

Dental Care for People With Hemophilia: A Rapid Response Literature Review



Main Points

- A search of the Embase[®] and PubMed[®] databases, as well as professional society websites, identified no primary research studies or systematic reviews that evaluated the effect of dental care on hemophilia treatment outcomes.
- Two practice guidelines and two reviews with consensus-based recommendations for dental care for people with hemophilia were identified and reviewed.
- Preventive care and patient education were highlighted as essential practices for people with hemophilia to avoid periodontal disease, gum bleeding, and the need for major surgical intervention.
- No primary research evidence was available to conclude the appropriate timing for hemophilia patients to receive dental care in order to improve outcomes in response to factor replacement treatment.
- All included guidelines advocated for access to dental services and the inclusion of dental care as part of a multidisciplinary approach to hemophilia management.
- All included publications shared the recommendation that people with hemophilia undergoing dental services should consult with a hematologist or coordinate with a hemophilia treatment center and that dental services should occur with adequate hemostatic measures. Several guidelines recommended that dental treatment be scheduled to occur in tandem with factor replacement therapy, if indicated, to minimize risks of bleeding due to dental treatments. Dental procedures should be performed as close to the time of administration of factor concentrate as possible.
- Specific dental care recommendations may vary based on the severity of hemophilia and age. In dental procedures that required local anesthesia, it was recommended that children on routine prophylaxis receive factor replacement therapy prior to administration of anesthesia.
- All recommendations aimed at the management of hemophilia during dental services, not incorporating dental care as a strategy to improve hemophilia treatment outcomes.



Background

Hemophilia is a rare inherited disorder in which blood does not clot in the typical way due to missing or decreased blood-clotting proteins (clotting factors). Current U.S. estimates suggest that approximately 20,000 to 33,000 males live with hemophilia.¹ There are three distinct types of hemophilia (A, B, and C) according to the specific clotting factor that is deficient or missing (VIII, IX, and XI, respectively). Treatment for all three types is similar but may vary based on the severity of disease, and typically involves replacing the deficient or missing clotting factor.¹ Anticoagulation issues in these patients pose unique challenges for dental specialists providing care due to the increased risk of secondary bleeding following oral surgery.²

Hemophilia A (HA) and B (HB) are X-linked bleeding disorders caused by mutations in specific genes encoding coagulation factor VIII and factor IX (FVIII or FIX). Defects on the *F8* and *F9* genes present as HA and HB, respectively. Both the *F8* and *F9* genes are located on the X chromosome, and therefore hemophilia is more prevalent in men than in women. Hemophilia C (HC), a deficiency in factor XI, is less common than HA and HB, and is relatively mild. Factor XI deficiency presents more often when trauma occurs in the oral and nasal cavities or the urinary tract because those tissues are richer in fibrinolytic activity.³ The disease severity in hemophilia is determined according to the plasma level of FVIII or FIX activity. Patients of any type of hemophilia have prolonged activated partial thromboplastin time (aPTT), which indicates extended periods of time until fibrin formation, resulting in delayed clotting. Severe forms of hemophilia are classified as factor levels <1% of normal, moderate form as factor levels of 1-5%, and the mild form as factor levels >5 but <40%.³ Patients with severe hemophilia often develop spontaneous hemorrhages in joints, muscles, or soft tissues without any apparent cause and can even encounter life-threatening bleeding episodes such as intracranial hemorrhages. People with mild and moderate factor deficiencies rarely experience spontaneous hemorrhages. However, excessive bleeding can occur following trauma or an invasive procedure, such as dental extractions.³

The standard treatment for hemophilia is replacement of the missing blood clotting factor to enable proper blood coagulation. Clotting factor replacement therapy is typically done by injecting clotting factor concentrates intravenously. Replacement therapy can be done through episodic care, which stops a spontaneous bleeding episode, or through prophylactic care, which prevents bleeding from occurring. There are two forms of factor concentrates—plasma derived and recombinant. Plasma derived factor concentrate is collected via donations from healthy people; the plasma undergoes several processes to separate the components and produce plasma derived concentrate. The concentrate is tested and treated to kill any potential viruses and bacteria, then frozen and packaged for use.¹

More recently, the U.S. Food and Drug Administration (FDA) approved the use of recombinant factors VIII and IX concentrate in hemophilia patients, which is not derived from human plasma. Instead, this type of treatment is genetically engineered using DNA technology, and therefore cannot spread any bloodborne viruses.¹ The disadvantage of using both recombinant and plasma derived clotting factor replacement therapy is the potential development of inhibitors by patients, which reduces the ability for the treatment to form necessary blood clots.¹

Inhibitor development of anti-FVIII or anti-FIX antibodies neutralizes the activity of the infused clotting factor and presents a major complication of replacement therapy in hemophilia patients. FVIII inhibitor antibodies develop in approximately 25-30% of severe HA patients, whereas FIX inhibitors develop in roughly 3-5% of patients treated with factor concentrates.⁴ Immune tolerance induction (ITI) is a treatment strategy to eliminate inhibitors that have developed. The treatment consists of frequent

intravenous administration of factor concentrate until the inhibitor is eradicated, the hemostatic activity is restored, and bleeding episodes respond to factor replacement therapy again.⁵ ITI is not an ideal treatment because it is expensive and time consuming. Alternative coagulation therapies such as emicizumab and antifibrinolytic agents such as epsilon amino caproic acid (EACA) can be used to promote blood clotting when inhibitors develop.

Patients with hemophilia seek care at hemophilia treatment centers (HTCs), as well as self-administering clotting factor treatment at home, especially when treating spontaneous bleeding. Comprehensive HTCs provide patients with care and education from a team of interdisciplinary clinicians such as hematologists, nurses, and physical therapists who have specialized training in bleeding disorders.^{1,6,7}

Although clotting factor replacement therapy is the standard of care for the treatment of hemophilia, there is uncertainty as to whether dental care before, during, or after treatment of hemophilia improves clinical outcomes in patients. Excessive bleeding is commonly associated with invasive or traumatic dental care; therefore the timing of dental treatment in conjunction with factor replacement therapy may have an effect. The Centers for Medicare & Medicaid Services (CMS) has partnered with the Agency for Healthcare Research and Quality (AHRQ) to identify dental services that are inextricably linked and substantially related to the clinical success of Medicare-covered medical services for people with hemophilia. AHRQ has commissioned a rapid response summarizing recent evidence on this topic. This resulting rapid response aims to support CMS in decision-making regarding dental services for people with hemophilia.



Key Questions

This review was guided by five Key Questions (KQs), which are illustrated in the analytic framework (Figure 1).

KQ1. Does dental care before, during, or after treatment of hemophilia A with clotting factor VIII improve clinical outcomes?

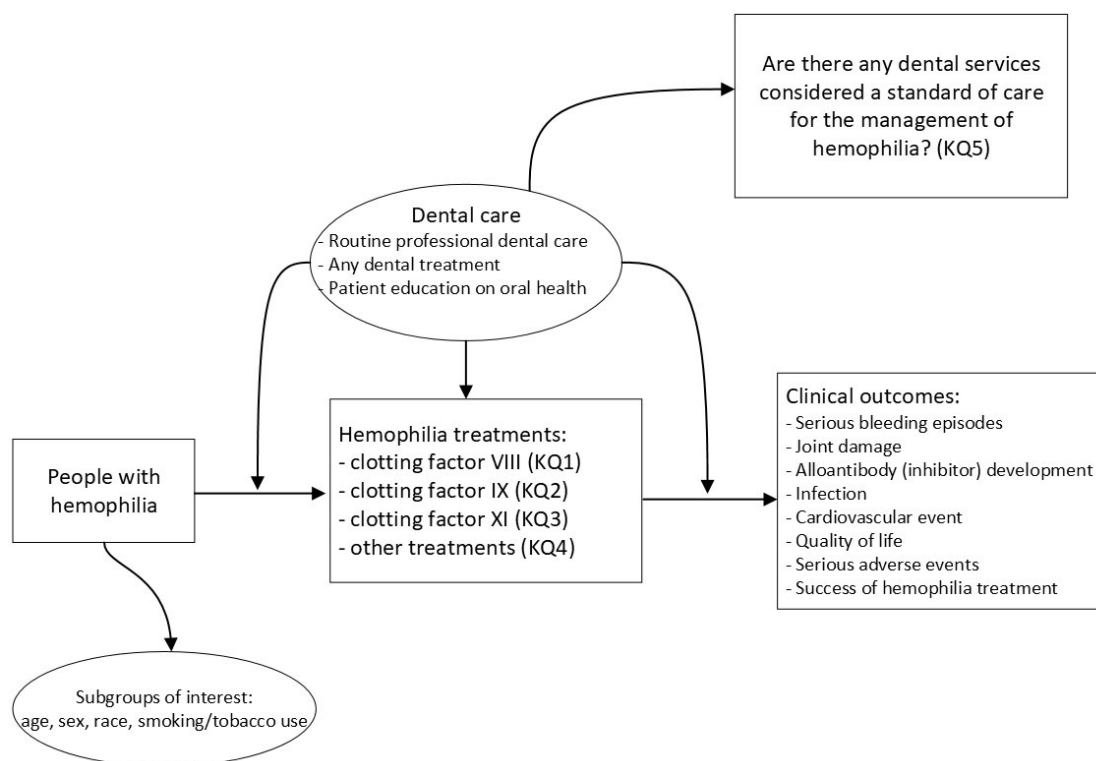
KQ2. Does dental care before, during, or after treatment of hemophilia B with clotting factor IX improve clinical outcomes?

KQ3. Does dental care before, during, or after treatment of hemophilia C with clotting factor XI improve clinical outcomes?

KQ4. Does dental care before, during, or after treatment of hemophilia with treatments other than clotting factor replacement (e.g., desmopressin, antifibrinolytic drugs, gene therapy, platelet transfusions) improve clinical outcomes?

KQ5. Are there any dental services considered a standard of care for the management of hemophilia?

Figure 1. Analytic framework



KQ = Key Question

Methods

This rapid response on dental care for people with hemophilia followed established best methods used in systematic review (SR) research while allowing for modifications to meet rapid response project timeframes.⁸⁻¹⁰

Literature Search

A medical research librarian developed a comprehensive search strategy to search PubMed® and Embase® for SRs, randomized controlled trials (RCTs), controlled observational studies, and clinical practice guidelines. The search strategies used in PubMed and Embase are outlined in Appendix A (Tables A-1 to A-4). The search was limited to English language publications from 1960 to the present. We chose 1960 to cover a breadth of potential use of clotting factors in the treatment for hemophilia. Our review of the search results focused on identifying primary research studies, SRs, and clinical guidelines published by professional societies. We also scanned the reference lists of all included studies.

The medical research librarian also conducted a grey literature search in relevant stakeholder organizations (e.g., National Hemophilia Foundation, American Society of Hematology, World Federation of Hemophilia, National Bleeding Disorders Foundation, American Dental Association, National Heart, Lung, and Blood Institute); government and nonprofit agencies (e.g., Centers for

Disease Control and Prevention, National Institutes of Health, World Health Organization); clinical trial registries (e.g., ClinicalTrials.gov); and other sources identified by the clinical subject matter expert. The search strategies used in the grey literature search are outlined in Appendix A (Table A-5).

