

# Hemophilia in the Managed Care Setting

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**H**emophilia A and B are chronic inherited bleeding disorders that together rank as one of the most expensive chronic diseases in the United States. These conditions impose a high level of burden to affected individuals, caregivers, and society.<sup>1,2</sup> Despite its relatively low incidence, hemophilia is associated with high aggregate costs. Most of the total costs of hemophilia are related to direct costs such as anti-hemophilic medication, healthcare services (eg, comprehensive care visits, clinician visits), hospitalization, surgical procedures, laboratory tests, medical devices, and nonmedical costs.<sup>1,3</sup> Advances in hemophilia care have resulted in longer survival and a growing patient population, as well as greater complexity in management of the disorder and rising costs of treatment.<sup>4</sup> This article discusses the resource impacts of hemophilia (direct, indirect, and total costs), new therapies and evolving standards of care, and strategies to address current insurance barriers.

## Direct, Indirect, and Total Costs of Hemophilia

Hemophilia is a condition that requires lifetime treatment and is associated with substantial direct, indirect, and total costs of care.<sup>1,2</sup>

### Direct and Total Costs

The mainstay of hemophilia care is lifetime treatment with factor replacement therapy, which is used both for prophylaxis and on-demand therapy.<sup>5</sup> Factor replacement products (FRPs) are among the most expensive therapies, with a total annual cost rising to more than \$250,000 per adult patient in the United States.<sup>6</sup> The overall cost per patient with hemophilia and complications associated with the development of inhibitors can be as much as \$1 million annually.<sup>7</sup>

FRP concentrates comprise 45% to 93% of the total medical cost for hemophilia, depending on disease severity and treatment regimen.<sup>8-10</sup> The cost of replacement therapy can be considerable for patients and third-party payers.

The financial impact of inpatient hospitalization for hemophilia care can be significant. It is estimated that the

## Abstract

Hemophilia A and B are chronic inherited bleeding disorders that together rank as one of the most expensive chronic diseases in the United States. Factor replacement products, which are the mainstay of treatment, are among the most expensive therapies, with a total annual cost of more than \$250,000 per adult patient in the United States. Indirect costs also contribute to the economic burden and include lost productivity, caregivers' unpaid costs, and hemophilia-related disability. Advances in hemophilia care have resulted in longer survival and a growing patient population, greater complexity in management of the disorder, and rising treatment costs. The establishment of federally recognized Hemophilia Treatment Centers has decreased costs and improved patient outcomes and quality of life by promoting outpatient, preventive, and home-based care. Successful collaboration among providers and managed care programs can improve outcomes and decrease costs for the delivery of hemophilia services.

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average inpatient claim costs for patients with hemophilia A are more than 9 times greater than the average insurance member claim costs and almost 2 times greater than those for patients with hemophilia B (\$9661, \$1065, and \$5384, respectively).<sup>11</sup> Similar trends were observed with claim costs in the Medicaid population.<sup>11</sup>

While attention is often directed to the cost of medications and hospitalization, many variables impact the total cost of care. To accurately estimate the cost of hemophilia care, it is necessary to determine the number of patients with hemophilia in an insurance plan. Familial clustering, phenotypic variability, the potential for surgery, and the development of inhibitor antibodies may contribute to cost unpredictability. The genetic basis of hemophilia increases the probability of a family population having multiple members with the disorder. The phenotype variability in bleeding patterns, age, response to therapy, need for surgery, and risk of inhibitor development will also have a large impact on the different levels of treatment.<sup>1,11</sup>

Disease severity, which is categorized by factor levels (severe: <1%; moderate: 1%-5%; mild: >5%), has a strong influence on the cost of hemophilia care.<sup>12</sup> The percentage of patients with hemophilia who have severe, moderate, and mild disease is 50%, 10%, and 40%, respectively.<sup>13</sup> Patients with severe hemophilia are at greater risk of hemophilia-related complications, including hemarthrosis, hemophilic arthropathy, and development of inhibitor antibodies.<sup>14-16</sup> As the largest group of the hemophilia population and consisting of those who need the highest level of service, patients with severe disease account for most of the cost of care.

