Chronic complications and age-related comorbidities in people with hemophilia

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INTRODUCTION

Hemophilia A (factor VIII [factor 8] deficiency) and hemophilia B (factor IX [factor 9] deficiency) are X-linked inherited coagulation factor deficiencies. The availability of factor replacement products has dramatically improved care for individuals with these conditions, resulting in dramatic improvements in life expectancy. However, as people with hemophilia live longer, they are more likely to develop chronic complications of hemophilic bleeding as well as age-related comorbidities such as heart disease and cancer, and many of the treatments for heart disease, cancer, and other conditions also create hemostatic challenges that may increase the risk of bleeding.

This topic review discusses the management of these chronic complications and age-related comorbidities in people with hemophilia.

Separate topic reviews discuss diagnosis, routine care including factor prophylaxis, treatment of bleeding, surgery, inhibitor eradication, and genetics of hemophilia.

- **Diagnosis** – (See "Clinical manifestations and diagnosis of hemophilia".)
- **Comprehensive care including factor prophylaxis** – (See "Hemophilia A and B: Routine management including prophylaxis".)

- **Surgery and treatment of bleeding** – (See "Acute treatment of bleeding and surgery in hemophilia A and B".)
- **Inhibitor eradication** – (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication".)
- **Genetics** – (See "Genetics of hemophilia A and B".)

CHRONIC COMPLICATIONS

The major long-term complications of hemophilia are chronic hemarthrosis with hemophilic arthropathy; other sequelae of bleeding, especially central nervous system bleeding, which can be devastating; infections transmitted by plasma-derived factor concentrates in many patients who received plasma-derived replacement factor during the 1970s, 1980s, and first half of the 1990s; and development of antibodies to infused factor (inhibitors), which make treatment of bleeding very challenging.

Arthropathy — Arthropathy is a chronic condition in which repeated hemarthroses and synovitis lead to pain and joint destruction. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Hemophilic arthropathy'.)

Several conservative measures are available for managing arthropathy:

- Short-term or long-term prophylaxis with factor administration for several weeks to months, also referred to as intermittent prophylaxis (table 1). When provided to patients with target joints, this can interrupt bleeding cycles and slow the rate of joint deterioration [1]. Dosing is in the range of three to four times per week for standard half-life factor VIII and two times per week for standard half-life factor IX; sometimes more aggressive prophylaxis is used to target higher trough levels. Details and other schedules are presented separately. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Age of initiation and dosing schedule'.)

- A short course of glucocorticoids to decrease inflammation or anti-inflammatory agents such as cyclooxygenase 2 (COX-2) inhibitors.

- Joint injection with a glucocorticoid or artificial synovial fluid [2-4].

- Weight loss for individuals who are overweight or obese [5].

- Ambulation and exercise to reduce the risk of contractures and increase the stability of the affected joint. The local hemophilia treatment center and/or clinicians with expertise in physical therapy for people with hemophilia can assist with specific interventions. (See

"Hemophilia A and B: Routine management including prophylaxis", section on 'Exercise and athletic participation'.)

When conservative therapy is ineffective, there are several options for the treatment of synovitis and the reduction of recurrent bleeding and further joint destruction [6-8]; attention to the risk of inhibitor development and screening for predisposing factor VIII genetic variants is important. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Predisposing influences'.)

- Synovectomy for selected patients. This can be performed via an open procedure, arthroscopically, or by injection of a radioactive material into the joint (radiosynovectomy) [9-11]. Radiosynovectomy is preferred in patients with inhibitors, advanced HIV infection, hepatitis, multiple joint involvement, or in resource-limited countries where a sustainable source of clotting factor concentrates may not be available to support joint surgery. In this latter instance, chemical synovectomy may substitute for radiosynovectomy.

  - Small observational studies have shown surgical synovectomy to be effective in producing clinical improvement, although impaired range of motion may not improve [8,12,13].