Study Selection

Study eligibility was based on the population, intervention, comparator, outcome(s), timing, and setting (PICOTS) criteria, as depicted in Table 1. Study selection was done in a two-step process. In the first step, titles and abstracts of all citations retrieved from literature searches were screened by a single reviewer. In the second step, full texts of the abstracts that were categorized as relevant or potentially relevant were retrieved and reviewed. Exclusion reasons were documented at the full-text level. All screening was done in DistillerSR to maximize efficiency, and EndNote was used to track citations. The scientific lead conducted a final review to confirm inclusions and exclusions.

Table 1. Study eligibility criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	Pediatric and adult patients with hemophilia (Subgroups of interest: age, sex/gender, race/ethnicity, smoking/tobacco use)	None
Intervention	Dental services before, during, or after treatment for hemophilia: <ul style="list-style-type: none"> • Routine professional dental care (exam/cleaning) • Any dental treatment • Patient education on oral health 	Interventions other than professional dental services
Comparison	No dental services before, during, or after treatment for hemophilia	Studies were excluded if they did not report any of the specified comparators.
Outcomes	<ul style="list-style-type: none"> • Serious bleeding episodes • Joint damage • Alloantibody (inhibitor) development • Infection • Cardiovascular event • Quality of life • Serious adverse events • Success of hemophilia treatment 	<p>Studies were excluded if they did not report any of the specified outcomes.</p> <p>Dental health outcomes and dental procedure outcomes were excluded.</p>
Timing	Before, during, or after treatment for hemophilia	None
Setting	United States, Canada, Europe, Australia, New Zealand	Countries not listed in the inclusion list
Study Design	<ul style="list-style-type: none"> • SRs/MAs • RCTs • Controlled observational studies • Clinical practice guidelines 	<ul style="list-style-type: none"> • Noncontrolled observational studies • Laboratory studies • Animal studies • Nonclinical publications
Language	English language publications	Non-English language publications
Publication Dates	1960–November 2023 for RCTs and controlled observational studies 2013–23 for SRs/MAs and clinical practice guidelines	Prior to 1960 for RCTs and controlled observational studies Prior to 2013 for SRs/MAs and clinical practice guidelines

Abbreviations: MAs: Meta-analyses; RCTs: Randomized controlled trials; SRs: Systematic reviews

Data Extraction

Data were extracted into Word tables. For each included primary study, the following information was included:

- General study characteristics: author, year of publication, objective, country
- Study design: study design, study dates, sample size, followup duration, setting
- Study population characteristics: age, gender/sex, race/ethnicity, smoking/tobacco use, comorbidities, hemophilia treatment received (clotting factors VIII, IX, XI; desmopressin; antifibrinolytic drugs; gene therapy)
- Intervention: dental services including routine professional dental care (exam/cleaning), any dental treatment, any patient education on oral health by a dentist or dental professional, timing of dental services
- Outcomes of interest: serious bleeding episodes, joint damage, alloantibody (inhibitor) development, infection, cardiovascular event, quality of life, serious adverse events, and success of hemophilia treatment

For each included SR, we extracted the date ranges of the literature search, the primary conclusions, and any strength of evidence assessment that was performed.

Quality Assessment

Methodological quality of included primary studies was assessed using United States Preventive Services Task Force (USPSTF) criteria.¹¹ This assessment instrument is widely recognized, easy to apply, and readily understandable for diverse stakeholder groups.

Data Synthesis

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was developed to illustrate the number of studies involved in the literature search and each step of the study selection process.¹² Data were compiled into evidence tables and synthesized narratively and visually, whenever appropriate. We highlighted any gaps in evidence, with attention given to direct comparisons between receipt of dental care and hemophilia treatment success. We did not conduct meta-analysis or perform GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) Strength of the Evidence Base assessment. The clinical subject matter expert reviewed the final report to ensure accurate clinical contextualization of any findings.

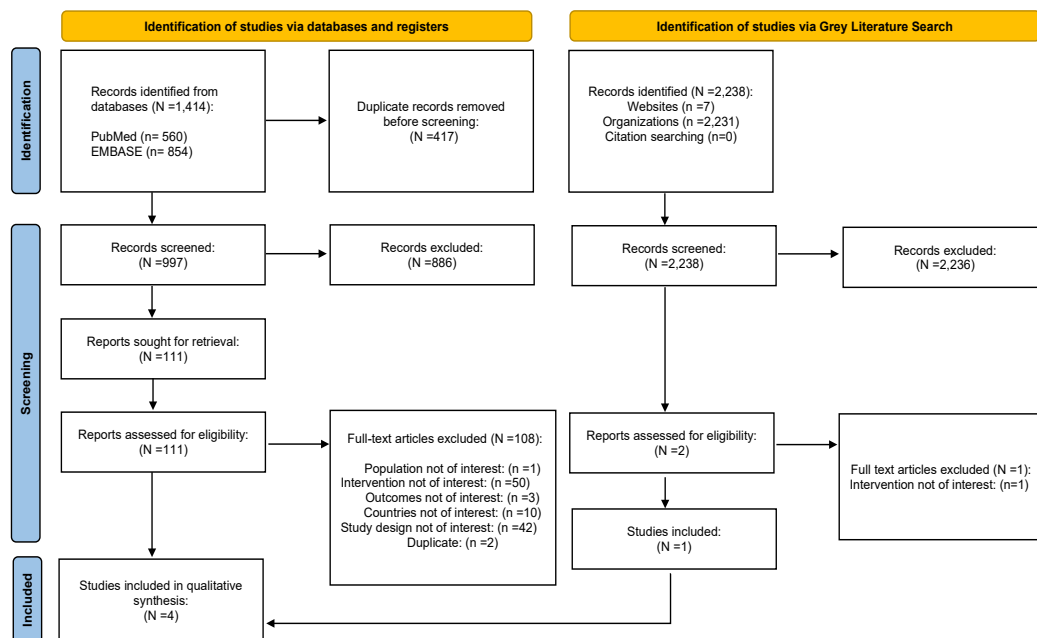


Results

Literature Search

Figure 2 presents the PRISMA flow diagram summarizing the results of the literature search. An electronic database search was conducted on November 30, 2023. A total of 1,414 citations were found in the database search. Among them, 417 were duplicates and were excluded. After de-duplication, 997 titles and abstracts were screened for eligibility, and 886 abstracts were excluded. Of the 111 full-text articles retrieved and reviewed for eligibility, 108 articles were excluded: 1 had irrelevant study population, 50 had intervention not of interest, 3 had outcomes not of interest, 42 had study design not of interest, 10 were conducted outside of countries of interest, and 2 were duplicates. The three studies excluded due to outcomes reported dental health status measured by plaque index or decay-missing-filled teeth index;¹³ the efficacy of dental splint usage in patients;¹⁴ and outpatient versus inpatient dental extractions.¹⁵ A list of references excluded at the full-text level along with their reasons for exclusion is available in Appendix D. Supplementary grey literature searches identified 2,238 records, of which 1 was assessed to be a relevant record. Thus, a total of four unique publications were included, extracted, and evaluated in this rapid response.

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram



Key Questions 1–4: Does Dental Care Before, During, or After Treatment of Hemophilia Improve Clinical Outcomes?

Our review did not identify any primary studies that evaluated whether dental services before, after, or during any type of hemophilia treatment affect clinical outcomes. No data synthesis regarding the dental management of hemophilia patients can be performed due to the lack of available literature at this time.

Key Question 5: Are There Any Dental Services Considered a Standard of Care for the Management of Hemophilia?

Our review identified four publications—two practice guidelines and two reviews with recommendations—that addressed dental care for patients with hemophilia. One practice guideline was published by the global collaboration group World Federation of Hemophilia (WFH),⁶ and another was authored by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Dental Working Party.¹⁶ The two reviews with recommendations were written by a group of Italian doctors who specialized in congenital hemophilia¹⁷ and a group of dentists in the United States.⁷ Two publications focused entirely on the dental management and care of hemophilia patients.^{7,16} Two publications addressed overall management of hemophilia patients such as economic factors, activities of daily living, psychological considerations, and dental care.^{6,17} For the purpose of this rapid response, we focused on the sections specific to dental care. One publication provided guidance on the pediatric population,¹⁷ two provided guidance on the adult population,^{7,16} and one provided information on both populations.⁶ Information from the two practice guidelines and the two reviews with recommendations are available in Appendix B, and Appendix C, respectively.

Practice Guidelines

The 3rd edition of the World Federation of Hemophilia (WFH) Guideline for the Management of Hemophilia devoted a subchapter, with 13 consensus-based recommendations, to dental care and management, oral care, and dental surgery and invasive procedures.⁶ WFH recognized people with hemophilia as a priority group because dental treatment in this population can cause severe and prolonged bleeding. Preventive care and patient education were highlighted as essential practices for severe and moderate hemophilia patients to avoid periodontal disease, gum bleeding, and the need for major dental surgical intervention. The guideline recommended that invasive dental procedures such as dental implantation, periodontal surgery, or gum biopsy be performed after consultation with a hematologist. WFH also recommended that systemic hemostatic measures be taken preoperatively, with consultation of a hematologist, to avoid hematomas during higher risk dental procedures such as nerve blocks, inferior alveolar dental block, and other intramuscular oral injections. As an adjunct treatment to factor replacement therapy in hemophilia patients undergoing dental care, WFH recommended the use of systemic or topical tranexamic acid, or EACA, both pre- and post-operatively to reduce the need for factor replacement therapy. Per the guidelines, recommendations made by WFH were consensus based, and were not graded because the evidence base was insufficient to conduct a meta-analysis. Overall, these recommendations were aimed at preventing bleeding during dental procedures, and not as guidelines to improve outcomes of hemophilia.⁶

The UKHCDO Dental Working Party created a consensus-based guideline for patients with hemophilia and other bleeding disorders.¹⁶ The guideline included 13 total key recommendations, with 3 focused on access to dental care, 1 on preventive care, and 9 on dental procedures. Authors emphasized the importance of preventive care education among hemophilia patients and encouraged the use of patient pamphlets. Dental care recommendations differed depending on severity of hemophilia. In dental procedures that required local anesthesia, recommendations for factor therapy differed for adults versus children—it was recommended that children on routine prophylaxis receive factor replacement therapy prior to administration of anesthesia. The guideline acknowledged that patients seeking dental care may already be on prophylactic factor regimens at least three times weekly. The guideline recommended that dental treatment be scheduled to occur in tandem with factor replacement therapy to minimize risks of dental treatment. Specifically, the UKHCDO stated that dental procedures should be performed as close to the time of administration of factor concentrate as possible, normally within 30 minutes to an hour. While the majority of the recommendations were consensus-based, authors provided GRADE ratings for the use of tranexamic acid (GRADE 1B), tranexamic acid mouthwash (GRADE 2C), and combination systemic and local antifibrinolytic therapy (GRADE 2C) among hemophilia patients undergoing dental care.¹⁶ Similar to the WFH guidelines, the UKHCDO guidelines focused on preventing complications during or after dental services, not using dental services as a strategy to improve hemophilia treatment outcomes.

