohorts, and a similarly spare prescription and usage rates applied to blood pressure lowering drugs, glucose-lowering drugs in diabetes and statins in patients with hyperlipidemia (**Table 2**). These findings indicate that there is a tendency to use with caution cardiovascular medications in PWH, contrasting with the frequent use of these drugs in age-matched peers without hemophilia. In the report of the ATHN cohort, there is no information on the concomitant use of more than one drug and thus on the frequency of polypharmacy, the usage rate being reported as split by each class of medications. The issue of polypharmacy was first tackled by a pilot study conducted in a single HTC[33] and then in the context of the baseline data of the prospective SPHERA cohort of aging PWH regularly followed up in Italy by 14 HTC.[22,23] In their monocentric and retrospective cross-sectional study Riva et al[33] chose to obtain data on medications, together with other clinical and laboratory variables, from 135 PWH (with a mean age of 47,7 years, 27.4%

Table 1. Features of the ongoing multicenter perspective studies on aging patients with severe hemophilia A and B.

Country	Starting year	Case number	Mean or media age at enrolment	Comparator	Planned follow-up (years)	Baseline data publication
UK and Netherlands	2009	344	47 years	General population	2 to 10	2013 Ref. 17
Italy (AICE SPHERA)	2011	102	64 years	matched controls (n=204) from practitioners	5 to 10	2017, 2018 Ref. 22,23
USA (ATHN)	2012	200	61 years	ARIC and NHANES cohorts	Not known	2018 Ref. 18

Table 2. Medication usage at enrolment in aging PWH compared with age-matched controls from the US-based ARIC and NHANES cohorts.

Type of medication	PWH	ARIC	NHANES
Aspirin	10%	59%	23%
Antihypertensive	36%	76%	85%
Lipid lowering	27%	26%	67%
Glucose lowering	45%	56%	76%

of them being older than 55 years). On the whole, the drugs more often taken, particularly by patients older than 55 years, were antihypertensives (particularly ACE inhibitors) and proton pump inhibitors, whereas the use of anti-inflammatory and analgesic drugs was rather spare. Regarding polypharmacy, the rate of patients with this feature was low, being somewhat higher in older PWH (27% vs 16%).[33]

The limitations of this exploratory study were subsequently addressed by an analysis planned and carried out in the context of the SPHERA prospective cohort, which included 102 older PWH (mean age 64 years) and 204 age- and-residence-matched older people without hemophilia chosen randomly by the same general practitioners of the PWH.[23] In broad agreement with the results obtained in the pilot study, PWH took in average less drugs than their age peers without hemophilia attended by the same practitioners. Barring the very frequently used drugs for replacement therapy and those for HIV and HCV infections, PWH took more frequently non-steroidal anti-inflammatory drugs and proton pump inhibitors than their non-hemophilic age-peers, who in turn used more statins, antihypertensive and antithrombotic drugs. Importantly, the prevalence of potentially relevant and dangerous drug-drug interactions was lower in PWH than in controls, in spite of the fact that they were both followed by the same general practitioners in the routine care and that hemophilia-related comorbidities accrued more illness to the PWH group. This low rate of potential drug-drug interactions can be taken as a proxy of appropriateness of the chosen drugs, suggesting that the difference favoring PWH is related to the fact that they are regularly followed not only by their practitioners but also by the specialized HTC. These data emphasize an additional and hitherto unknown benefit of the comprehensive care implemented by HTC, that have obviously added to their routine a process of evaluation of the risks carried by some drugs, and thus implemented deprescribing in order to limit drug use in these frail and vulnerable

patients. It remains to be seen whether this optimistic picture is generalizable, particularly when PWH will become older. Data on drug intake are being actually collected in the SPHERA cohort also at the 5- and 10 years of follow up, when patients will be older, more likely to increase drug intake and thus more susceptible to the adverse effects of polypharmacy.

Conclusions. This report shows that at least in high-income countries and in the specialized HTC there is awareness that PWH are aging, and that this obviously favorable event demands a change in the practice of the specialized care of these patients, until recently mainly concentrated on the problems of pediatric and adolescent patients. The advent of highly active anti-HIV drugs in the middle 1990s and of drugs able to eradicate HCV in the last decade have dramatically changed the clinical picture of the corresponding chronic infections, that are well controlled for HIV and very often cured in HCV-infected patients. Arthropathy is being ameliorated by the feasibility and related implementation in PWH of arthroplasties of the knee, ankle and hip, and by multidisciplinary rehabilitation programs that, involving physiotherapists, psychologists, occupational therapists and geriatricians, are becoming more and more tailored to the need of older PWH.[34] This basically optimistic picture on the clinical future of PWH demands that, as recommended by the Council of Europe,[35] the comprehensive hemophilia treatment team involves afresh in the management of older PWH also generalist physicians such as internists and geriatricians, more experienced than pediatricians and hematologists in the specific management of complex older patients.[34,36] In this context, it is also important that the likely increased usage of multiple drugs associated with further aging is dealt with in collaboration with pharmacists and clinical pharmacologists. To my knowledge, there is at the moment no centenarian with hemophilia, but the more and more successful aging of these patients makes this event no longer unrealistic!

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