  - For radioactive procedures, several radioisotope-colloid complexes have been used. Comprehensive reviews of radiosynovectomy using different radioisotopes have found the procedure to be well-tolerated and associated with a reduced frequency of bleeding, and have provided protocols and advice regarding specific radioisotopes [14,15].

  A complication associated with synovectomy is decreased range of motion, an important issue in the young child who cannot fully cooperate with a program of physical therapy. In the above study, arthroscopic synovectomy was associated with increased range of motion, and open synovectomy was associated with no change or reduced range of motion [16]. Synovectomy of the knee is discussed in more detail separately. (See "Synovectomy for inflammatory arthritis of the knee".)

- Joint replacement surgery, which is often used in individuals who have developed chronic arthropathy and contractures in the knee or hip [17-21]. Chronic ankle arthropathy can be treated with ankle fusion, elbow arthropathy can be treated with synovectomy and excision arthroplasty [22]. Elbow and ankle replacement therapies are also available [23,24]. Shoulder replacement can also be performed.

One study evaluated the effects of total knee arthroplasty in 11 patients (13 knees) [18]. Arthroplasty produced functional improvement and pain relief, with a reduction in the burden of disease to levels similar to those of patients with osteoarthritis undergoing hip arthroplasty. Functional ability did not reach normal levels because of residual symptoms and impairment of other joints. Another series from 2015 focused on the longevity of the 88 prosthetic knees in 74 people with hemophilia who underwent total knee arthroplasty over a 13-year period, the prosthetic remained in place in 81 cases (92 percent) [25]. A study that reviewed total knee arthroplasty in >4000 people with hemophilia and population controls found that people with hemophilia had higher rates of postoperative bleeding, deep vein thrombosis and pulmonary embolism, and infection around the prosthesis [26]. Other studies have reported complication rates of approximately 30 percent and arthroplasty revision rates of 6 to 20 percent [27,28]. Five-year implant survival rate is lower in people with hemophilia than controls, but implant survival remains high at >90 percent [29].

Another complication of joint disease and the associated decline in physical activity is the development of osteopenia and osteoporosis [30-32]. Age-appropriate risk-factor assessment for osteoporosis, screening for vitamin D deficiency, and adequate calcium intake should be ensured for individuals with hemophilia beginning at an early age. (See "Screening for osteoporosis in postmenopausal women and men" and "Geriatric nutrition: Nutritional issues in older adults", section on 'Vitamin D deficiency' and "Geriatric nutrition: Nutritional issues in older adults", section on 'Inadequate intake of calcium'.)

CNS and other bleeding sequelae — Sequelae of bleeding in other sites may also be associated with serious morbidities, especially for central nervous system (CNS) bleeding, which occurs most commonly in children but can also affect adults.

CNS bleeding can lead to chronic neurocognitive, educational, and behavioral deficits.

- A meta-analysis of intracerebral hemorrhage in people with hemophilia that included 45 studies (>50,000 patients) found a pooled incidence rate of 0.23 per 100 person-years [33]. Divided by age, the pooled incidence in neonates was 2.1 percent per 100 live births, and in children and young adults, 0.74 per 100 person-years. Hemorrhage was spontaneous in 35 to 58 percent.

- A 2012 study compared academic and behavioral outcomes in 16 boys with hemophilia who had a history of intracranial hemorrhage (ICH) versus 16 controls who were matched for age, type of hemophilia (A or B), disease severity, and maternal education level; all were HIV negative [34]. Compared with controls, boys with a history of intracerebral

bleeding had mildly reduced functioning in some but not all domains. There were reductions in intellectual functioning, vocabulary, and fine motor control. Scores were similar to controls for socio-emotional function, executive functioning, and socialization. Further study in this area and in interventions to support these individuals is needed.