Reviews With Recommendations

Halpern et al. published a review on the dental treatment and management options for surgical success in patients with hemophilia.⁷ The review stated that the dental management of a hemophilia patient should take into consideration severity of hemophilia, potential inhibitor levels, and any previous surgical interventions. Halpern et al. stated that a patient's factor levels should be at 70% to 80% of the normal range preoperatively based on the depth and type of dental procedure performed to prevent hemorrhage. The guideline emphasized that FVIII has a half-life of 6 to 16 hours and FIX has a half-life of 14 to 27 hours, suggesting that dental care should be done during factor replacement therapy treatment. Consultation with a patient's hematologist was recommended prior to the dental care to allow for an optimal surgical intervention.⁷

A review on hemophilia management for the pediatric population by Bertamino et al. included a section for dental care.¹⁷ Authors acknowledged the importance of prophylactic factor replacement treatment that is initiated prior to surgical intervention to prevent hemophilic atrophy. The review recommended that dental procedures, such as dental extractions or surgical procedures in the oral cavity, be conducted at a hemophilia treatment center. Also, the guideline stated that intra-papillary and intra-ligamentary injections as part of regular dental care should be administered under a factor cover between 20% and 40% to avoid hemorrhaging. Bertamino et al. stressed the importance of educating patients with hemophilia on proper oral hygiene and maintenance to prevent dental caries and periodontal disease. In addition to preventive hygiene, orthodontic appliances can be used to maintain optimal oral health, but care should be taken to not damage the gingiva and prevent further harm to the patient with hemophilia.¹⁷



Discussion

This rapid response sought to identify available evidence that informed the potential effect of dental care on hemophilia treatment outcomes, and to review standard of practice for dental care in this patient population. The current evidence on the effect of dental services on hemophilia treatment outcomes is lacking. Two hemophilia professional organizations published consensus-based guidelines that aimed at minimizing bleeding during or after dental treatment, not as a strategy to improve hemophilia treatment outcomes. The included guidelines varied in complexity and breadth, but consistently advocated for a specified coagulation factor level present prior to dental services or dental intervention. The stated goals of the recommended dental management of hemophilia patients were to prevent hemorrhage after dental intervention, to include consultation with a hematologist or bleeding disorder specialist to provide a personalized treatment plan, and to time dental care services to be performed during or shortly after factor replacement therapy.

The included publications shared the recommendation that patients with hemophilia undergoing dental services should consult with a hematologist or coordinate with a hemophilia treatment center. Dentists and hematologists were encouraged to participate in interdisciplinary collaboration to determine the best approach for dental work, whether patients were receiving treatment or not. Ultimately, the recommendation to perform dental services during hemophilia treatment with coagulation factor replacement therapy was shared by all included guidelines. All four reviewed publications focused on dental services among patients with hemophilia A and B, with little or no mention of hemophilia C.

In 2006 (prior to our publication year criterion), the WFH published a guideline specific to dental health management of hemophilia patients, which discussed the various aspects of dental care, including preventive measures, orthodontic treatment, anesthesia, and pain management.¹⁸ This guideline outlined specific factor level thresholds that were recommended to be present in a patient preoperatively. The guideline recommended a level that is 30% of normal clotting factor concentrates for infiltration anesthesia of lower jaw and periodontal curettage. However, factor level concentration can increase to 50-100% of normal during more invasive interventions. The more recent 3rd edition WFH guideline published in 2020, which was included in our review, reformed the previously set recommendation by advocating for a more individualized approach to dental care for hemophilia patients.⁶ The 3rd edition WFH guideline emphasized collaborative treatment planning with dentists and hematologists to develop the most appropriate factor clotting regimen for individual hemophilia patients undergoing dental care.⁶

Our grey literature search identified a guideline developed by the Medical and Scientific Advisory Council (MASAC) of the National Bleeding Disorder Foundation (formerly known as the National Hemophilia Foundation), in conjunction with the Health Resources and Services Administration (HRSA), International Society on Thrombosis and Haemostasis (ISTH), and Centers for Disease Control and Prevention (CDC).¹⁹ However, this guideline did not make recommendations for dental procedures in hemophilia patients undergoing factor replacement therapy. The treatment addressed in the included guidelines was coagulation factor replacement therapy and its relation to hemophilia patients' dental management.

This rapid response was strengthened by the comprehensive database search that covered 73 years of publications, as well as an extensive grey literature search that included sources from various professional organizations, agencies, and stakeholder groups. Our scope was not restricted to the United States, and hence allowed for a review of practice guidelines from established global collaborative groups. Despite the lack of primary evidence that informed the potential effect of dental care on

hemophilia treatment outcomes, all included consensus-based guidelines advocated for access to dental services and the inclusion of dental care as part of a multi-disciplinary approach to hemophilia management.



Conclusions

The body of evidence evaluating dental services before, during, or after the treatment of hemophilia is lacking in primary clinical data and is limited to available guidelines. Several clinical guidelines advocated for professional dental care to be performed during hemophilia treatment with clotting factor replacement therapy to minimize bleeding complications, not as a strategy to improve hemophilia treatment outcomes. Prophylactic treatment with factor replacement therapy remains the standard of care. However, when inhibitors are developed, alternative treatments can be utilized. Guidelines also recommended that dentists should work collaboratively with hematologists and other specialists when determining the appropriate timing and factor level needed in patients before performing dental services. The absence of primary clinical data assessing the benefit of dental care before, after, or during hemophilia treatment highlights a need for future research. Despite the lack of primary evidence that informed the potential effect of dental care on hemophilia treatment outcomes, all included guidelines advocated for access to dental services and the inclusion of dental care as part of a multidisciplinary approach to hemophilia management.



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(<https://www.hemophilia.ca/>).

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This Rapid Response was prepared by the AHRQ Evidence-based Practice Center (EPC) Program using streamlined literature review methods to assist end-users in making specific decisions in a limited timeframe. To shorten timelines, reviewers made strategic choices about which processes to abridge compared to a comprehensive systematic review. The adaptations made for expediency may limit the certainty and generalizability of the findings from the review.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Afterword

Recognized for excellence in conducting comprehensive systematic reviews, the Agency for Healthcare Research and Quality (AHRQ) is expanding its portfolio to include rapid evidence products. The program has begun to develop a range of rapid evidence products to assist end-users in making specific decisions in a limited timeframe.

To shorten timelines, reviewers must make strategic choices about which processes to abridge. Common adaptations include: narrowly focusing questions, limiting the number of databases searched and/or modifying search strategies, using a single reviewer and/or abstractor with a second to provide verification, and restricting to studies published in the English language. However, these adaptations may limit the certainty and generalizability of the review findings, particularly in areas with a large literature base. Transparent reporting of the methods used, the resulting limitations of the evidence synthesis, and the quality of included studies is extremely important. While tradeoffs will likely differ for each topic, they are described so readers can adjudicate the limitations of the findings of the review.

AHRQ expects that these rapid evidence products will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to AHRQ.

If you have comments on this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Appendix A. Search Strategy

The International Consulting Associates, Inc., Medical Librarian conducted searches of the peer-reviewed and grey literature, following established systematic review protocols. Searches were conducted of the following biomedical databases: MEDLINE (PubMed interface) and Embase for practice guidelines, systematic reviews, randomized controlled trials and practice guidelines. The search strategies used a combination of medical subject headings (i.e., controlled vocabularies) and keywords, and were written in the syntax of each database. The search strategies used terms for the intervention and condition as well as Boolean operators. All search results were limited to the English language and human species. Searches were restricted to the date range of 1960 to 2023 for RCTs and controlled observational studies and 2013 to 2023 for SRs and clinical practice guidelines. This was done to ensure the literature was relevant to current trends.

Tables A-1 to A-5 depict the search strategies and report results for searches in databases before deduplication.

Table A-1. PubMed search history on November 30, 2023

Search Number	Query	Results
1	"Dental Prophylaxis"[Mesh] OR "Periodontal Diseases"[Mesh:NoExp] OR "dental assess"[Title/Abstract:~3] OR "dental assessment"[Title/Abstract:~3] OR "dental assessments"[Title/Abstract:~3] OR "dental care"[Title/Abstract:~3] OR "dental consult"[Title/Abstract:~3] OR "dental consults"[Title/Abstract:~3] OR "dental consultation"[Title/Abstract:~3] OR "dental consultations"[Title/Abstract:~3] OR "dental evaluate"[Title/Abstract:~3] OR "dental evaluates"[Title/Abstract:~3] OR "dental evaluation"[Title/Abstract:~3] OR "dental evaluations"[Title/Abstract:~3] OR "dental foci"[Title/Abstract:~3] OR "dental focus"[Title/Abstract:~3] OR "dental health"[Title/Abstract:~3] OR "dental infection"[Title/Abstract:~3] OR "dental infections"[Title/Abstract:~3] OR "dental disease"[Title/Abstract:~3] OR "dental diseases"[Title/Abstract:~3] OR "dental inflammatory"[Title/Abstract:~3] OR "dental inflammation"[Title/Abstract:~3] OR "dental inflammations"[Title/Abstract:~3] OR "dental management"[Title/Abstract:~3] OR "dental screen"[Title/Abstract:~3] OR "dental screens"[Title/Abstract:~3] OR "dental screening"[Title/Abstract:~3] OR "dental screenings"[Title/Abstract:~3] OR "dental treat"[Title/Abstract:~3] OR "dental treats"[Title/Abstract:~3] OR "dental treatment"[Title/Abstract:~3] OR "dental treatments"[Title/Abstract:~3] OR "dental treating"[Title/Abstract:~3] OR "dental caries"[Title/Abstract:~3] OR "dental cavity"[Title/Abstract:~3] OR "dental cavities"[Title/Abstract:~3] OR "dental caries"[Title/Abstract:~3] OR "dental extracted"[Title/Abstract:~3] OR "dental extraction"[Title/Abstract:~3] OR "dental extractions"[Title/Abstract:~3] OR "dental prophylaxis"[Title/Abstract:~3] OR "dental prophylaxes"[Title/Abstract:~3] OR "dental prophylactic"[Title/Abstract:~3] OR "oral assess"[Title/Abstract:~3] OR "oral assessment"[Title/Abstract:~3] OR "oral assessments"[Title/Abstract:~3] OR "oral care"[Title/Abstract:~3] OR "oral consult"[Title/Abstract:~3] OR "oral consults"[Title/Abstract:~3] OR "oral consultation"[Title/Abstract:~3] OR "oral consultations"[Title/Abstract:~3] OR "oral evaluate"[Title/Abstract:~3] OR "oral evaluates"[Title/Abstract:~3] OR "oral evaluation"[Title/Abstract:~3] OR "oral evaluations"[Title/Abstract:~3] OR "oral foci"[Title/Abstract:~3] OR "oral focus"[Title/Abstract:~3] OR "oral health"[Title/Abstract:~3] OR "oral infection"[Title/Abstract:~3] OR "oral infections"[Title/Abstract:~3] OR "oral disease"[Title/Abstract:~3] OR "oral diseases"[Title/Abstract:~3] OR "oral inflammatory"[Title/Abstract:~3] OR "oral inflammation"[Title/Abstract:~3] OR "oral inflammations"[Title/Abstract:~3] OR "oral management"[Title/Abstract:~3] OR "oral screen"[Title/Abstract:~3] OR "oral screens"[Title/Abstract:~3] OR "oral screening"[Title/Abstract:~3] OR "oral screenings"[Title/Abstract:~3] OR "oral treat"[Title/Abstract:~3] OR "oral treats"[Title/Abstract:~3] OR "oral	558,697

