Interventions for Hemophilia A and B: Clinical Practice Guidelines and Cost-effectiveness

A Report for the Washington State Bleeding Disorder Collaborative for Care

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Objectives

The goal of this report is to identify clinical practice guidelines on drug interventions for hemophilia A and B and conduct a review for estimates on the cost and cost-effectiveness of those interventions. This report is prepared for the Washington State Bleeding Disorder Collaborative of Care.

Key Findings

Clinical Practice Guidelines

- The search for clinical practice guidelines identified four relevant documents from the Australian Haemophilia Centre Directors' Organisation (Australian Haemophilia Centre Directors' Organisation, 2016), the Nordic Hemophilia Council (Nordic Hemophilia Council guideline working group, 2015), the United Kingdom Haemophilia Centre Doctors Organization (Collins et al., 2013), and the World Federation of Hemophilia (Srivastava et al., 2013).
- Three were of poor methodologic quality (Collins et al., 2013; Nordic Hemophilia Council guideline working group, 2015; Srivastava et al., 2013) for absence of clearly defined evidence process, method for translating evidence to recommendations, and editorial independence. One was of fair methodologic quality (Australian Haemophilia Centre Directors' Organisation, 2016), which heavily relied on the World Federation of Hemophilia (WFH) guideline for evidence. They had fair-quality methods of translating evidence to recommendations and reporting of conflicts of interest.
- The United Kingdom, Nordic, and Australia guidelines recommend recombinant factors over plasma-derived. The World Federation of Hemophilia recommends both viral-eradicated plasma-derived and recombinant factors.
- Prophylaxis is recommended by all identified guidelines and should begin by age three and the second clinical bleeding episode. All identified guidelines were consistent in stating an array of options for prophylaxis regimens exist and protocols may vary within and across countries.
- All identified guidelines support the use of either rFVIIa or aPCC for bleeding episodes in patients with inhibitors.

Evidence on Estimates of Direct and Indirect Medical Costs and Cost-effectiveness

- The evidence search did not identify any estimates of cost or outcomes comparing specific clotting factor preparations.
- Estimates of cost and cost-effectiveness for prophylaxis compared to on-demand therapy vary widely depending on the methods used in the analyses.

- The evidence search identified one fair methodologic quality systematic review on economics analyses analyzing the use of bypass agents (i.e. aPCC, rFVIIa) to treat mild to moderate bleeding episodes in patients with hemophilia complicated by inhibitors.
- Estimates of total direct costs to treat a single mild to moderate bleeding episode in a patient with hemophilia complicated by inhibitors (typically treated in the home setting) ranged from $11,485 to $49,010 for aPCC and $9,078 to $49,507 for rFVIIa (using 2010 United States [U.S.] dollars). Estimates of efficacy were frequently based on industry-funded studies using higher efficacy estimates and lower doses for their products (typically based on estimates from single arm clinical trials). Findings from head-to-head trials did not support superior efficacy for either product (i.e. aPCC and rFVIIa). The authors called for additional head-to-head clinical trials of rFVIIa and aPCC to better elucidate the ideal dosing regimen, clinical efficacy, and potential that the medications may be synergistic or have differences in treatment effects among subgroups of patients.

Background

Hemophilia A and B are X-linked inherited disorders of bleeding that disproportionately impact males. The prevalence of hemophilia A is 1 in 5,000 males who are born, while hemophilia B is rarer, at 1 in 30,000 males. The majority of cases arise in families with a known hemophilia history (Peyvandi, Garagiola, & Young, 2016). Individuals may produce insufficient quantities of or dysfunctional factor VIII (hemophilia A) or IX (hemophilia B). Based on the activity of their factors, individuals with hemophilia can be categorized into mild, moderate, or severe disease (Table 1). Individuals with severe disease, constituting over 50% of patients with hemophilia, can experience bleeding episodes after minimal trauma or can have spontaneous (atraumatic) bleeds.

Children with severe hemophilia may experience their first bleeding episode by 6 to 8 months of life as their activity levels increase. Morbidity and mortality arise from bleeding complications. Individuals with hemophilia may spontaneously bleed into their brain, joints, head and neck tissues, or deep muscles creating life threatening emergencies or progressive, repeated destruction of joint cartilage leading to early arthritis and disability.