Individuals who experience an intracerebral hemorrhage (children or adults) should undergo neuropsychiatric evaluation. In addition, all individuals with neurocognitive and/or behavioral dysfunction should be offered age-appropriate educational resources and other supports. A general review of such resources is presented separately. (See "Specific learning disorders in children: Educational management".)

Hemophilic pseudotumors can arise in areas of bleeding [35,36]. Pseudotumors are collections that can develop as organizing blood is incompletely resorbed and becomes encompassed within a fibrous capsule [37]. Biopsy can distinguish pseudotumors from true tumors (benign or malignant). Surgical management of hemophilic pseudotumor may be effective in cases with significant deformity [36,38]. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Joints and muscle'.)

HIV and HCV infection — Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection due to factor infusion affect a large number of people with hemophilia who received plasma-derived factor products before routine screening of donated blood for these viruses and pathogen-inactivation methods for plasma-derived factor were initiated. Some patients were co-infected with HIV and HCV. In a 2002 series of 1816 HCV-seropositive individuals with hemophilia, 1192 (65 percent) were HIV co-infected [39].

- **HIV** – HIV infection was first reported in a person with hemophilia in 1982. Serologic testing for HIV in blood products was not introduced until the mid-1980s, and the first recombinant products were not introduced until the 1990s (recombinant factor VIII in 1992 and recombinant factor IX in 1997) [40]. Thus, the cohort of people with hemophilia born in the 1970s, 1980s, and early 1990s is estimated to be the most affected by HIV and AIDS [40]. (See "The natural history and clinical features of HIV infection in adults and adolescents", section on 'Introduction'.)

- **HCV** – Many patients who received plasma-derived factor in the 1970s and 1980s developed HCV infection. Serologic testing for HCV in blood products was initiated in approximately 1990. (See "Blood donor screening: Laboratory testing", section on 'Hepatitis C virus'.)

The major concerns with chronic HCV infection are progressive hepatic injury, which is more pronounced in patients who are co-infected with HIV or those who have cirrhosis or

hepatocellular carcinoma [41-44]. In the study of 1816 individuals with HCV infection mentioned above, end-stage liver disease developed in 127 of the HIV/HCV co-infected individuals, with an estimated 16-year cumulative incidence of 14 percent, compared with 3 percent development of end-stage liver disease for those with HCV alone [39,45]. Intensified eradication of HCV is warranted to reduce the risk of chronic liver disease [45]. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection" and "Epidemiology and risk factors for hepatocellular carcinoma".)

Importantly, hemophilia is not a contraindication to HIV or HCV treatment. In fact, treatment of these infections may improve thrombocytopenia, in turn lowering the risk of bleeding. The optimal management of HIV and HCV infection and choice of antiviral therapy depends on a number of factors; these are presented in detail separately. (See "When to initiate antiretroviral therapy in persons with HIV" and "Selecting antiretroviral regimens for treatment-naïve persons with HIV-1: General approach" and "Overview of the management of chronic hepatitis C virus infection" and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection".)

Non-HIV-infected patients with hemophilia who develop cirrhosis can be treated with liver transplantation, which also will cure the hemophilia [46,47]. A number of patients with HIV and HCV co-infection and liver failure have also been treated with liver transplantation. Outcomes of liver transplantation in 26 individuals with hemophilia who received an orthotopic liver transplant revealed better survival rates of those who were not HIV infected [46,48]. Survival of the 20 non-HIV-infected individuals was 90 percent at one year and 83 percent at three years, whereas survival of the six HIV-infected individuals was 67 percent at one year and 23 percent at three years. All patients who survived the transplant had resolution of their hemophilia (factor IX is produced in hepatocytes, and factor VIII is produced in endothelial cells presented in the vasculature of the transplanted liver).

Inhibitor development — Inhibitors can develop in individuals with any severity of hemophilia. This important subject is discussed separately. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication".)