Search Number	Query	Results
	<p>treatment"[Title/Abstract:~3] OR "oral treatments"[Title/Abstract:~3] OR "oral treating"[Title/Abstract:~3] OR "oral caries"[Title/Abstract:~3] OR "oral cavity"[Title/Abstract:~3] OR "oral cavities"[Title/Abstract:~3] OR "oral caries"[Title/Abstract:~3] OR "oral extracted"[Title/Abstract:~3] OR "oral extraction"[Title/Abstract:~3] OR "oral extractions"[Title/Abstract:~3] OR "oral prophylaxis"[Title/Abstract:~3] OR "oral prophylaxes"[Title/Abstract:~3] OR "oral prophylactic"[Title/Abstract:~3] OR "periodontal assess"[Title/Abstract:~3] OR "periodontal assessment"[Title/Abstract:~3] OR "periodontal assessments"[Title/Abstract:~3] OR "periodontal care"[Title/Abstract:~3] OR "periodontal consult"[Title/Abstract:~3] OR "periodontal consults"[Title/Abstract:~3] OR "periodontal consultation"[Title/Abstract:~3] OR "periodontal consultations"[Title/Abstract:~3] OR "periodontal evaluates"[Title/Abstract:~3] OR "periodontal evaluation"[Title/Abstract:~3] OR "periodontal evaluations"[Title/Abstract:~3] OR "periodontal foci"[Title/Abstract:~3] OR "periodontal focus"[Title/Abstract:~3] OR "periodontal health"[Title/Abstract:~3] OR "periodontal infection"[Title/Abstract:~3] OR "periodontal infections"[Title/Abstract:~3] OR "periodontal disease"[Title/Abstract:~3] OR "periodontal diseases"[Title/Abstract:~3] OR "periodontal inflammatory"[Title/Abstract:~3] OR "periodontal inflammation"[Title/Abstract:~3] OR "periodontal inflammations"[Title/Abstract:~3] OR "periodontal management"[Title/Abstract:~3] OR "periodontal screen"[Title/Abstract:~3] OR "periodontal screens"[Title/Abstract:~3] OR "periodontal screening"[Title/Abstract:~3] OR "periodontal screenings"[Title/Abstract:~3] OR "periodontal treat"[Title/Abstract:~3] OR "periodontal treats"[Title/Abstract:~3] OR "periodontal treatment"[Title/Abstract:~3] OR "periodontal treatments"[Title/Abstract:~3] OR "periodontal treating"[Title/Abstract:~3] OR "periodontal caries"[Title/Abstract:~3] OR "periodontal cavity"[Title/Abstract:~3] OR "periodontal cavities"[Title/Abstract:~3] OR "periodontal caries"[Title/Abstract:~3] OR "periodontal extracted"[Title/Abstract:~3] OR "periodontal extraction"[Title/Abstract:~3] OR "periodontal extractions"[Title/Abstract:~3] OR "periodontal prophylaxis"[Title/Abstract:~3] OR "periodontal prophylaxes"[Title/Abstract:~3] OR "periodontal prophylactic"[Title/Abstract:~3] OR molar[Title/Abstract] OR odont*[Title/Abstract] OR periodont*[Title/Abstract] OR pulpitis[Title/Abstract] OR "root canal"[Title/Abstract] OR stomatitis[Title/Abstract] OR teeth[Title/Abstract] OR tooth*[Title/Abstract] OR "dental care"[Title/Abstract] OR "dental disease"[Title/Abstract] OR "dental health"[Title/Abstract] OR "dental hygiene"[Title/Abstract] OR "dental infection"[Title/Abstract] OR "oral care"[Title/Abstract] OR "oral disease"[Title/Abstract] OR "oral health"[Title/Abstract] OR "oral hygiene"[Title/Abstract] OR "oral infection"[Title/Abstract] OR gingivitis[Title/Abstract]</p>	

Search Number	Query	Results
2	"Hemophilia A"[Mesh:NoExp] OR "Hemophilia B"[Mesh:NoExp] OR "Factor XI Deficiency"[Mesh:NoExp] OR hemophilia*[Title/Abstract] OR Haemophilia*[Title/Abstract] OR "Factor VIII Deficiency"[Title/Abstract] OR "Factor IX Deficiencies"[Title/Abstract] OR "Factor IX Deficiency"[Title/Abstract] OR "Plasma Thromboplastin Component Deficiency"[Title/Abstract] OR "F9 Deficiency"[Title/Abstract] OR "F9 Deficiencies"[Title/Abstract:~3] OR "Christmas Disease"[Title/Abstract] OR "subhemophilia"[Title/Abstract] OR "subhaemophilia"[Title/Abstract] OR "ahf deficiency"[Title/Abstract] OR "ahg deficiency"[Title/Abstract] OR "blood clotting factor 8 deficiency"[Title/Abstract:~3] OR "blood clotting factor viii deficiency"[Title/Abstract:~3] OR "congenital antihemophilic factor deficiency"[Title/Abstract:~3] OR "congenital antihemophilic globulin deficiency"[Title/Abstract:~3] OR "congenital antihemophilic globulin deficiency"[Title/Abstract:~3] OR "congenital blood clotting factor 8 deficiency"[Title/Abstract:~3] OR "congenital blood clotting factor viii deficiency"[Title/Abstract:~3] OR "congenital clotting factor 8 deficiency"[Title/Abstract:~3] OR "factor viii deficiency"[Title/Abstract] OR hemophylia*[Title/Abstract] OR "mckusick 30670"[Title/Abstract:~3] OR "blood clotting factor 9 deficiency"[Title/Abstract:~3] OR "blood clotting factor ix deficiency"[Title/Abstract:~3] OR "congenital blood clotting factor ix deficiency"[Title/Abstract:~3] OR "congenital clotting factor 9 deficiency"[Title/Abstract:~3] OR "mckusick 30690"[Title/Abstract:~3] OR "blood clotting factor xi deficiency"[Title/Abstract:~3] OR "clotting factor 11 deficiency"[Title/Abstract:~3] OR "factor xi deficiency"[Title/Abstract] OR hemophilioid[Title/Abstract] OR haemophilioid[Title/Abstract] OR "plasma thromboplastin antecedent deficiency"[Title/Abstract] OR "rosenthal disease"[Title/Abstract] OR "rosenthal factor deficiency"[Title/Abstract:~3] OR "blood clotting factor 11 deficiency"[Title/Abstract:~3] OR "Factor Eleven Deficiencies"[Title/Abstract:~3] OR "Factor 11 Deficiency"[Title/Abstract] OR "Factor Eleven Deficiency"[Title/Abstract:~3] OR "Rosenthal's Syndrome"[Title/Abstract] OR "Rosenthal's Syndromes"[Title/Abstract:~3] OR "Rosenthals Syndrome"[Title/Abstract:~3] OR "Rosenthal Syndrome"[Title/Abstract] OR "Rosenthal Syndromes"[Title/Abstract] OR "Factor 11 Deficiencies"[Title/Abstract:~3] OR "Factor XI Deficiencies"[Title/Abstract:~3] OR Hemophilic[Title/Abstract] OR Haemophilic[Title/Abstract] OR hemophilia*[ot] OR Haemophilia*[ot] OR "Factor VIII Deficiency"[ot] OR "Factor IX Deficiency"[ot] OR "Christmas Disease"[ot] OR "factor viii deficiency"[ot] OR "factor xi deficiency"[ot] OR "plasma thromboplastin antecedent deficiency"[ot] OR "rosenthal disease"[ot] OR "Rosenthal's Syndrome"[ot] OR "Rosenthal Syndrome"[ot] OR Hemophilic[ot] OR Haemophilic[ot]	32,778
3	English[Language]	31,564,707
4	#1 AND #2 AND #3	570
5	((("Animals"[MESH] OR "Animal Experimentation"[MESH] OR "Models, Animal"[MESH] OR "Vertebrates"[MESH]) NOT ("Humans"[MESH] OR "Human experimentation"[MESH]))	5,165,346
6	#4 NOT #5	560

Table A-2. PubMed field tag key

PubMed Field Tag	Description
[Mesh]	Includes all MeSH terms found below the term in the MeSH hierarchy
[Mesh:NoExp]	Does NOT include MeSH terms found below the term in the MeSH hierarchy
[Title/Abstract]	Searches the title and abstracts of the bibliographic record
[Title/Abstract:~N]	PubMed proximity search operator where N=the maximum number of words appearing between the search terms