Table 1: *Categories of Hemophilia by Factor Activity*

Severity	Factor Activity Level
Mild	0.05 to 0.4 IU/ml (5 to 40% of normal)
Moderate	0.01 to 0.05 IU/ml (1 to 5%)
Severe	0.01 IU/ml (1% or less)

Treatments for hemophilia constituted derivatives from human blood until the 1990s when the first recombinant product was produced. Table 2 provides a list of potential drug interventions for individuals with hemophilia. Agents vary by origin (i.e. human, porcine, or recombinant) but have similar pharmacokinetics (Carcao, 2014). Newer recombinant agents in clinical trials currently may provide lengthened factor half-life in the patient's circulation (e.g. through PEGylation, fusing to IgG or albumin) and thus alter current prophylaxis recommendations (Carcao, 2014; Peyvandi et al., 2016).

Prophylactic use of Clotting Factor Concentrates

Prophylactive use of clotting factor concentrates (CFCs) started in Sweden in 1958 after clinicians observed that patients with moderate hemophilia were less likely to experience spontaneous bleeds and maintained joint function longer than those with severe disease(Fischer et al., 2013). The rationale behind prophylaxis is to maintain higher circulating factor levels continuously as opposed to providing factors only on-demand for use at the time of a bleed.

Primary prophylaxis begins early in life, prior to the onset of joint disease, while secondary prophylaxis may be initiated or continued in those with joint disease. Prophylaxis regimens vary by dose and frequency based on the specific half-life of each agent (Peyvandi et al., 2016).

Table 2. *Therapeutic Agents for Hemophilia A or B*

Drug Name	Type	Brand Names
Factor VIII Agents		
Antihemophilic Factor	Human	Hemofil M, Koate-DVI Monoclate-P
Antihemophilic Factor	Recombinant	Eloctate Helixate FS Kogenate FS Novoeight Nuwiq Recombinate Refacto
Antihemophilic Factor	Recombinant Porcine	Obizur
Antihemophilic Factor Plasma/Albumin Free Method (rAHF PFM)	Recombinant	Advate
Antihemophilic Factor Platelet Activating Factor (rAHF PAF)	Recombinant	Xyntha
Antihemophilic Factor/Von-Willebrand Factor Complex	Human	Alphanate Humate-P

		Wilate
Factor IX Agents		
Factor IX	Human	AlphaNine SD Mononine
Factor IX	Recombinant	Alprolix BeneFIX Ixinity Rixubis
Prothrombin Complex Concentrates (PCC)		
3-factor Prothrombin Complex Concentrate (factor IX, prothrombin (factor II), factor X ,low levels of factor VII)	Human	Bebulin Bebulin Vapor Heated (VH) Profilnine Profilnine Solvent/Detergent treated (SD)
4-factor Prothrombin Complex Concentrate (factor II, VII, IX, X)	Human	Kcentra
Bypass Agents		
Activated Prothrombin Complex Concentrate (aPCC: non-activated factors II, IX, X and activated VII)	Human	FEIBA
Factor VIIa (rVIIa)	Recombinant	NovoSeven RT

Inhibitors

Inhibitors are an uncommon but serious complication for individuals with hemophilia. The development of inhibitors often occurs within the first 30 days after initial receipt of a factor concentrate (Peyvandi et al., 2016). Estimates for inhibitor prevalence range from 3.6% to 32% (Matino, Makris, Dwan, D'Amico, & Iorio, 2015). Depending on the response of the inhibitor, treatments may consist of higher doses of CFCs for those with low-responding inhibitors or require the use of bypass agents for high-responding cases. Bypass agents support clot formation by going downstream in the clotting cascade, passed the factor VIII or XI step (which is blocked by the inhibitor). Immune tolerance induction (ITI) is a treatment option for patients with inhibitors. The aim of ITI is to eliminate or reduce the activity of the inhibitor. Protocols for ITI utilize high doses of CFCs, with associated cost implications. However, this report focuses on specific drug agents and does not include cost or cost-effectiveness evidence for ITI specifically.

Future Directions for Hemophilia Treatments

In addition to research on extending the half-life of CFCs, other clinical trials are investigating novel methods to promote clotting through synthetic antibody production and alternate pathways. Gene replacement therapy, holding a potential curative intervention for individuals

with hemophilia, may not be too far off. As of 2016, six clinical trials are in process, many still in recruitment phases, investigating the use of gene therapy for hemophilia B. While a 2014 Cochrane review did not identify any RCTs on gene therapy, the authors highlighted the need for long-term safety evaluations and provided a review on the current status of research in this developing field (Sharma, Easow Mathew, Sriganesh, Neely, & Kalipatnapu, 2014).