AGE-RELATED COMORBIDITIES

As life expectancy increases, a growing number of people with hemophilia develop age-related comorbidities including cancer, cardiovascular disease, and chronic renal disease. The increased bleeding risk in hemophilia complicates therapy for these conditions. Evidence-based guidelines for managing these comorbidities are lacking [49].

Cancer — Some tumors are more highly represented in this population, probably related to viral infection:

- A 2012 review of 127 cancers in 122 patients with hemophilia found that the two most common cancers were hepatocellular carcinoma (in 40 percent, all associated with hepatitis C virus [HCV] infection) and non-Hodgkin lymphoma (in 61 percent, mostly associated with HIV infection) [50].

- A 2014 review of 1067 patients with hemophilia reported 45 malignancies in 43 patients over a 10-year period (4 percent) [51]. The most common malignancy was hepatocellular carcinoma, which occurred in 12 patients, all associated with HCV infection. Other cancers included prostate cancer, lung cancer, and other solid tumors. While the incidence of these cancers in people with hemophilia relative to people without hemophilia cannot be estimated from this small study, the study demonstrated that appropriate diagnostic testing and therapy were feasible in patients with hemophilia. Most patients received standard cancer management, and there were few bleeding events associated with diagnostic biopsies or surgical procedures when appropriate hemostatic therapy was provided (5 and 7 percent with biopsies or other invasive procedures, respectively). Five of 37 patients (14 percent) changed from on-demand to prophylactic factor infusion during treatment of the malignancy [52,53].

As a general rule, therapy that causes thrombocytopenia should be accompanied by factor prophylaxis to reduce the risk of bleeding. Attention to nutrition to avoid vitamin K deficiency and the associated coagulopathy is also advised. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Prophylaxis to reduce bleeding episodes'.)

Cardiovascular disease — A variety of observational studies have documented the risks of cardiovascular disease in people with hemophilia as they age; generally cardiovascular disease appears to be less prevalent in people with hemophilia compared with age-matched controls [54-59]. Ischemic heart disease was increased in association with standard risk factors such as age, hypertension, and hyperlipidemia; other heart diseases (eg, cardiomyopathy, dysrhythmias) were correlated with HIV infection.

The optimal management of cardiovascular disease will be an increasing challenge to clinicians caring for patients with hemophilia, as some interventions such as the use antiplatelet agents or anticoagulants interfere with hemostasis, and studies are needed to determine the best approach [60,61]. In the absence of high quality evidence for the benefits and risks of various interventions, the following approach is prudent [49,58,62-67]:

- Risk factor screening and reduction should be emphasized, including interventions for smoking, hypertension, diabetes, and dyslipidemia [68].

- Decisions regarding antiplatelet agents for primary and secondary cardiovascular risk reduction must be individualized. Antiplatelet agents appear to be well-tolerated [69]. We are more likely to use low-dose aspirin for individuals with established ischemic cardiovascular disease who have mild hemophilia or who are receiving routine prophylactic factor for moderate or severe hemophilia [70,71].

- Decisions regarding anticoagulation for atrial fibrillation are especially challenging and require coordination between the cardiologist and hemophilia treatment center (HTC). Issues to discuss include balancing the risk of stroke with the risk of bleeding, potential role of cardioversion and possible use of aspirin rather than an anticoagulant [72]. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Hemophilia treatment centers'.)

- Patients with acute coronary syndromes or coronary artery disease who require percutaneous coronary intervention (PCI) or revascularization should be managed by a team that includes a cardiologist and a hemophilia expert from an HTC [70].

  - Guidelines for managing acute coronary syndromes in people with hemophilia were published by the European Society of Cardiology in 2013; these were based mostly on expert opinion rather than controlled studies [73]. Issues to address include the need for PCI, revascularization, or fibrinolytic therapy, with appropriate factor replacement during these procedures; radial rather than femoral approach; use of bare metal stents rather than drug-eluting stents; maintenance of adequate factor levels in individuals treated with anticoagulants or dual antiplatelet therapy; and minimizing exposure to anticoagulant and antiplatelet therapies to the shortest duration needed [72]. Revascularization and secondary prevention with antiplatelet agents appears to be feasible and effective [69].