Table A-3. Embase search history on November 30, 2023

Search Number	Query	Results
#1	'hemophilia'/de OR 'hemophilia a'/de OR 'hemophilia b'/de OR 'blood clotting factor 11 deficiency'/de	49931
#2	hemophilia*:ab,ti,kw OR haemophilia*:ab,ti,kw OR hemophilic:ab,ti,kw OR haemophilic:ab,ti,kw OR 'rosenthal* syndrome*' OR 'christmas disease':ab,ti,kw OR 'subh*emophilia':ab,ti,kw OR hemophyllia*:ab,ti,kw OR haemophyllia*:ab,ti,kw OR 'mckusick 30670':ab,ti,kw OR 'mckusick 30690':ab,ti,kw OR hemophilioid:ab,ti,kw OR haemophilioid:ab,ti,kw OR 'rosenthal disease':ab,ti,kw OR ((ahf OR ahg OR 'factor 8' OR 'antih*emophilic factor' OR 'antih*emophilic globulin' OR 'factor viii' OR 'factor ix' OR 'factor ix' OR 'factor xi' OR 'plasma thromboplastin component' OR 'factor 8' OR 'factor 9' OR f9 OR 'factor 11' OR 'factor eleven' OR 'plasma thromboplastin antecedent' OR 'rosenthal factor') NEAR/2 (deficiency OR deficiencies))	48051
#3	#1 OR #2	56214
#4	'dental procedure'/de OR 'dental prevention'/exp OR 'tooth disease'/de OR 'periodontal disease'/exp OR 'dental health'/de OR 'dental examination'/exp	259661
#5	dentistry:ab,ti,kw OR ((dental OR tooth OR teeth OR oral) NEAR/2 (care OR caries OR esthetics OR aesthetics OR health OR service* OR technique* OR treat* OR procedure OR cavity OR cavities OR extract*))	399563
#6	'furcation defects':ab,ti,kw OR 'mesial movement of teeth':ab,ti,kw OR 'paradontopathy':ab,ti,kw OR 'paraodontopathy':ab,ti,kw OR 'parodontopathy':ab,ti,kw OR 'periodontopathy':ab,ti,kw OR 'pericoronitis':ab,ti,kw OR ((dental OR root OR tooth OR parodont* OR parodont* OR peridont* OR parodont* OR teeth OR gingiva*) NEAR/2 (disease* OR disorder* OR leakage OR resorption OR ankylos*s OR dystopia OR loss OR migrat* OR mobility OR atrophy OR atroph* OR infect* OR recession OR inflam* OR exfoliation OR health))	132637
#7	(dental OR periodont*) NEAR/2 (assessment* OR exam* OR health OR consult* OR evaluat* OR management OR screening*)	55068
#8	'fluoridation':ab,ti,kw OR 'toothbrushing':ab,ti,kw OR 'tooth brushing':ab,ti,kw OR ((dental OR periodontal OR tooth OR teeth OR mouth OR 'full-mouth') NEAR/2 ('check up' OR 'checkup' OR 'check-up' OR 'disease prevention' OR prevention OR polish* OR cleaning OR prophylaxis OR debridement OR scaling OR brushing))	29792
#9	#4 OR #5 OR #6 OR #7 OR #8	548652
#10	english:la	37562615
#11	#3 AND #9 AND #10	1518
#12	('animal'/exp OR 'animal experiment'/de OR 'nonhuman'/de OR 'invertebrate'/exp OR 'amphibia'/exp OR 'fish'/exp OR 'boreoeutheria'/exp OR 'afrotheria'/exp OR 'dermoptera'/exp OR 'glires'/exp OR 'scandentia'/exp OR 'sauropsid'/exp OR 'laurasiatheria'/exp OR 'ungulate'/exp OR 'reptile'/exp OR 'cercopithecidae'/exp OR 'marsupial'/exp OR 'monotremate'/exp OR 'prosimian'/exp OR 'tarsiiform'/exp OR 'hylobatidae'/exp OR 'xenarthra'/exp OR 'platyrrhini'/exp OR 'chimpanzee'/exp OR 'gorilla'/exp OR 'orang utan'/exp OR 'homo neanderthalensis'/exp OR 'cephalochordata'/exp OR 'hyperotreti'/exp OR 'urochordata'/exp OR 'ambulacraria'/exp OR 'coelomata'/exp OR 'protostomia'/exp OR 'pseudocoelomata'/exp OR 'coelenterate'/exp OR 'mesozoa'/exp OR 'placozoa'/exp OR 'porifera'/exp OR 'juvenile animal'/exp OR 'male animal'/exp OR 'female animal'/exp OR 'primate'/de OR 'haplorhini'/de OR 'mammal'/de OR 'catarrhini'/de OR 'simian'/de OR 'ape'/de OR 'amniote'/de OR 'tetrapod'/de OR 'vertebrate'/de OR 'chordata'/de OR 'deuterostomia'/de OR 'bilateria'/de OR 'therian'/de OR 'hominid'/de OR 'euarchontoglires'/de OR 'placental mammals'/de) NOT ('human'/exp OR 'human experiment'/de)	7878520
#13	#11 NOT #12	1504
#14	#11 NOT #12 AND ([article]/lim OR [article in press]/lim OR [review]/lim OR [preprint]/lim)	854

Table A-4. Embase field tag key

Embase Field Tag	Description
/de	Index term
/exp	Exploded terms
/lim	Limit
:ab	Abstract
:ti	Title
:kw	Author keyword
NEAR/n	Requests terms that are within 'n' words of each other in either direction
*	Wildcard for variable truncation (i.e., one or more letters)

Table A-5. Grey literature search strategy

Date	Database Name and URL	Search Strategy(s)/Words Searched Including (if Applicable) How Items Were Selected	# of Items Retrieved/Search Results
2023-11-3	ClinicalTrials.gov https://classic.clinicaltrials.gov	1. AREA[ConditionSearch] Hemophilia AND AREA[InterventionSearch] (dental OR periodontal OR teeth OR tooth) 1. AREA[ConditionSearch] Hemophilia AND AREA[InterventionSearch] (dental AND (care OR service OR services OR hygiene))	1. 6 1. 1
2023-11-3	World Federation of Hemophilia	http://www.wfh.org 1. http://www.wfh.org internal website search: "dental care" 2. http://www.wfh.org internal website search: "oral care" 3. http://www.wfh.org internal website search: dental 4. http://www.wfh.org internal website search: periodontal 5. http://www.wfh.org internal website search: "dental health" 6. http://www.wfh.org internal website search: "oral health"	1. 3 2. 1 3. 16 4. 1 5. 0 6. 6
2023-11-3	National Bleeding Disorders Foundation	www.hemophilia.org 1. Hemophilia.org internal website search: dental 2. Hemophilia.org internal website search: periodontal 3. Hemophilia.org internal website search: "dental health"	1. 43 2. 2 3. 26

Date	Database Name and URL	Search Strategy(s)/Words Searched Including (if Applicable) How Items Were Selected	# of Items Retrieved/Search Results
2023-11-3	National Organization for Rare Disorders	https://rarediseases.org 1. Rarediseases.org internal website search: "dental health" 2. Rarediseases.org internal website search: "oral health" 3. Rarediseases.org internal website search: periodontal	1. 0 2. 3 3. 2
2023-11-3	World Health Organization	www.who.int 1. Who.int internal website search: hemophilia dental 2. Who.int internal website search: hemophilia AND (dental OR oral OR periodontal)	1. 0 2. 1,560
2023-11-3	Centers for Disease Control and Prevention	www.cdc.gov Cdc.gov internal website Advanced Search: hemophilia AND (dental OR oral OR periodontal)	# of retrievals too many to count
2023-11-3	American Dental Association	www.ada.org 1. Ada.org internal website search: hemophilia Ada.org internal website search: hemophiliac	1. 2 2. 0
2023-11-3	American Academy of Pediatric Dentistry	www.aapd.org 1. Aapd.org internal website search: hemophilia 2. Aapd.org internal website search: hemophiliac	1. 6 2. 2
2023-11-3	American Society of Hematology	www.hematology.org 1. Hematology.org internal website search: hemophilia AND dental 2. Hematology.org internal website search: hemophilia AND periodontal	1. 28 2. 370
2023-12-1	European Haemophilia Consortium	http://www.ehc.eu/ 1. www.ehc.eu internal website search: dental care 2. www.ehc.eu internal website search: "dental care" 3. www.ehc.eu internal website search: oral care 4. www.ehc.eu internal website search: "oral care" 5. www.ehc.eu internal website search: "oral hygiene" 6. www.ehc.eu internal website search: periodontal	1. 10 2. 8 3. 10 4. 2 5. 1 6. 0

Date	Database Name and URL	Search Strategy(s)/Words Searched Including (if Applicable) How Items Were Selected	# of Items Retrieved/Search Results
2023-12-1	Haemophilia Scotland	https://haemophilia.scot/ 1. Haemophilia.scot internal website search: dental 2. Haemophilia.scot internal website search: "dental care" 3. Haemophilia.scot internal website search: "oral care" 4. Haemophilia.scot internal website search: "oral hygiene" 5. Haemophilia.scot internal website search: periodontal	1. 6 2. 6 3. 2 4. 4 5. 4
2023-12-1	Haemnet	https://www.haemnet.com/	No internal website search functionality
2023-12-1	Hemophilia Alliance	https://hemoalliance.org/	No internal website search functionality
2023-12-1	National Heart, Lung, and Blood Institute (NHLBI)	https://www.nhlbi.nih.gov/ 1. Nhlbi.nih.gov internal website search: hemophilia dental 2. Nhlbi.nih.gov internal website search: hemophilia oral 3. Nhlbi.nih.gov internal website search: hemophilia periodontal	1. 7 2. 7 3. 1
2023-12-1	Haemophilia Foundation Australia	https://www.haemophilia.org.au/ 1. Haemophilia.org.au internal website search: dental 2. Haemophilia.org.au internal website search: oral 3. Haemophilia.org.au internal website search: periodontal	1. 55 2. 24 3. 2
2023-12-1	Irish Haemophilia Society	https://haemophilia.ie/ 1. Haemophilia.ie internal website search: "dental care" 2. Haemophilia.ie internal website search: "oral health" 3. Haemophilia.ie internal website search: "oral hygiene" 4. Haemophilia.ie internal website search: periodontal	1. Undetermined 2. 3 3. 1 4. 0
2023-12-1	Canadian Hemophilia Society	https://www.hemophilia.ca/ 1. Hemophilia.ca internal website search: "dental care" 2. Hemophilia.ca internal website search: "oral care" 3. Hemophilia.ca internal website search: "oral health" 4. Hemophilia.ca internal website search: "oral hygiene" 5. Hemophilia.ca internal website search: periodontal	1. 7 2. 0 3. 0 4. 0 5. 0

Appendix B. Guidelines From Relevant Organizations and Professional Societies

Table B-1. Recommendations from relevant organizations and professional societies

Note: References are located in the reference list in the body of the report.

Recommendations on Dental Services	Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
Organizations that provided recommendations on dental services	World Federation of Hemophilia ⁶	WFH Guidelines for the Management of Hemophilia, 3rd edition	2020	People with hemophilia undergoing dental care	<p>"For patients with hemophilia, the WFH recommends that dental extraction or other invasive procedures within the oral cavity (e.g., dental implantation, periodontal surgery, or gum biopsy) be performed only with a personalized plan for hemostasis management in consultation with a hematologist"</p> <p>"For patients with hemophilia requiring higher-risk intramuscular oral injections commonly associated with the provision of surgical dentistry (such as inferior alveolar dental block [IDB], superior alveolar nerve block, or injections in the floor of the mouth or vascular lingual tissues), the WFH recommends systemic hemostatic measures preoperatively to avoid the risk of hematoma. These measures should be established in consultation with the hematologist."</p>	Not applicable

Recommendations on Dental Services	Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
	United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Dental Working Party ¹⁴	Guidance on the dental management of patients with haemophilia and congenital bleeding disorders. British dental journal, 215(10), 497-504.	2013	People with hemophilia undergoing dental care.	<p>"Patients may be on prophylactic factor regimens. This involves the administration of factor replacement therapy prescribed on an individual basis, usually on alternate days or three times weekly, to minimize spontaneous bleeding. It is important that dental treatment should be scheduled to take place at times of factor administration to minimize the risks of therapies and reduce overall treatment costs."</p> <p>"The timing of administration is important as factor levels will decline, therefore dental procedures should be performed as close to the time of administration of factor concentrate as possible, normally within 30 minutes to an hour."</p>	Not applicable
<u>Organizations that did not provide recommendations on dental services</u>	National Bleeding Disorders Foundation, Health Resources and Services Administration (HRSA), International Society on Thrombosis and Haemostasis (ISTH), and the Centers for Disease Control (CDC) ¹⁹	Medical and Scientific Advisory Council Document 269- Standards and Criteria for the Care of Persons with Congenital Bleeding Disorders	2022	People with congenital bleeding disorders	The guideline document does not make recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable

Recommendations on Dental Services	Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
	National Organization for Rare Disorders²⁰	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	World Health Organization²¹	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	Centers for Disease Control and Prevention¹	Not applicable	NA	Not applicable	The guideline document does not make recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	American Dental Association²²	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	American Academy of Pediatric Dentistry²³	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	American Society of Hematology²⁴	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	European Haemophilia Consortium²⁵	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable

Recommendations on Dental Services	Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
	Haemophilia Scotland²⁶	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	Haemnet²⁷	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	Hemophilia Alliance²⁸	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	National Heart, Lung, and Blood Institute (NHLBI)²⁹	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	Haemophilia Foundation Australia³⁰	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	Irish Haemophilia Society³¹	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable
	Canadian Hemophilia Society³²	Not applicable	NA	Not applicable	There is no guideline document that makes recommendations for dental procedures in hemophilia patients who are undergoing factor replacement treatment.	Not applicable

Appendix C. Recommendations of Dental Care for Hemophilia Patients From Review Articles

Table C-1. Recommendations of dental care for hemophilia patients from review articles

Publication	Type of Treatment	Recommendation of Care	Quality of Treatment/ Reduced Likelihood of Hemorrhage	Improved Clinical Outcomes/Success of Medical Procedure	Standard of Care for Dental Management of Hemophiliac Patients	Additional Comments
Halpern, L. R., Adams, D. R., & Clarkson, E. (2020). Treatment of the dental patient with bleeding dyscrasias: etiologies and management options for surgical success in practice. Dental Clinics, 64(2), 411-434. ⁷	Factor VIII or IX	<p>"In general, the goal is to raise factor levels at 70% to 80% preoperatively based upon the depth of surgical intervention (i.e., dentoalveolar surgery requires 50% to 70% factor present before and 50% 5 to 7 days postoperatively). Factor VIII has a half-life of 6 to 16 hours, while Factor IX has a half-life of 14 to 27 hours. This will determine the degree of factor replacement required."</p> <p>"The specific guidelines for factor replacement suggest a dose of 1.0 IU/kg of factor VIII to increase factor VIII by 2%. Factor IX requires 1.0 IU/kg to increase by 1%. A dose of 50 IU/kg of factor VIII and 1000 IU/kg of factor IX concentrate is required for major surgery. The administration of factor concentrate requires a window of 10 to 20 minutes to avoid decreased effectiveness and as such, repeated dosing every 12 hours in hemophilia A and 24 hours in hemophilia B"</p>	"The treatment of inhibitor adverse events is based on immune tolerance induction (ITI) that will prevent active bleeding during surgery. Patients who suffer from hemophilia A or B can receive high doses of factor VIII or IX, respectively, to override the inhibitor's ability to produce enough IgG as a causation for increased bleeding"	"Treatment success will be predicated upon plasma factor peak serum levels measured over a time period of 30 minutes, with factor recovery at 66% better than predicted, and inhibitor titers less than 20%."	Not applicable	Not applicable

Publication	Type of Treatment	Recommendation of Care	Quality of Treatment/ Reduced Likelihood of Hemorrhage	Improved Clinical Outcomes/Success of Medical Procedure	Standard of Care for Dental Management of Hemophiliac Patients	Additional Comments
Bertamino, M., Riccardi, F., Banov, L., Svahn, J., & Molinari, A. C. (2017). Hemophilia care in the pediatric age. Journal of clinical medicine, 6(5), ¹⁷	Coagulation factor replacement therapy	"Infiltration, intra-papillary, and intra-ligamentary injections are often done under factor cover (20–40%), though it may be possible for those with adequate experience to administer these injections without it. It is advisable that complicated dental procedures, such as dental extraction or surgical procedures carried out within the oral cavity, should be performed in a Hemophilia Treatment Center."	Not applicable	Not applicable	Not applicable	Not applicable

Appendix D. Studies Excluded at Full-Text Screening

Table D-1. Studies excluded at full-text screening

Article	Reason for Exclusion
Abed, H.,Ainousa, A. (2017). Dental management of patients with inherited bleeding disorders: a multidisciplinary approach Gen Dent, 65(6), 56-60	Study design not of interest
Ah Pin, P. J. (1987). The use of intraligamental injections in haemophiliacs British dental journal, 162(4), 151-152	Intervention not of interest
Alpkiliç Baskirt, E.,Ak, G.,Zulfikar, B. (2009). Oral and general health-related quality of life among young patients with haemophilia Haemophilia, 15(1), 193-8	Country not of interest
Alqahtani, H. (2019). Medically compromised patients in orthodontic practice: Review of evidence and recommendations International orthodontics, 17(4), 776-788	Intervention not of interest
Arrieta-Blanco, J. J.,Oñate-Sánchez, R.,Martínez-López, F.,Oñate-Cabrerizo, D.,Cabrerizo-Merino, M. C. (2014). Inherited, congenital and acquired disorders by hemostasis (vascular, platelet & plasmatic phases) with repercussions in the therapeutic oral sphere Medicina Oral, Patología Oral y Cirugía Bucal, 19(3), e280-e28	Population not of interest
Bartlett, J. A.,Sweeney, J. D.,Sadowsky, D. (1985). Exodontia in combined factor V and factor VIII deficiency Journal of Oral and Maxillofacial Surgery, 43(7), 537-539	Study design not of interest
Berntorp, E.,Dargaud, Y.,Hart, D.,Lobet, S.,Mancuso, M. E.,d'Oiron, R.,Perry, D.,Pollard, D.,van den Berg, M.,Blatný, J.,Chambost, H.,Doria, A. S.,Holme, P. A.,Kaczmarek, R.,Mantovani, L.,McLaughlin, P.,Nanayakkara, L.,Petrini, P.,Sanní, T.,Laane, E.,Maia, R.,Dettoraki, A.,Farrell, A.,Halimeh, S.,Raza, S.,Taylor, S. (2017). The second Team Haemophilia Education Meeting, 2016, Frankfurt, Germany European Journal of Haematology, 98(#issue#), 1-15	Study design not of interest
Björlin, G.,Nilsson, I. M. (1973). Tooth extractions in hemophiliacs after administration of a single dose of factor VIII or factor IX concentrate supplemented with AMCA Oral Surg Oral Med Oral Pathol, 36(4), 482-9	Intervention not of interest
Brewer, A. K.,Giangrande, P. L. (2005). Good dental care Br Dent J, 198(4), 217	Study design not of interest
Brewer, A. K.,Roebuck, E. M.,Donachie, M.,Hazard, A.,Gordon, K.,Fung, D.,Clarkson, J. (2003). The dental management of adult patients with haemophilia and other congenital bleeding disorders Haemophilia, 9(6), 673-7	Intervention not of interest
Brown, M. C.,Hastie, E.,Shumake, C.,Waters, B.,Sidonio, R. F., Jr. (2022). Dental habits and oral health in children and adolescents with bleeding disorders: A single-institution cross-sectional study Haemophilia, 28(1), 73-79	Intervention not of interest
Chaichareon, P.,Im-Erbsin, T. (1993). Comprehensive care of hemophilia: role of the dentist Southeast Asian J Trop Med Public Health, 24 Suppl 1(#issue#), 34-6	Country not of interest
CHIONO, O. (1973). Evaluation of Dental Procedures on Hemophilic Patients in a Comprehensive Program for the Care of Hemophilia (Part 3). The Journal of Nihon University School of Dentistry, 15(2), 58-69.	Study design not of interest
Chuansumrit, A.,Hathirat, P.,Pintadit, P.,Isarangura, P. (1993). Response of patients with bleeding disorder to DDAVP administration The Southeast Asian journal of tropical medicine and public health, 24 Suppl 1(#issue#), 174-179	Country not of interest
Clinical relevance of isolated prolongation of the activated partial thromboplastin time in a cohort of adults undergoing surgical procedures Tagariello, G.,Radossi, P.,Salviato, R.,Zardo, M.,De Valentin, L.,Basso, M.,Castaman, G.	Intervention not of interest

Article	Reason for Exclusion
Croll, T. P., Macko, D. J., Hoyer, L. W. (1978). Dental treatment for a hemophilia A patient with circulating antibodies to factor VIII J Pedod, 2(4), 344-52	Intervention not of interest
de Moerloose, P., Fischer, K., Lambert, T., Windyga, J., Batorova, A., Lavigne-Lissalde, G., Rocino, A., Astermark, J., Hermans, C. (2012). Recommendations for assessment, monitoring and follow-up of patients with haemophilia Haemophilia, 18(3), 319-25	Intervention not of interest
El Batawi, H. Y. (2013). Minimizing the risk of perioperative bleeding in a child with hemophilia A during dental rehabilitation under general anesthesia: a case report. International Journal of Clinical Pediatric Dentistry, 6(3), 217.	Study design not of interest
Escobar, M. A., Brewer, A., Caviglia, H., Forsyth, A., Jimenez-Yuste, V., Laudenbach, L., Lobet, S., McLaughlin, P., Oyesiku, J. O. O., Rodriguez-Merchan, E. C., Shapiro, A., Solimeno, L. P. (2018). Recommendations on multidisciplinary management of elective surgery in people with haemophilia Haemophilia, 24(5), 693-702	Study design not of interest
Evans, B. E. (1979). The role of the dentist in the comprehensive management of hemophilia. The Southeast Asian Journal of Tropical Medicine and Public Health, 10(2), 285-294.	Study design not of interest
Evans, B. E. (1977). Dental treatment for hemophiliacs: evaluation of dental program (1975-1976) at the Mount Sinai Hospital International Hemophilia Training Center Mt Sinai J Med, 44(3), 409-37	Other
Evans, B. E. (1977). The use of epsilon-aminocaproic acid for the management of hemophilia in dental and oral surgery patients J Am Dent Assoc, 94(1), 21	Study design not of interest
Evans, B. E. (1977). Considerations in the dental treatment of the hemophilic patient. Quintessence international, dental digest, 8(10), 117-120.	Study design not of interest
Evans, B. E. (1976). Consideration in the dental treatment of the hemophiliac patient J Dent Guid Counc Handicap, 15(2), 3-7	Intervention not of interest
Evans, B. E., Aledort, L. M., Klatell, J., Rubin, M. (1977). Dental care for hemophiliacs J Hosp Dent Pract, 11(2), 10-2	Intervention not of interest
Farrkh, A., Garrison, E., & Closmann, J. J. (2016). Dental surgical management of the patient with hemophilia. General dentistry, 64(4), 14-17.	Study design not of interest
Fiorillo, L., De Stefano, R., Cervino, G., Crimi, S., Bianchi, A., Campagna, P., Herford, A. S., Laino, L., Cicciù, M. (2019). Oral and Psychological Alterations in Haemophiliac Patients Biomedicine, 7(2), #Pages#	Intervention not of interest
Franchini, M., Rossetti, G., Tagliaferri, A., Pattacini, C., Pozzoli, D., Lorenz, C., Del Dot, L., Ugolotti, G., Dell'aringa, C., Gandini, G. (2005). Dental procedures in adult patients with hereditary bleeding disorders: 10 years experience in three Italian Hemophilia Centers Haemophilia, 11(5), 504-9	Intervention not of interest
Frachon, X., Pommereuil, M., Berthier, A. M., Lejeune, S., Hourdin-Eude, S., Quéro, J., ... & Garnier, J. (2005). Management options for dental extraction in hemophiliacs: a study of 55 extractions (2000-2002). Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 99(3), 270-275.	Intervention not of interest
Gaddam, K. R., Nuvvula, S., Nirmala, S., Kamatham, R. (2014). Oral health status among 6- to 12-year-old haemophilic children--an educational intervention study Haemophilia, 20(4), e338-41	Country not of interest
Gascoigne, E. W., Dash, C. H., Harman, C., Wilmot, D. (2004). A retrospective survey on the safety of Replenate®, a high-purity factor VIII concentrate Pharmacoepidemiology and Drug Safety, 13(4), 243-252	Intervention not of interest
Gascoigne, E. W., Dash, C. H., Harman, C., Wilmot, D. (2004). A retrospective survey on the safety of Replenine, a high-purity factor IX concentrate Pharmacoepidemiol Drug Saf, 13(3), 187-95	Duplicate
Geffner, I., & Porteous, J. R. (1981). Haemorrhage and pain control in conservative dentistry for haemophiliacs. British dental journal, 151(8), 256-258.	Study design not of interest
Glogoff, M., Baum, S. M., Sussman, R., Stewart, S., & Stoopack, J. C. (1972). Management of the hemophilic oral surgery patient. Journal of oral surgery (American Dental Association: 1965), 30(4), 252-262.	Study design not of interest