Another important factor influencing the cost of hemophilia care is age. Recommendations from the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation recommend that those with severe hemophilia begin prophylaxis at a young age.<sup>17</sup> In part because of the high cost associated with prophylaxis, it has been observed that children with hemophilia utilize significantly more factor concentrate at a greater cost compared with adult patients.<sup>18</sup> It has also been reported that incremental recovery rates with factor replacement treatment are lower for patients 15 years or younger than for those who are older than 15 years.<sup>19</sup> Children with hemophilia may also have higher outpatient costs due to more extensive monitoring requirements.<sup>2</sup> Additional consideration should also be given to the growing aging population of patients with hemophilia.<sup>20</sup>

### *Indirect Costs*

Indirect costs also contribute a large economic burden and include individuals' and caregivers' lost productivity, caregivers' unpaid costs, and individuals' hemophilia-related disability.<sup>21</sup> However, it has been difficult to quantify indirect costs associated with hemophilia, which depend primarily on patient and caregiver absenteeism, ability to work, amount of care needed, and level of disability. Patients with hemophilia have a greater number of days absent from work annually and higher rates of early retirement and disability benefit payments. Patients receiving hemophilia care in any setting (inpatient, outpatient, home therapy) experience lost time from work, education, and social activities. Intangible costs, which are difficult to measure in monetary terms, include reductions in health-related quality of life (QOL) among patients with hemophilia.<sup>2</sup>

### *Inhibitor Costs*

Treating people who develop inhibitors is complex and ranks as one of the biggest challenges in hemophilia care today. The healthcare costs associated with inhibitors can be staggering because of the cost and amount of factor product required to stop bleeding.

Inhibitors develop when the body's immune system reacts to factor (factor VIII for hemophilia A or factor IX for hemophilia B) as a foreign substance and produces antibodies, diminishing or preventing the factor's ability to eventually form a normal clot. The causes of inhibitors are not precisely known, but some of the risk factors include age, ethnicity, family history, genetic defects, types of factor products used, frequency and amount of treatment, and the presence of other immune disorders.

Immune tolerance induction (ITI) therapy is a method of treating patients who develop inhibitors that typically involves administering infusions of large doses of clotting factor concentrates to a patient on a daily basis for many weeks or months. The goal of ITI therapy is to stop the inhibitor reaction from occurring in the blood and to condition the body to accept clotting factor concentrate treatments. ITI therapy is highly effective and works in about 80% of people with inhibitors. Predictors of success include how soon the inhibitor was detected, how soon ITT was started, and the peak level of inhibitor titer. Factor VIII patients have a higher rate of success than factor IX patients.

Inhibitors are also labeled "low responding" or "high responding" based on how strongly a person's immune

system reacts or responds to repeated exposure to factor concentrate.

Inhibitor titer levels increase quickly when factor concentrates are given to patients with high-responding inhibitors, compromising the ability of the clotting factor concentrate to function in preventing or stopping a bleeding episode. Repeated exposure to clotting factor concentrates will cause more inhibitors to develop. To stop bleeds and prevent bleeds under these conditions, the use of special factor products, referred to as bypassing agents, is necessary. Instead of replacing the missing factor, these products go around (or bypass) the factors that are blocked by the inhibitor to help the body form a normal clot.

Inhibitor titer levels do not rise as significantly in patients with low-responding inhibitors. Patients who have low-responding inhibitors may be treated with higher amounts of factor concentrate to overcome the inhibitor and have enough left over to form a clot. It is important to perform blood tests to measure the factor level after this new treatment schedule is established, to see if the inhibitor is absent.

The cost of care for patients with high titers of inhibitors is routinely higher than that for noninhibitor patients. Also, people with hemophilia who develop an inhibitor are twice as likely to be hospitalized because of a bleeding complication.<sup>22,23</sup> Patients with inhibitors are considered cost outliers for Hemophilia Treatment Centers (HTCs) and insurers. Costs for patients with inhibitors can include the cost of bypassing agents, ITI therapy, inpatient cost due to hospitalization for severe bleeds, and surgical interventions.<sup>24</sup> The average total healthcare expenditure per patient with inhibitors has been estimated at \$697,000, which is 2 to 5 times the cost of treating noninhibitor patients.<sup>25,26</sup> In a study of healthcare expenditures among patients with inhibitors and those without, Ullman and colleagues found that although there was no significant difference in the cost of outpatient FRPs, hospital-related costs greatly increased overall expenditures for patients with inhibitors. Furthermore, overall costs for patients with inhibitors also showed greater variability.<sup>23</sup>