PICO and Key Questions

PICO

Population(s)

- Adult outpatients with hemophilia A or B
- Pediatric outpatients with hemophilia A or B

Interventions

- See list of interventions in Table 2 above

Comparators

- Usual care, other active interventions

Outcomes

- Direct and indirect economic costs; cost-effectiveness

Key Questions

1. What are the clinical practice guidelines of the interventions in Table 2 for hemophilia A and hemophilia B?
2. What are the estimated direct and indirect medical costs, non-medical costs, and cost-effectiveness associated with the interventions listed in Table 2 for hemophilia A and hemophilia B?

Methods

Center for Evidence-based Policy (Center) staff conducted a full search of the Medicaid Evidence-based Decisions Project (MED) core guidelines sources to identify clinical practice guidelines using the intervention terms listed in Table 2, as well as hemophilia A and hemophilia B. Searches of core sources were limited to citations published after January 1, 2006. Lateral searches (i.e. cited by) and reference list screening was conducted on eligible documents.

Center staff performed a full Ovid MEDLINE® search for systematic reviews on direct and indirect economic costs, and cost-effectiveness of interventions listed in Table 2 for hemophilia A and hemophilia B. The full search strategy can be found in Appendix A. Searches were limited

to systematic reviews, meta-analyses, and technology assessments published in English in the past 10 years (January 1, 2006 to April 20, 2016).

Center staff searched for clinical practice guidelines published in the last five years using the sources listed in Appendix A.

Exclusion Criteria

The following exclusion criteria were applied when reviewing search results. We excluded the study if the population, intervention, comparator, or outcome was not relevant to the project scope; the study design was ecological, qualitative or a narrative review; non-comparative; duplicative; or it was not published in English.

Clinical practice guidelines were excluded if they were not relevant to project scope or published in English.

Quality Assessment

Two Center staff reviewers independently evaluated the methodologic quality of the included systematic reviews and clinical practice guidelines for this report using a quality assessment process highlighted in Appendix B. The two reviewers compared and discussed the quality assessments, and when consensus was not reached, a third reviewer was involved to settle disagreement. It is important to note that Center staff only assessed the methodologic quality of the systematic reviews and did not assess the quality (risk of bias) of the individual studies included in each review or the evidence that was considered within clinical practice guidelines.

Findings

Search Results

Clinical Practice Guidelines

Center staff identified four guidelines on hemophilia treatment. Using the quality assessment process detailed in Appendix B, three of the guidelines were found to be of poor methodologic quality; often for lacking information on methods of identifying evidence, absence of clear methods for developing recommendations, failure to disclose funding sources or competing interests of authors (Collins et al., 2013; Nordic Hemophilia Council guideline working group, 2015; Srivastava et al., 2013). The National Blood Authority (NBA) of Australia released their draft guideline to public comment in late 2015 and anticipates releasing the final in June 2016. The draft document was reviewed and found to be of fair methodologic quality (Australian Haemophilia Centre Directors' Organisation, 2016).

The Australia document, produced by the Australian Haemophilia Centre Directors' Organization, reviewed the 2012 WFH guideline and adapted recommendations to the Australian setting and conducted evidence searches for areas needing further research (Australian Haemophilia Centre Directors' Organisation, 2016). Many of the recommendations from the WFH and Australia guidelines align. Center staff included the Australia guideline in summary below, but recommendations may change when the final document is released later in 2016.

The 2010 guideline from the United Kingdom Haemophilia Centre Doctors Organization (UK) is specific to patients with congenital hemophilia with inhibitors (Collins et al., 2013). The 2012 WFH guideline uses 2011 Oxford Center for Evidence-based Medicine levels of evidence for practice statements only (Srivastava et al., 2013). The 2015 Nordic Hemophilia Guidelines (Nordic) were produced in conjunction with Nordic national patient organizations (Nordic Hemophilia Council guideline working group, 2015).

All clinical practice guidelines are vast and comprehensive in their recommendations on appropriate care of patients with hemophilia. Center staff summarized guidelines where they make specific recommendations on agents listed in Table 2.