  - A 2015 review that included 15 people with hemophilia who underwent cardiac surgery (mostly coronary artery bypass grafting) demonstrated excellent hemostasis with factor replacement using an institutional protocol that was tailored to the patient [74]. Most received factor for 10 to 14 days. Two patients had postoperative bleeding that required reoperation; there were no deaths.

Chronic kidney disease — People with hemophilia appear to have a higher incidence of chronic kidney disease than population controls. Potential mechanisms may include HIV infection, HCV infection, hypertension, and hepatotoxic medications [75]. Renal bleeding does

not appear to be a major contributing factor [76]. For patients who require dialysis, options include peritoneal dialysis, hemodialysis without heparin in the extracorporeal circuit, hemodialysis with factor replacement, and renal transplantation. (See "Overview of the management of chronic kidney disease in adults".)

PROGNOSIS

Life expectancy — Life expectancy for people with hemophilia has risen over time with greater use of factor replacement. In resource-rich settings, life expectancy has become similar to that of the general population. This is illustrated in the following large series:

- In a 2007 study from the United Kingdom that followed 6018 people with hemophilia without HIV infection, median life expectancy was 63 years for those with severe disease and 75 years for those with mild to moderate disease [77]. Bleeding deaths were increased relative to the general population; cardiovascular deaths were decreased relative to population controls.

- In a 2006 study from the Netherlands that followed 967 people with hemophilia from 1992 to 2001, life expectancy was approximately 63 to 67 years [78]. The main causes of death were AIDS and HCV infection. When viral deaths were excluded, life expectancy was 72 years. Cancer-related deaths were almost twice as common as cardiovascular causes. The standardized mortality ratio (SMR) for all patients was 2.3; higher SMR correlated with severity of factor deficiency (5.1, 2.6, and 1.3 for severe, moderate, and mild disease, respectively). SMR was lower for HIV-negative individuals and was unaffected by the type of hemophilia (A or B).

- In a 2000 study from the Centers for Disease Control and Prevention (CDC) and state health departments in the United States in which mortality was assessed in 2950 individuals with hemophilia A or B over a three-year period, the median life expectancy was 38.7 years [79]. HIV infection or AIDS was the most common cause of death, accounting for 124 of the 236 deaths recorded (53 percent); liver disease accounted for an additional 19 deaths (8 percent). When HIV-infected people were excluded from the analysis, life expectancy was 64.1 years. As noted above, care through a hemophilia treatment center (HTC) was associated with a longer life expectancy. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Hemophilia treatment centers'.)

Quality of life — Patients with severe hemophilia can have reductions in quality of life (QOL), self-esteem, and social interactions because of repeated bleeding episodes, chronic hemarthroses, transfusion-related infections, and other side effects of treatment such as the development of inhibitors. As examples:

- Health-related quality of life (HR-QOL) was studied in 721 participants in the 2008 Hemophilia in the Netherlands 5 (HiN5) study [80]. Occupational disability was reported by 35 percent of the patients with severe hemophilia, compared with 9 percent in the general population (odds ratio [OR] for occupational disability with severe hemophilia, 3.1).

- The Hemophilia B Experiences, Results and Opportunities (HERO) studies in hemophilia B have documented a number of factors that can affect HR-QOL including chronic pain, depression, and anxiety [81-83]. Limitations on sports and recreational activities can have a negative impact [84].

Efforts are underway to study these issues in greater depth and to find additional ways to improve QOL in patients with severe hemophilia [85-88].