### Complications

Long-term complications can contribute substantially to the overall burden of hemophilia. Internal bleeding, which can cause permanent damage if untreated, commonly occurs in the spaces around joints and often results in pain and swelling, particularly in those with

severe hemophilia.<sup>27</sup> Bleeding into the joints (hemarthrosis) can result in chronic joint disease (hemophilic arthropathy), a common complication. Joints that are subjected to repeated episodes of bleeding, referred to as target joints, are also at high risk for developing debilitating arthropathy.<sup>28</sup> Chronic joint disease often restricts patients' activity and reduces productivity, thereby having a negative impact on QOL.<sup>29</sup> Infections can also be transmitted through infusion of FRPs and other blood products.<sup>29</sup> However, improved viral inactivation techniques and increased, ongoing monitoring and surveillance have greatly improved the safety of plasma-derived products, and there have been no reported cases of transmission of HIV through factor VIII or IX products in the United States since 1987.<sup>30</sup>

Complications from hemophilia treatment can also drive up cost. The major complication associated with treatment is the development of inhibitor antibodies, resulting in poor bleeding control and the need for alternative treatments.<sup>31</sup> Other complications may include adverse reactions to factor, including anaphylaxis and nephrotic syndrome.<sup>32</sup>

### Morbidity

Although it is a relatively uncommon disorder, hemophilia and its complications are associated with substantial morbidity for those affected.<sup>29</sup> The first estimate of hemophilia burden in the United States revealed that hemophilia was associated with more than 110,000 disability-adjusted life years (DALYs) in 2007, which translates to 37 DALYs per 100,000 individuals; this number of DALYs included 13,418 years of life lost resulting from mortality and 96,677 years of life lost resulting from morbidity.<sup>29</sup> In addition, like other chronic conditions, hemophilia is associated with considerable financial costs for the US healthcare system and society.<sup>33</sup>

### New Therapies and Evolving Standards of Care for Prophylaxis and Treatment

The choice of treatment approach (prophylaxis or on-demand treatment) can affect cost in the short term and long term. Prophylaxis has been recognized as the standard of care for the treatment of patients with severe hemophilia, and should be initiated at an early age.<sup>17</sup> Appropriate prophylaxis requires treating patients in advance to prevent bleeding episodes and to avoid complications such as hemophilic arthropathy, and prophylaxis is an alternative to managing bleeding episodes with on-demand treatment. While prophylaxis results

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in increased medication costs, it also has the ability to prevent disability and improve long-term total costs and clinical outcomes. The clinical benefits of prophylaxis over on-demand treatment for patients with hemophilia are well established in the literature, including the prevention of bleeding episodes, thereby eliminating or minimizing articular damage and the onset of conditions of permanent and grave impairment; improvements in QOL; and the reduction of societal costs for healthcare, treatment, and rehabilitation.<sup>34</sup>

On-demand (episodic) treatment involves the administration of factor replacement therapy to achieve hemostasis as quickly as possible after bleeding has started.<sup>35</sup> On-demand therapy utilizes less clotting factor than prophylactic treatment.<sup>35</sup> For example, for children 6 years of age receiving hemophilia treatment, it has been estimated that 2500 IU/kg of clotting factor is required annually for on-demand therapy versus 6000 IU/kg for prophylaxis.<sup>35</sup> However, patients utilizing on-demand therapy incur higher lifetime healthcare costs than those receiving prophylaxis because of associated costs not related to medications; these include, for example, costs for rehabilitation, surgical interventions, and intermittent hospitalizations.<sup>36</sup>

While the development of recombinant factors has provided a safe and reproducible source for the factors and increased the supply, the per patient cost of continuous prophylaxis can reach \$300,000 annually.<sup>15,18,21,35,37</sup> Although its cost can be double or triple that of on-demand therapy, prophylaxis decreases the frequency of bleeding, the number of joint hemorrhages, the days of hospitalization, and the days a patient is unable to work.<sup>34,38-40</sup> Prophylaxis may result in an increased ability to participate in normal activities, improvements in QOL, and avoidance of complications, thus reducing the long-term cost of care.<sup>35</sup> The results of a retrospective panel data analysis by Carlsson and colleagues demonstrated that prophylaxis resulted in approximately 50% lower costs associated with productivity loss compared with on-demand treatment. The difference was not offset by the higher cost of clotting factor for prophylaxis versus on-demand treatment. Factor concentrate accounted for 94% of the total costs for prophylaxis and 77% for those receiving on-demand treatment.<sup>21</sup>