Evidence

A two tier Ovid MEDLINE® search strategy was performed (Appendix A). The first tier limited results to systematic reviews, meta-analyses, literature reviews, and technical reports related to costs and cost-effectiveness (n = 32), while the second tier removed the limitation on type of publication (n = 58). For tier one, 28 citations were excluded based on title and abstract screening. Staff reviewed reference lists of included studies. Ultimately, staff identified four studies, three older studies (Knight, Dano, & Kennedy-Martin, 2009; Lyseng-Williamson & Plosker, 2007; Stephens, Joshi, Sumner, & Botteman, 2007) were included in the most recent publication (Hay & Zhou, 2011b). All identified systematic reviews addressed economic analyses comparing bypass agents (i.e. aPCC, rFVIIa) for mild to moderate hemophilia bleeds in patients with inhibitors.

Of note, Hay and Zhou (2010) published a letter to the editor regarding Knight's 2009 systematic review calling attention to industry influence, and repetitive use of models containing base case efficacy rates favoring rFVIIa that were based on single arm clinical trials (Hay & Zhou, 2010).

Baghaipour and Steen Carlsson (2015) subsequently published a narrative review, which included three trials published following the 2011 systematic review by Hay and Zhou (2010). Staff summarized the interval studies below given the paucity of data and the time since

completion of the systematic review (Baghaipour & Steen Carlsson, 2015). Additionally, all interval studies were identified through the tier two search strategy.

The MED core evidence sources search identified several relevant articles. One, a review article discussing variation in economic evaluations of prophylaxis with CFCs, provided useful background, analysis, and reflection upon needed research in the field (Miners, 2013) and is described below. The second provides estimates of cost and outcomes proposed from the use of a proposed treatment protocol for patients with hemophilia A complicated by inhibitors, also reviewed below (Bonnet et al., 2011).

Others, while outside the scope of this report or not meeting strict inclusion criteria, are included below for context. Two Cochrane reviews evaluating efficacy, not costs, are reviewed below as well (Iorio, Marchesini, Marcucci, Stobart, & Chan, 2011; Matino et al., 2015). The MED core evidence sources also identified a large multinational review of outcomes and costs comparing intermediate dose to high dose prophylaxis from the Netherlands and Sweden (Fischer et al., 2013), which is included given a paucity of findings relating to prophylaxis costs.

Summary of Clinical Practice Guidelines

Hemostatic Agents

The WFH guideline states that viral-inactivated plasma derived or recombinant concentrates are preferred to cryoprecipitate or fresh frozen plasma. They do not preferentially recommend recombinant over viral-inactivated factor products, stating the choice is up to local authorities. The WFH mentions a recombinant product, pending clinical trials, may replace porcine plasma derived factor VIII.

The Australian and UK guidelines recommend recombinant factors as first line treatment over plasma derived products. The rationale behind this decision is the potential (albeit with a low likelihood) for plasma based agents to spread infectious or prion diseases and the availability of recombinant products in these countries. The Nordic guideline recommends the use of recombinant over plasma derived products when available, without explanation.

The use of prothrombin complex concentrates (PCCs) includes other clotting factors (II, VII, and X), which may be activated and could increase the risk of thromboembolism. For patients with hemophilia B, factor IX replacement is recommended over PCC and in Australia, rIX is available and is the recommended product for bleeding with PCCs only used in emergency situations. This is consistent with the WFH recommendations, although they do not state a preference for plasma or recombinant preparations of factor IX.

Prophylaxis

The Nordic guideline recommend prophylaxis begin before age one, but also includes language similar to the WFH and Australian guidelines, which recommend primary prophylaxis begin before age three and the "second clinically evident large joint bleed" (Australian Haemophilia Centre Directors' Organisation, 2016, p. 21; Nordic Hemophilia Council guideline working group, 2015, p. 35).

The WFH, Australia, and Nordic guidelines mention two established protocols with long-term data for prophylaxis, the Malmo (Lee et al., 1998) and Utrecht (Blanchette, 2010) protocols, but mention that different protocols are followed within countries, and the optimal regimen "remains to be defined" and should be individualized as possible.

> Malmo protocol: 25 to 40 IU/kg per dose three times a week (hemophilia A), twice a week (hemophilia B)
>
> Utrecht protocol: 15 to 30 IU/kg per dose three times a week (hemophilia A), twice a week (hemophilia B)

In addition, the Nordic guideline recommends two more options for individuals with hemophilia A, the pharmacokinetic Swedish option (which can be reduced from high dosing in eligible patients) and the Candia dose, which up-titrates the dose based on bleeding frequency.