Causes of death — In a 2016 report from the CDC and the Hemophilia Treatment Center Network (HTCN) in the United States, in which cause of death was assessed in 7486 men with hemophilia A or B, liver failure was the most common cause of death overall, accounting for 33 percent [40]. Hemorrhage accounted for 15 percent of deaths in those with severe hemophilia and 11 percent in those with mild hemophilia. Life expectancy was not reported in this study, but, as noted above, other studies have shown increasing life expectancy over time, approaching that of the general population. (See 'Life expectancy' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hemophilia A and B".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more

sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hemophilia (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Major complications** – The major long-term complications of hemophilia are chronic hemarthrosis with hemophilic arthropathy; sequelae of other bleeding events such as intracranial hemorrhage; infections transmitted by plasma-derived factor concentrates in patients who received plasma-derived replacement factor during the 1970s, 1980s, and 1990s; and development of antibodies to infused factor (inhibitors), which make treatment of bleeding very challenging. (See 'Chronic complications' above.)

- **Management**

  - **Joint complications** – Available options for treating synovitis and reducing recurrent joint bleeding and further joint destruction include short-term factor prophylaxis, synovectomy, and total joint replacement. Exercise, weight loss, and risk assessment for vitamin D deficiency and adequate calcium intake may also be helpful. (See 'Arthropathy' above.)

  - **Intracerebral hemorrhage** – Individuals with hemophilia who experience an intracerebral hemorrhage should undergo neuropsychiatric evaluation. In addition, all individuals with neurocognitive and/or behavioral dysfunction should be offered age-appropriate educational resources and other supports. (See 'CNS and other bleeding sequelae' above.)

  - **HCV and HIV** – The major concerns with chronic hepatitis C virus (HCV) infection are progressive hepatic injury, which is more pronounced in patients who are co-infected with human immunodeficiency virus (HIV); as well as cirrhosis and hepatocellular carcinoma. Hemophilia is not a contraindication to HIV or HCV treatment. Liver transplantation is an option for those with severe liver disease; this also will cure the hemophilia. (See 'HIV and HCV infection' above.)

- **Factor inhibitors** – (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication".)

- **Age-related comorbidities** – As life expectancy increases, more people with hemophilia are developing age-related comorbidities including cancer, cardiovascular disease, and chronic renal disease. Optimal management of these conditions is challenging because many of the interventions routinely used to treat these conditions increase bleeding risk. Multidisciplinary planning and practices that minimize bleeding risk are critical. (See 'Age-related comorbidities' above.)

- **Quality of life** – In resource-rich settings, life expectancy for people with hemophilia has become similar to that of the general population. However, quality of life and school/work performance can be affected, as is the case for many chronic diseases. Efforts are underway to study these issues. (See 'Prognosis' above.)

- **Other aspects of management** – (See "Clinical manifestations and diagnosis of hemophilia" and "Acute treatment of bleeding and surgery in hemophilia A and B" and "Hemophilia A and B: Routine management including prophylaxis" and "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication" and "Genetics of hemophilia A and B".)

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GRAPHICS

Types of prophylaxis for patients with hemophilia A or B

Type of treatment	Definition
Episodic (on demand) treatment	Replacement factor given at the time of bleeding
Continuous (regular) prophylaxis	Replacement factor given to prevent bleeding for at least 45 of 52 weeks (85%) of a year
▪ Primary prophylaxis	Continuous prophylaxis started before age three years and before the second large joint bleed
▪ Secondary prophylaxis	Continuous prophylaxis started after two or more large joint bleeds but before the onset of chronic arthropathy
▪ Tertiary prophylaxis	Continuous prophylaxis started after the onset of arthropathy to prevent further damage
Intermittent (periodic) prophylaxis	Replacement factor given to prevent bleeding for short periods of time such as during and after surgery

Replacement factor includes plasma-derived or recombinant factor concentrates. Refer to UpToDate for indications and details of factor administration and additional therapies for patients with hemophilia.

Adapted from:

1. *Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013; 19:e1.*
2. *Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: Communication from the SSC of the ISTH. J Thromb Haemost 2014; 12:1935.*

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