Despite its ability to improve patient outcomes and QOL, prophylaxis remains underused primarily because of cost. However, prophylaxis may be personalized with knowledge of a patient's pharmacokinetics combined with other information.<sup>41</sup>

As discussed earlier, the development of inhibitor antibodies is an important concern for patients treated with factor replacement therapy. Inhibitor development, which affects up to 30% of people with severe hemophilia A and up to 5% of those with severe hemophilia B, limits the efficacy of further treatment with factor VIII and IX concentrates, thus complicating management.<sup>42</sup> To determine the impact of FRPs and product switching on inhibitor development, Gouw and colleagues performed a study to evaluate the risk of inhibitor development in children who were receiving plasma-derived factor and then switched to a recombinant factor versus those who received only plasma-derived factor. The authors also assessed the association between switching among various types of factor VIII products and the development of inhibitors. The study results showed similar risks of inhibitor development with plasma-derived and recombinant factor. In addition, third-generation recombinant products were associated with a lower risk of inhibitor development compared with second-generation products.<sup>31</sup>

Many different factor products are on the market, and several products are in clinical development. Recombinant factor products in development are being formulated with longer half-lives, allowing for less frequent dosing to attain desired plasma levels and also potentially leading to an increase in medication adherence with better control of bleeding episodes.<sup>41</sup> Incorporating new hemophilia therapies into the current treatment paradigm and evolving standards of care for this disease will require changes to management plans, including those for acute bleeding episodes, prophylaxis, and surgical interventions.<sup>43</sup>

### **Multidisciplinary Care: Optimizing Outcomes and Efficacy**

The combination of the staggering costs of hemophilia therapies and the limited number of treatment alternatives has prompted the development of multidisciplinary care strategies to optimize outcomes and efficacy of hemophilia treatment regimens.

### **Hemophilia Treatment Centers**

Because of the rarity of the disease, most providers—even hematologists—do not encounter the volume of patients required to develop expertise to effectively treat and manage patients with hemophilia and related bleeding disorders. To address this unmet need, nearly 40 years ago, legislation established and funded a more sophisti-

cated delivery system for hemophilia care through the establishment of federally recognized HTC.44

A multidisciplinary team approach allows HTCs to improve patient outcomes and QOL by promoting outpatient, preventive, and home-based care. Annual outpatient comprehensive evaluation may involve such services as laboratory testing for initial and ongoing monitoring of coagulation; services provided by pediatric and adult hematologists and orthopedists; nursing services (eg, education, teaching self-infusion technique to the patient or caregiver); physical therapy; genetic counseling; social work services and support; dental services; and nutrition services. HTCs encompass outpatient, inpatient, and community settings, and services include diagnosis, treatment, rehabilitation, education, counseling, care coordination, case management, outreach clinics, surveillance, research, pharmacy, and referral.<sup>7</sup> This approach has reduced the substantial cost of factor for many hospital budgets by reducing emergency department visits and avoiding hospitalization.<sup>5</sup>

Working with HTCs allows patients to receive annual comprehensive care assessments and have treatment recommendations transmitted to their primary physician, ensuring continuity of care.<sup>45</sup>

Approximately 70% of patients with hemophilia in the United States receive care through HTCs.<sup>7</sup> Patients who receive their care at HTCs have been shown to have better outcomes at lower cost compared with those who obtain their care outside HTC networks. A 40% survival advantage and 40% reduction in bleed-related hospitalizations have been reported in patients who used an HTC at least once in a 3-year study period. Improvements were shown in the study population despite having more severe symptoms and higher proportions of patients with HIV and hepatitis than their peers who received care outside the HTC setting.<sup>46,47</sup>

As a result of their covered entity status, many HTC programs offer integrated pharmacy services, through what is frequently referred to as a 340B pharmacy. These programs allow access to discounted FRPs that result in savings that can be passed on to the payer while providing program income to support the services of the HTC.<sup>7</sup>

## Specialty Pharmacy Services

### *Role of Specialty Pharmacy*

Specialty pharmacies focus on the provision of high-cost, high-touch medication therapies (requiring special storage or handling of the medications combined with close monitoring of the patient's drug therapy) for

patients with complex disease states.<sup>48</sup> Patients with hemophilia can have their prescriptions filled and delivered to the home by specialty pharmacies, which also offer a variety of clinical management and adherence programs designed to improve outcomes and lower costs. These programs may provide medication information, access to pharmacists and nurses with specialized training, home visits and teaching for patients to learn how to self-infuse factor product, refill reminders, submission of patient bills to insurers, and other services.<sup>49</sup>

Variables that contribute to the complexity of clotting factor dosing include the patient's weight, disease severity, bleeding patterns, presence of comorbidities, and the variety of commercially available clotting factor products.<sup>4</sup> Information on these variables should be collected via specialty pharmacy services to analyze the relationship with cost variation and to better manage factor use.