Inhibitors

Guidelines recommend consultation with a hemophilia treatment center when managing bleeding in a patient with an inhibitor. Low responding inhibitors may be treated with a higher dose of factor, while high responding inhibitors, but with low titers, may be treated similarly. Patients with high responding inhibitors and high titres may require bypass agents (i.e. rFVIIa, aPCC).

The WFH and Australia guideline state that the efficacy of two doses of rFVIIa and one dose of aPCC is "essentially equivalent" (Australian Haemophilia Centre Directors' Organisation, 2016, p. 84; Srivastava et al., 2013, p. 60). They also mention that some patients may respond better to one agent over the other and recommend an individualized approach.

The Nordic guideline recommends either rFVIIa (90 to 120 µ g/kg every 2 to 3 hours) or aPCC (50 to 100IU/kg every 6 to 12h) for bleeding in patients with high responding inhibitors.

The UK guideline lists a single dose of aPCC (50 to 100 µ k/kg), single high dose of rFVIIa (270ug/kg), or 1 to 3 standard doses of rFVIIa (90 µ g/kg) as treatment options for early

hemarthroses in patients with high responding inhibitors. For non-joint bleeds, aPCC or rFVIIa are treatment options.

Discussion of Costs in Guidelines

The available guidelines reported mixed results regarding the cost-effectiveness of prophylaxis. The Nordic guideline suggests that prophylaxis may be more clinically effective than on-demand treatment, but at a greater financial cost (Nordic Hemophilia Council guideline working group, 2015). The WFH states that prophylaxis may be cost-effective over the long-term via avoided costs from managing joint damage and possible improvements in quality of life.

For older children who have hemophilia A, the Nordic guideline suggests the cost-benefit ratio of prophylaxis treatment may be maximized using daily FVIII injections (specified as 10 to 20 IU/kg).

Summary of Evidence Findings

Systematic Review of Bypass Agents: aPCC compared to rFVIIa

Hay and Zhou reviewed 11 studies and converted estimates to a cost per bleeding episode in 2010 U.S. dollars (Hay & Zhou, 2011b). Nine studies were industry funded comparative economic estimates of treating a single bleeding episode; eight took a cost-minimization approach. Two studies were longitudinal cost-effectiveness studies over a 1-year timeframe or lifetime and were evaluated separately from the other studies.

Estimates of total direct costs for a single mild to moderate bleeding episode for a patient with inhibitors typically treated in the home setting (in 2010 U.S. dollars) ranged from $11,485 to $49,010 for aPCC, $9,078 to $49,507 for rFVIIa.

The authors highlight that all industry-funded studies used higher efficacy estimates and lower doses for their products (typically based on estimates from single arm clinical trials), whereas available head-to-head trials between aPCC and rFVIIa did not support superior efficacy for either product. Seven trials used nearly identical decision models with minor modifications to address country-specific features. The authors emphasize that estimates of cost-effectiveness or cost-minimization hinge on efficacy and dosing assumptions and call for further head-to-head clinical trials to address efficacy and dosing estimates (Hay & Zhou, 2011b, p. 524):

> The cost-effectiveness analyses of these bypass agents have only obfuscated the current clinical uncertainties under a patina of complex mathematical models. The results of these models are driven by favorable selection of baseline clinical parameters for each of the bypass agents. Until head-to-head clinical trials of rFVIIa and aPCC clearly resolve the underlying clinical efficacy and dosing differences, including the possibility that

> medications may be synergistic and have heterogeneous treatment efficacy response, cost-effectiveness analysis will confuse rather than clarify the underlying clinical decisions (p. 524).

Review of Cost Comparisons for Prophylaxis Compared to On-Demand Therapy

Miners reviewed the literature on costs and outcomes for prophylaxis compared to on-demand treatment (Miners, 2013). His review article compares and contrasts findings while offering explanations for the wide variety of cost estimates observed in 10 studies (five utilized a cost-utility analysis approach, four a cost-effectiveness analysis, and one a cost-benefit approach).

Cost effectiveness estimates spanned the full range of potential outcomes with reported positive net benefits to treatment with prophylaxis through incremental cost-effectiveness ratios of over €1 million per additional quality-adjusted life-year (QALY). A typical willingness to pay threshold to determine if an intervention is cost-effective is US$50,000 per QALY gained.