Article	Reason for Exclusion
Harrington, B. (2000). Primary dental care of patients with haemophilia Haemophilia, 6 Suppl 1(#issue#), 7-12	Intervention not of interest
Hayward, J. R. (1965). DENTAL MANAGEMENT OF EXTRACTIONS IN THE HEMOPHILIAC J Mich State Dent Assoc, 47(#issue#), 209	Intervention not of interest
Hermans, C.,Altisent, C.,Batorova, A.,Chambost, H.,De Moerloose, P.,Karafoulidou, A.,Klamroth, R.,Richards, M.,White, B.,Dolan, G. (2009). Replacement therapy for invasive procedures in patients with haemophilia: Literature review, European survey and recommendations Haemophilia, 15(3), 639-658	Intervention not of interest
Hewson, I. D., Daly, J., Hallett, K. B., Liberali, S. A., Scott, C. L. M., Spaike, G., ... & Winters, J. (2011). Consensus statement by hospital based dentists providing dental treatment for patients with inherited bleeding disorders. Australian dental journal, 56(2), 221-226.	Study design not of interest
Hewson, I.,Makhmalbaf, P.,Street, A.,McCarthy, P.,Walsh, M. (2011). Dental surgery with minimal factor support in the inherited bleeding disorder population at the Alfred Hospital Haemophilia, 17(1), e185-8	Intervention not of interest
Hobson, P.,Evans, D. I. (1982). Dental care of children with haemophilia and related conditions Br Dent J, 152(8), 262	Study design not of interest
Hobson, P. (1981). Dental care of children with haemophilia and related conditions Br Dent J, 151(8), 249-53	Study design not of interest
Hobson, P. (1977). Dental treatment of children with haemophilia and related conditions Proc Br Paedod Soc, 7(#issue#), 8-10	Study design not of interest
Hoots, W. K.,Buchanan, G. R.,Parmley, R. T.,Alperin, J. B.,Kletzel, M.,Sexauer, C. L. (1991). Comprehensive care for patients with hemophilia: an expanded role in reducing risk for human immunodeficiency virus Tex Med, 87(6), 73-5	Intervention not of interest
Kalsi, H., Nanayakkara, L., Pasi, K. J., Bowles, L., & Hart, D. P. (2012). Access to primary dental care for patients with inherited bleeding disorders. Haemophilia, 18(4), 510-515.	Study design not of interest
Katz, J. O., & Terezhalmay, G. T. (1988). Dental management of the patient with hemophilia. Oral surgery, oral medicine, oral pathology, 66(1), 139-144.	Study design not of interest
Kozma, A.,Clevet, O.,Traila, A.,Ursu, E.,Jinca, C.,Oancea, R.,Boeriu, E.,Boia, E.,Ritli, L.,Șerban, M.,Lackner, A. K.,Lăzărescu, H.,Popovici, C.,Diac, I.,Stănescu, A. M. A.,Enachescu, C. I.,Arghirescu, S. (2019). The impact of replacement therapy on dental health in haemophilia Romanian Journal of Legal Medicine, 27(2), 200-204	Intervention not of interest
Laguna, P.,Klukowska, A. (2005). Management of oral bleedings with recombinant factor VIIa in children with haemophilia A and inhibitor Haemophilia, 11(1), 2-4	Intervention not of interest
Lee, A. P.,Boyle, C. A.,Savidge, G. F.,Fiske, J. (2005). Effectiveness in controlling haemorrhage after dental scaling in people with haemophilia by using tranexamic acid mouthwash Br Dent J, 198(1), 33-8; discussion 26	Intervention not of interest
Ljung, R. C., & Knobe, K. (2012). How to manage invasive procedures in children with haemophilia. British journal of haematology, 157(5), 519-528.	Study design not of interest
Lucas, O. N.,Albert, T. W. (1981). Epsilon aminocaproic acid in hemophiliacs undergoing dental extractions: a concise review Oral Surg Oral Med Oral Pathol, 51(2), 115-20	Intervention not of interest
Lucas, O. N.,Tocantins, L. M. (1964). PROBLEMS IN HEMOSTASIS IN HEMOPHILIC PATIENTS UNDERGOING DENTAL EXTRACTIONS Ann N Y Acad Sci, 115(#issue#), 470-80	Intervention not of interest
Lurie, A.,Silverman, N. H.,Jackson, F. R. (1972). An approach to dental extractions in haemophilia and related bleeding disorders in children S Afr Med J, 46(45), 1743-6	Country not of interest
Lurie, R.,Smith, I.,Lurie, A. (1977). Dental extraction in haemophilic patients J Dent Assoc S Afr, 32(9), 517-20	Country not of interest

Article	Reason for Exclusion
Maas, D. P. M. S. M.,Saes, J. L.,Blijlevens, N. M. A.,Cnossen, M.,den Exter, P. L.,Kruis, I. C.,Meijer, K.,Nieuwenhuizen, L.,Peters, M.,Schutgens, R. E. G.,van Heerde, W. L.,Schols, S. E. M. (2022). Treatment of patients with rare bleeding disorders in the Netherlands: Real-life data from the RBiN study Journal of Thrombosis and Haemostasis, 20(4), 833-844	Intervention not of interest
Mahlangu, J.,Powell, J. S.,Ragni, M. V.,Chowdary, P.,Josephson, N. C.,Pabinger, I.,Hanabusa, H.,Gupta, N.,Kulkarni, R.,Fogarty, P.,Perry, D.,Shapiro, A.,Pasi, K. J.,Apte, S.,Nestorov, I.,Jiang, H.,Li, S.,Neelakantan, S.,Cristiano, L. M.,Goyal, J.,Sommer, J. M.,Dumont, J. A.,Dodd, N.,Nugent, K.,Vigliani, G.,Luk, A.,Brennan, A.,Pierce, G. F. (2014). Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A Blood, 123(3), 317-325	Outcomes not of interest
Maloney, W. J.,Raymond, G.,Hershkowitz, D.,Rochlen, G. (2015). An Analysis of the hemophilia of the royal families of Europe, its startling implication and dentistry's role in treating the hemophiliac patient N Y State Dent J, 81(2), 38-41	Intervention not of interest
Mannucci, P. M.,Ruggeri, Z. M.,Pareti, F. I.,Capitanio, A. (1977). 1-Deamino-8-d-arginine vasopressin: a new pharmacological approach to the management of haemophilia and von Willebrands' diseases Lancet, 1(8017), 869-72	Study design not of interest
Mariana, G.,Ciavarella, N.,Mazzucconi, M. G.,Antoncecchi, S.,Solinas, S.,Ranieri, P.,Pettini, P.,Agrestini, F.,Mandelli, F. (1984). Evaluation of the effectiveness of DDAVP in surgery and in bleeding episodes in haemophilia and von Willebrand's disease. A study on 43 patients Clin Lab Haematol, 6(3), 229-38	Intervention not of interest
Mauser-Bunschoten, E. P.,Koopman, M. M.,Goede-Bolder, A. D.,Leebeek, F. W.,van der Meer, J.,van Marwijk Kooij, G. M.,van der Linden, P. W. (2002). Efficacy of recombinant factor VIIa administered by continuous infusion to haemophilia patients with inhibitors Haemophilia, 8(5), 649-56	Intervention not of interest
McIntyre, H. (1965). DENTAL EXTRACTIONS IN PATIENTS WITH HEMOPHILIA SYNDROME; A METHOD OF LOCAL MANAGEMENT Oral Surg Oral Med Oral Pathol, 19(issue#), 163-73	Intervention not of interest
McIntyre, H.,Barrett, K. E.,Israels, M. C.,Wilkinson, J. F. (1964). DENTAL TREATMENT IN THE HAEMOPHILIA SYNDROME Lancet, 1(7333), 584-5	Intervention not of interest
McKown, C. G.,Shapiro, A. D. (1991). Oral management of patients with bleeding disorders. 2. Dental considerations J Indiana Dent Assoc, 70(2), 16-21	Study design not of interest
Middleton, D. S.,Davies, S. H.,Cumming, R. A.,Kamel, K.,Cameron, A. (1965). EXPERIENCE WITH THIRTY-SIX DENTAL EXTRACTIONS IN PATIENTS WITH HEMOPHILIA AND CHRISTMAS DISEASE Oral Surg Oral Med Oral Pathol, 19(issue#), 283-91	Intervention not of interest
Mingot-Castellano, M. E.,Álvarez-Román, M. T.,López-Fernández, M. F.,Altisent-Roca, C.,Canaro-Hirnyk, M. I.,Jiménez-Yuste, V.,Cid-Haro, A. R.,Pérez-Garrido, R.,Sedano-Balbas, C. (2016). Spanish consensus guidelines on prophylaxis with bypassing agents for surgery in patients with haemophilia and inhibitors Eur J Haematol, 96(5), 461-74	Intervention not of interest
Morimoto, Y.,Yoshioka, A.,Shima, M.,Kirita, T. (2003). Intraoral hemostasis using a recombinant activated factor VII preparation in a hemophilia A patient with inhibitor Journal of Oral and Maxillofacial Surgery, 61(9), 1095-1097	Study design not of interest
Mulkey, T. F. (1976). Outpatient treatment of hemophiliacs for dental extractions. Journal of Oral Surgery (American Dental Association: 1965), 34(5), 428-434.	Study design not of interest
Mulkey, T. F. (1971). Dental extraction in hemophiliacs N Engl J Med, 284(9), 502	Study design not of interest
Nakai, T. R., Peterson Jr, J. C., & Law, D. B. (1974). Current concepts in the management of the hemophilic pedodontic patient. ASDC journal of dentistry for children, 41(5), 361-366.	Study design not of interest