Most insurance plans, including Medicaid programs, utilize specialty pharmacies to manage the care of patients needing specialty drugs. Nearly 40% of Medicaid managed care plans require patients with hemophilia to obtain FRPs from specialty pharmacies.<sup>50</sup> Many specialty pharmacies and hemophilia home care companies operate under pharmacy benefit managers, which are drug plans that manage retail, mail order, and specialty pharmacy drug benefits for employers and health insurers. Through their expanded market size and therapeutic scope, specialty pharmacies are able to leverage purchasing power and implement systems to manage costs.<sup>49</sup> Case management programs through specialty pharmacies can provide a monthly savings of approximately \$6000 per patient.<sup>51</sup>

### *Considerations When Dispensing FRPs*

The potency of most FRPs varies from batch to batch during the production and manufacturing. This variability must be considered every time FRP is procured. Although administering higher doses than prescribed is typically not harmful, overutilization provides no additional benefit and can result in excessive costs of treatment since the cost to the payer depends on the total number of units of FRP dispensed.

Assay management—that is, the process of filling a prescription for FRP as close as possible to the prescribed dose—is an important tool that can help control and lower these costs. While MASAC recommendation #188 proposes dispensing within plus or minus 5% to 10% of the prescribed target dose, barring extenuating circumstances, many specialty pharmacies as well as payers strive for even tighter standards ( $\pm 1\%$  to  $3\%$ ).<sup>52</sup> Challenges

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that may impact this process include but are not limited to:

- Availability of factor in the desired range at any given time
- The range of assays commercially available
- Pediatric dosing in which weight-based dosing and the matching/selection of suitable factor assays is more problematic

Specialty pharmacists can monitor bleeds, clotting factor inventory, utilization patterns, and use of adjunctive therapies to assess treatment, facilitate patient-physician communication, and optimize outcomes.<sup>4</sup>

FRPs and home infusion services can be delivered by specialty pharmacies, 340B pharmacies, and specialized pharmacy benefit managers.

### Addressing Current Insurance Barriers

The escalating cost of hemophilia treatments is a potential barrier to patient access. It is important that managed care plans provide comprehensive coverage for hemophilia care. Patients with hemophilia can be covered by private health insurance, Medicaid, or Medicare, or may be uninsured.<sup>7</sup> Patients with hemophilia who have no health insurance or insufficient health insurance may encounter difficulties obtaining necessary medications in a timely manner. In turn, the failure to receive proper and timely treatment may result in excessive inpatient admissions and emergency department utilization.

In a study by Zhou and colleagues, insurance coverage was reported as one of the most common barriers to care for adult patients.<sup>53</sup> Almost one-half of patients with hemophilia are covered by Medicaid, and another one-third are uninsured or have insufficient health insurance.<sup>7,54</sup> Despite the cost-effectiveness associated with prophylaxis, patients with public insurance are more likely to receive on-demand therapy, which is associated with lower short-term healthcare costs.<sup>55</sup>

Although most insurance coverage includes factor replacement therapy, coinsurance rates of 10% can be costly and prohibitive for many families. Some families may reduce their employment to qualify for Medicaid or because of disability, which places the cost burden on taxpayers.<sup>53</sup> In 2007, 6% (\$139 million) of the Medicaid budget in California was spent on blood products including factor, placing it as the sixth-most expensive therapeutic class by total expenditure, up from tenth in 2004.<sup>56</sup> In contrast, the combined medical and pharmacy cost of a typical commercial insurer is estimated

to be a relatively small portion of the total budget. According to a Milliman actuarial study of costs related to hemophilia, the estimated claims cost for an average commercial population is \$0.42 per member per month for hemophilia A and B medical and pharmacy costs, which is less than 0.2% of a typical commercial insurer's total budget.<sup>11</sup>