Poorly described on-demand treatment protocols for models, failure to describe or inconsistent unit costs for CFCs, time horizons ranging from 6 months to 70 years, and failure to adhere to published standards on economic analyses are all given as reasons for limited accuracy and utility of this body of evidence.

Recent Economic Analyses on Bypass Agents

Baghaipour and Carlsson (2015), as part of the Advanced International Hemophilia course in Sweden, performed a PubMed literature review and published the work as a narrative review. Their literature review included the three trials identified above. Cost perspectives (e.g., third party payers, national health systems) and setting (e.g., at home use, in hospital use) varied across trials and prevented synthesis of cost estimates.

Their literature search identified three trials (Hay & Zhou, 2011a; Jimenez-Yuste, Nunez, Romero, Montoro, & Espinos, 2013; Salaj et al., 2012) published after the search date of Hay and Zhou's 2011 systematic review. All were identified in the tier two search.

Two studies used a decision analytic model (Hay & Zhou, 2011a; Jimenez-Yuste et al., 2013), while Salaj and colleagues used retrospective analysis to guide their efficacy rates. Only Hay and Zhou presumed equal efficacy for aPCC and rFVIIa based on a concurrent Cochrane review, while the remaining two used higher efficacy rates for rFVIIa. Additionally, Hay and Zhou was the only trial to provide the mean number of doses required to address a mild-to-moderate bleed (rVIIa = 3; aPCC = 2).

When the efficacy of rFVIIa was greater than that for aPCC (both trials used >90% efficacy for rFVIIa and ~60% efficacy for aPCC), rFVIIa was found to provide the best value for money

(Jimenez-Yuste et al., 2013; Salaj et al., 2012). When their efficacy was equal (at 85%), aPCC provided the best value for money. Their review did not standardize costs to a single denomination across trials complicating comparisons.

Estimates of Costs from Proposed Treatment Protocol for Hemophilia A with Inhibitors

Bonnet and colleagues convened an expert panel and using a modified Delphi process, they developed a proposed treatment protocol for individuals with severe hemophilia A complicated by high-titer inhibitors (Bonnet et al., 2011). The panel also provided estimates on effectiveness to inform the cost effectiveness model of adhering or not adhering to the proposed protocol.

Adhering to their proposed model increased the number of patients with improved clinical symptoms by 72 hours (74.4% vs. 56.7%), with fewer patients requiring sequential therapy (25.6% vs. 43.3%), and a lower average cost ($87,436 vs. $92,604 based on 2008 Medicare Part B payment limits) regardless of which bypass agent was initially started.

Multinational Report on Costs – Intermediate vs High Dose Prophylaxis

The search strategy identified a large multinational review of outcomes and costs comparing intermediate dose to high-dose prophylaxis from the Netherlands and Sweden (Fischer et al., 2013). While the study did not meet strict inclusion criteria, it is described here given the paucity of findings relating to prophylaxis costs.

Sweden and the Netherlands opted to implement different national prophylaxis protocols (high-dose and intermediate-dose, respectively) in the 1960s. In their retrospective analysis, Fischer and colleagues (2013) capitalized on this natural experiment to analyze costs and outcomes for a birth cohort of 128 individuals with hemophilia without inhibitors born between 1970 and 1994, and receiving care at one of three hemophilia treatment centers. While protocols changed over time, the total amount of CFCs used still differs by country. The authors report that as of 2013, a Dutch citizen with hemophilia A used 3 x 1000 IU of FVIII/week compared to 3 x 1500 to 2000IU every other day for an adult in Sweden (Fischer et al., 2013).

Clinical joint status was the primary outcome and was prospectively assessed using the Hemophilia Joint Health Score (HJHS) by trained physiotherapists. Secondary outcomes included annual number of joint bleeds, self-reported activities, and quality of life. The authors calculated direct (factor concentrate and other medical) and indirect costs (days of work lost) for both cohorts (Fischer et al., 2013).

At a median age of 24 years, more of the high-dose prophylaxis cohort remained free of significant arthropathy compared to the intermediate dose cohort (89% vs. 54%, $p<0.01$). Mean annual costs were estimated at US$179,600 for Dutch patients compared to $297,900 for

Swedish patients based on 2010 exchange rates. Nearly all of the difference in cost estimates is attributed to greater factor consumption in the high prophylaxis group. A limitation of this evaluation was that prophylaxis initiation occurred at a statistically significantly later age among the Dutch compared to Swedish patients (Median age 1.8 vs. 0.6 years, [p<0.01]), after the onset of joint bleeding (Fischer et al., 2013).