Article	Reason for Exclusion
Neal, R. G. (1979). A dental approach to hemophilia and other coagulopathies Virginia dental journal, 56(2), 18-28	Intervention not of interest
Needleman, H. L.,Kaban, L. B.,Kevy, S. V. (1976). The use of epsilon-aminocaproic acid for the management of hemophilia in dental and oral surgery patients J Am Dent Assoc, 93(3), 586-90	Intervention not of interest
O'Callaghan, D. J.,Russell, J. G. (1973). Dental haemorrhage and haemophilia Journal of the Irish Medical Association, 66(8), 215-217	Intervention not of interest
O'Neil, D. W., Lowe, J. W., & Mariscal, R. (1989). Dentistry and the hemophiliac: a review of current literature, Part I. Compendium (Newtown, Pa.), 10(2), 86-89.	Study design not of interest
O'Neil, D. W.,Lowe, J. W.,Mariscal, R. (1989). Dentistry and the hemophiliac: a review of current literature, Part I Compendium, 10(2), 86-9	Study design not of interest
Onishi, H.,Izuchi, K.,Matsumoto, T.,Kato, R.,Kusunose, K. (1971). Clinical experiences with chromatographic DEAE adsorbed prothrombin complex for control of bleeding and multiple tooth extraction in hemophilia B patients Nihon Ketsueki Gakkai Zasshi, 34(4), 513-6	Country not of interest
Orchen, J. J. (1979). The hemophiliac--a review of the literature and dental treatment recommendations. Journal of the Kentucky Dental Association, 31(3), 24-28.	Study design not of interest
Pathirana, U. G., Gunawardena, N., Abeysinghe, H., Copley, H. C., & Somarathne, M. D. (2014). Acquired haemophilia A associated with autoimmune thyroiditis: a case report. Journal of Medical Case Reports, 8, 1-3.	Study design not of interest
Pizzoni, D.,Cortellaro, M.,Mannucci, P. M. (1971). Replacement therapy and local measures for dental extractions in haemophiliacs: comparison of various schemes of treatment Rass Int Stomatol Prat, 22(4), 153-7	Intervention not of interest
Proctor, D. B. (1969). Dental care for hemophiliacs Can Dent Hyg, 3(1), 10-1	Intervention not of interest
Ramstrom, G.,Blomback, M.,Egberg, N.,Johnsson, H.,Ljungberg, B.,Schulman, S. (1989). Oral surgery in patients with hereditary bleeding disorders. A survey of treatment in the Stockholm area (1974-1985) International Journal of Oral and Maxillofacial Surgery, 18(6), 320-322	Intervention not of interest
Raso, S.,Napolitano, M.,Sirocchi, D.,Siragusa, S.,Hermans, C. (2022). The important impact of dental care on haemostatic treatment burden in patients with mild haemophilia Haemophilia, 28(6), 996-999	Intervention not of interest
Reich, W.,Kriwalsky, M. S.,Wolf, H. H.,Schubert, J. (2009). Bleeding complications after oral surgery in outpatients with compromised haemostasis: Incidence and management Oral and Maxillofacial Surgery, 13(2), 73-77	Intervention not of interest
Rodriguez-Merchan, E. C. (2019). What does the 'Cochrane database of systematic reviews' tell us about hemophilia? Expert Rev Hematol, 12(11), 919-922	Intervention not of interest
Romney, G.,Glick, M. (2009). An updated concept of coagulation with clinical implications J Am Dent Assoc, 140(5), 567-74	Study design not of interest
Sachs, S. A., Lipton, R., & Frank, R. (1978). Management of ambulatory oral surgical patients with hemophilia. Journal of Oral Surgery (American Dental Association: 1965), 36(1), 25-29.	Study design not of interest
Saunders, S. D. (1982). The comprehensive hemophilia program: new directions for treatment Rhode Island dental journal, 15(4), 10, 12-13	Outcomes not of interest
Schaffer, R., Duong, M. L., Wachter, B., Arana, E., & Frances, D. (2016). Access to dental care for people with bleeding disorders: survey results of hemophilia treatment centers in the US. Special Care in Dentistry, 36(6), 295-299.	Study design not of interest
Shankar, S.,Lee, R. (1984). DDAVP and tranexamic acid for dental extractions in a mild haemophiliac Br Dent J, 156(12), 450-2	Study design not of interest
Shastri, S. P.,Kaul, R.,Baroudi, K.,Umar, D. (2014). Hemophilia A: Dental considerations and management J Int Soc Prev Community Dent, 4(Suppl 3), S147-52	Country not of interest

Article	Reason for Exclusion
Shotts, N. (1967). Dental treatment of children with the haemophilia syndrome Practitioner, 199(193), 664-8	Country not of interest
Shteyer, A., Hershko, A., Azaz, B. (1970). Oral surgical treatment of patients with hemophilia "A", treated by cryoprecipitated factor 8 Refuat Hapeh Vehashinayim, 19(#issue#), 27-30	Country not of interest
Shurafa, M., MacIntosh, R. B. (1987). Management of dental extractions in two hemophilia A patients with factor VIII inhibitor J Oral Maxillofac Surg, 45(8), 698-701	Study design not of interest
Snyder, D. T., Penner, J. A. (1970). Preventive and restorative dental care for the hemophiliac J Mich State Dent Assoc, 52(1), 6-8	Intervention not of interest
Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., Key, N. S., Kitchen, S., Llinas, A., ... & Treatment Guidelines Working Group The World Federation Of Hemophilia. (2013). Guidelines for the management of hemophilia. Haemophilia, 19(1), e1-e47.	Duplicate
Stapp, W. F. (1967). Tooth extraction in hemophilia. Brief review of the literature with some new suggestions for management Wis Med J, 66(7), 293-8	Intervention not of interest
Stewart, D. J. (1965). A dental service for children with bleeding disorders British dental journal, 119(12), 544-548	Intervention not of interest
Stubbs, M., & Lloyd, J. (2001). A protocol for the dental management of von Willebrand's disease, haemophilia A and haemophilia B. Australian Dental Journal, 46(1), 37-40.	Study design not of interest
Sudheesh, K. M., Bharani, K. S., Kiran, H. Y., & Hanagavadi, S. (2016). "Antihemophilic factor is not the only answer for all factor VIII deficiencies." Case report of odontogenic infection in a patient with hemophilia A, complicated by factor VIII inhibitors, and managed by transfusion of antihemophilic factor and factor VIII inhibitor bypass activity. Indian Journal of Dentistry, 7(3), 149.	Study design not of interest
Todo, K., Ohmae, T., Osamura, T., Kiyosawa, N., Sugimoto, M., Shima, M., ... & Imashuku, S. (2015). Exsanguinating bleeding following tooth extraction in a 12-year-old girl: a rare case of acquired haemophilia A. Blood Coagulation & Fibrinolysis, 26(8), 964-966.	Study design not of interest
Van Creveld, S., Buchner, R. (1970). Dental extractions and the use of Christmas factor concentrate in cases of haemophilia B Vox Sang, 18(5), 441-9	Intervention not of interest
van Creveld, S., Buchner, R. (1971). Dental extractions in hemophilia A and B Jama, 215(11), 1826-7	Study design not of interest
Vierrou, A. M., de la Fuente, B., Poole, A. E., Hoyer, L. W. (1985). DDAVP (desmopressin) in the dental management of patients with mild or moderate hemophilia and von Willebrand's disease Pediatr Dent, 7(4), 297-301	Study design not of interest
Watts, R. G., & Cook, R. P. (2012). Operative management and outcomes in children with congenital bleeding disorders: a retrospective review at a single haemophilia treatment centre. Haemophilia, 18(3), 421-425.	Study design not of interest
Webster, W. P., Roberts, H. R. (1970). Dental treatment of patients with hemorrhagic disorders Bibl Haematol, 34(#issue#), 139-48	Intervention not of interest
White, G. E. (1979). Factor VIII deficiency and pedodontics The Journal of pedodontics, 3(2), 176-192	Outcomes not of interest
Wilson, C. J. (1965). DENTAL CARE OF THE HEMOPHILIAC J Wis State Dent Soc, 41(#issue#), 167-9	Intervention not of interest
Windyga, J., Lissitchkov, T., Stasyshyn, O., Mamonov, V., Ghandehari, H., Chapman, M., Fritsch, S., Wong, W. Y., Pavlova, B. G., Abbuehl, B. E. (2014). Efficacy and safety of a recombinant factor IX (Bax326) in previously treated patients with severe or moderately severe haemophilia B undergoing surgical or other invasive procedures: A prospective, open-label, uncontrolled, multicentre, phase III study Haemophilia, 20(5), 651-658	Intervention not of interest

Article	Reason for Exclusion
Yee, R.,Duggal, M. S.,Wong, V. Y. Y.,Lam, J. C. M. (2021). An Update on the Dental Management of Children with Haemophilia Prim Dent J, 10(4), 45-51	Study design not of interest
Zaliuniene, R.,Peciuliene, V.,Brukiene, V.,Aleksėjuniene, J. (2014). Hemophilia and oral health Stomatologija / issued by public institution "Odontologijos studija" ... [et al.], 16(4), 127-131	Intervention not of interest
Zanon, E.,Martinelli, F.,Bacci, C.,Zerbinati, P.,Girolami, A. (2000). Proposal of a standard approach to dental extraction in haemophilia patients. A case-control study with good results Haemophilia, 6(5), 533-6	Intervention not of interest

Appendix E. Abbreviations and Acronyms

Abbreviation	Definition
AHRQ	Agency for Healthcare Research and Quality
aPTT	Activated partial thromboplastin time
CMS	Centers for Medicare & Medicaid Services
EACA	Epsilon amino caproic acid
FDA	US Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HA	Hemophilia A
HB	Hemophilia B
HC	Hemophilia C
HRSA	Health Resources and Services Administration
HTC	Hemophilia Treatment Center
ICA	International Consulting Associates, Inc.
ISTH	International Society on Thrombosis and Hemostasis
ITI	Immune tolerance induction
KQ	Key Question
MA	Meta-analysis
MASAC	Medical and Scientific Advisory Council
N/A	Not applicable
PICOTS	Population, intervention, comparison, outcome(s), timing, setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SME	Subject matter expert
SR	Systematic Review
UKHCDO	United Kingdom Haemophilia Centre Doctors' Organisation
USPSTF	United States Preventative Services Task Force
WFH	World Federation of Hemophilia