Cochrane Review on Efficacy of Prophylaxis versus On-demand Dosing

In a systematic review of studies comparing prophylactic use of CFCs to on-demand dosing and the impact on bleeding episodes, Iorio and colleagues identified six studies consisting of 142 participants with hemophilia (Iorio et al., 2011). Each eligible trial used a different intervention and the authors were unable to calculate pooled outcome estimates with the exception of two meta-analyses on effectiveness of three-times-a-week prophylaxis vs. on-demand in children (these were presented with caveats about their limitations). They found a pooled rate ratio of 0.30 (95% CI 0.12 to 0.76) for all bleeding episodes and 0.22 (95% CI 0.08 to 0.63) for joint bleeding, both significantly favored prophylaxis. However, these meta-analyses revealed significant statistical heterogeneity (Chi-square = 196.78, p<0.0001 and I^2 = 99% and Chi-square = 63.31, p<0.0001 and I^2 = 98%), indicating that combining these data in an overall analysis was likely inappropriate. Included trials also varied by participant age (i.e. trial 1 enrolled only children under 30 months, trial 2 enrolled children up to 7 years of age), which may explain some of the variation between the study outcomes.

Two studies investigated differing prophylaxis regimens. They did not identify statistically significant differences in bleeding episodes. The authors reported non-statistically significant increases in infections for patients receiving prophylaxis, as they require the placement and use of long-term venous access. Inhibitor occurrences were also not statistically significantly different for prophylaxis patients compared to those receiving on-demand CFCs.

While costs were outside the scope of this Cochrane review, the authors reported for standard prophylaxis of factor VII concentrate that the mean difference in monthly CFC usage was 5.27 x1000 IUs (95% CI 4.23 to 6.32) greater for participants receiving prophylaxis.

Cochrane Review on Efficacy of Agents for Patients with Inhibitors – rFVIIa vs. Plasma-derived Concentrates)

Matino and colleagues updated a 2010 systematic review of trials investigating the effectiveness of rVIIa or plasma-derived concentrates (PCC or aPCC). The authors reviewed the two trials eligible for analysis, containing a total of 69 individuals with hemophilia complicated by inhibitors. Both included trials were reported by the authors as at high risk of bias. The authors were unable to perform a meta-analysis based on insufficient outcome reporting in each trial. They analyzed additional data provided by the authors using a marginal probability of

success approach. Their analysis found that available trials did not demonstrate superiority of one method or another (i.e. rFVIIA and aPCC).

Summary and Limitations

The available clinical practice guidelines support the use of recombinant factor products over plasma derived in Nordic countries, the United Kingdom, and Australia. The WFH supports recombinant or viral-inactivated plasma derived products. Prophylaxis is supported by all clinical practice guidelines to protect bone health and avoid disability from joint destruction.

Evidence on costs of treatments for hemophilia hinge on estimates of efficacy and dosing that vary from study to study. The current evidence search did not identify any cost estimates for preparations of clotting factors aside from two agents for patients with inhibitors (rFVIIa and aPCC). As the available evidence and guidelines indicate that these two options have essentially similar efficacy, the use of cost minimization approaches may be most useful, but are lacking. A 2011 systematic review found that aPCC may provide better value for money when used first for mild-to-moderate bleeds in patients with inhibitors. Several authors highlight the limitations of available economic analyses. Specifically, estimates are likely biased by choice of efficacy rates and factor doses, which may favor particular types of products in industry-sponsored studies.

Conclusion

Estimates of cost and cost-effectiveness for treatments for hemophilia are limited by a paucity of head-to-head clinical trials on CFCs and bypass agents. Hemophilia is a rare condition with significant morbidity and mortality from bleeding complications. Future treatments for hemophilia, including the potential for gene therapy, are likely to increase intervention costs, but may have long-term safety benefits that reduce costs from complications, surgeries, hospitalizations, or improve quality of life.

Appendix A: *Methods*

MED Core Evidence Sources

1. Cochrane Library
2. BMJ Clinical Evidence
3. National Institute for Health and Care Excellence (NICE)
4. BlueCross and BlueShield Center for Clinical Effectiveness (CCE)
5. Hayes, Inc.
6. Veterans Administration TA and ESP programs
7. Canadian Agency for Drugs and Technologies in Health (CADTH)
8. Washington State Health Technology Assessment Program
9. United States Preventive Services Task Force (USPSTF)
10. Agency for Healthcare Research and Quality (AHRQ)
11. Tufts Cost Effectiveness Analysis

MED Core Guidelines Sources

1. Australian Government National Health and Medical Research Council (NHMRC)
2. Centers for Disease Control and Prevention (CDC) – Community Preventive Services
3. Institute for Clinical Systems Improvement (ICSI)
4. National Guidelines Clearinghouse
5. NICE
6. New Zealand Guidelines Group
7. Scottish Intercollegiate Guidelines Network (SIGN)
8. USPSTF
9. Veterans Administration/Department of Defense (VA/DOD)
10. World Federation of Hemophilia
11. National Hemophilia Foundation for all Bleeding Disorders
12. Nordic Hemophilia Council
13. National Blood Authority Australia

Search Strategy

Database: Ovid MEDLINE(R) <1946 to April 2016>

1 Antihemophilic Factor.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (335)

2 RAHF-PFM.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (20)

3 (3-factor Prothrombin Complex Concentrate or PCC).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (6273)

4 4-factor Prothrombin Complex Concentrate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (17)

5 Factor VIIa.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4463)

6 Hemofil M.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (27)

7 Koate-DVI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4)

8 Monoclate-P.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (13)

9 Eloctate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3)

10 Helixate FS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3)

11 Kogenate FS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (23)

12 Novoeight.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5)

13 Nuwiq.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1)

14 Recombinate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (79)

15 Refacto.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (44)

16 Obizur.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1)

17 Advate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (56)

18 Xyntha.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5)

19 Alphanate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (14)

20 Humate-P.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (43)

21 Wilate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (18)

22 AlphaNine SD.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5)

23 Mononine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (26)

24 Alprolix.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1)

25 BeneFIX.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (22)

26 Ixinity.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)

27 Rixubis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4)

28 Bebulin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (11)

29 Bebulin VH.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2)

30 Profilnine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (15)

31 Profilnine SD.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (9)

32 Kcentra.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (9)

33 FEIBA.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (306)

34 NovoSeven RT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4)

35 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (11511)

36 (Hemophilia A or Hemophilia B or Haemophilia A or Haemophilia B).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (20927)

37 (Factor VIII or Factor IX or FVIII or FVIX).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (24801)

38 36 or 37 (35537)

39 35 and 38 (2076)

40 (cost* or saving* or economi* or return on investment or return-on-investment or ROI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (646959)

41 39 and 40 (181)

42 limit 41 to yr="2006 -Current" (94)

43 limit 42 to english language (90)

44 limit 43 to (meta analysis or "review" or systematic reviews or technical report) (32) (Tier 1)

45 43 not 44 (58) (Tier 2)

Appendix B: *Quality Assessment*

Staff assessed the methodological quality of the included systematic reviews using standard instruments developed and adapted by the Medicaid Evidence-based Decisions Project (MED) that are modifications of the systems in use by the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) (Guyatt et al., 2008; National Institute for Health and Care Excellence (NICE), 2009; Scottish Intercollegiate Guidelines Network (SIGN), 2009). Two experienced staff raters independently assessed all studies. In cases where there was not agreement about the quality of a study, a third rater resolved the disagreement.

Each rater assigned the study a rating of good, fair, or poor, based on its adherence to recommended methods and potential for biases. In brief, good-quality systematic reviews include a clearly-focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to select studies for inclusion (e.g., randomized controlled trials) and assess study quality, and assessment of similarities between studies to determine if combining them is appropriate for evidence synthesis. Fair-quality systematic reviews have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. Poor-quality systematic reviews have clear flaws that could introduce significant bias.

Center staff also assigned quality rating to clinical practice guidelines. Good quality clinical practice guidelines provide methods of a systematic literature search to inform recommendations. The underlying evidence is rated based on methodologic quality, and there is an explicit link between the evidence and recommendations. In addition, good quality guidelines have editorial independence from any funding source, they relevant stakeholders are represented, and recommendations are unambiguous. Fair-quality clinical practice guidelines have incomplete information about methods that might mask important limitations. Poor-quality clinical practice guidelines have clear flaws that could introduce bias.

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