Third-party payers continue to be scrutinized for having insufficient resources to provide optimal care in a cost-effective fashion. To address this need, third-party payers have recognized and adapted the model of comprehensive care. In one study, Globe and colleagues examined the annual utilization and cost of hemophilia-related healthcare services; based on an evaluation of 336 retrospective chart reviews of 5 comprehensive HTC in the United States, the total annual cost of care was shown to be \$139,102.<sup>8</sup> More recently, a study by Guh and colleagues, who collected data from the MarketScan Medicaid Multi-State Commercial and Medicare Supplemental databases, estimated average Medicaid expenditures in 2008 among a total of 511 Medicaid-enrolled patients with hemophilia at \$142,987 (median, \$46,737).<sup>25</sup>

Recent insurance reform and other healthcare reform changes will impact access to care for individuals with hemophilia. The 2010 Affordable Care Act implemented health reforms that will affect insurance coverage. These changes, which include prohibiting lifetime and annual limits on coverage for essential benefits, providing relief for Medicare seniors who hit the prescription "donut hole" or coverage gap, offering insurance for the uninsured with preexisting conditions, and expanding Medicaid eligibility, have the potential to be beneficial to those with hemophilia.<sup>49</sup>

Key considerations identified for Medicaid health plans to anticipate the needs of members with hemophilia are<sup>6</sup>:

- Treatment access and quality—including network management and medical management to ensure access to specialized providers, including HTCs
- Care management—encompassing coordinating multidisciplinary services and designating a lead care coordinator to interact with the patient and family
- Cost management—including ensuring appropriate pricing and administration of costly FRPs
- Pharmacy management—encompassing contracting with the most appropriate pharmacies to provide cost-effective and timely factor replacement services for routine and emergency needs
- Risk selection—including proactively developing financing solutions to mitigate adverse risk selection

- Patient involvement—focusing on engaging patients in self-management and health plan decision making, and helping to ensure QOL

Additional research and education are needed to understand the effects of health insurance on hemophilia care and expenditures, to evaluate treatment strategies, and to implement strategies to improve outcomes and reduce costs of care.<sup>57</sup>

### Utilization Management

Utilization management programs can be used to help ensure the optimal use of clotting factor and supplies. Several proven strategies can be incorporated to control costs while continuing to provide high-quality care. Regular review of clotting factor dosing is recommended to verify that it is within recommended parameters and that the patient is experiencing the appropriate clinical response.

Prophylactic regimens should be reassessed and adjusted when changes occur in the patient's individual circumstances. Together with patient education and factor management, protocols can be developed to minimize waste and ensure adequate supply.<sup>4</sup>

### Conclusion

It is critical to tailor treatment and management protocols to manage hemophilia cases effectively. Hemophilia treatment should be individualized based on the patient's age, weight, bleeding pattern, joint health, physical activity, clotting factor levels, and compliance.<sup>41</sup> Successful collaboration and cooperation between providers and managed care programs can improve outcomes and lower costs in the delivery of hemophilia services. Further research is needed to establish criteria regarding when to initiate prophylaxis, the optimal regimen to prescribe, and when to discontinue therapy.

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## REFERENCES

- Escobar MA. Health economics in haemophilia: a review from the clinician's perspective. *Haemophilia*. 2010;16(suppl 3):29-34.
- Gater A, Thomson TA, Strandberg-Larsen M. Haemophilia B: impact on patients and economic burden of disease. *Thromb Haemost*. 2011;106(3):398-404.
- Johnson A, Zhou ZY. Cost of care in hemophilia and possible implications of health care reform. *Hematology Am Soc Hematol Educ Program*. 2011;2011:413-418.
- Blankenship CS. To manage costs of hemophilia, patients need more than clotting factor. *Biotechnol Healthc*. 2008;5(4):37-40.
- Baker JR. *Design for an Evaluation of Hemophilia Treatment Center 340B Drug Pricing Programs* [dissertation]. Los Angeles, CA: University of California; 2013. <https://escholarship.org/uc/item/01p6s37v>. Accessed February 17, 2015.
- Kaufman RJ, Powell JS. Molecular approaches for improved clotting factors for hemophilia. *Blood*. 2013;122(22):3568-3574.
- Medicaid Health Plans of America. *Addressing the Needs of Members With Hemophilia in Medicaid Managed Care: Issues and Implications for Health Plans*. 2013. [http://www.mhpa.org/\\_upload/MHPA%20Hemophilia%20Issue%20Brief%20final%20082113.pdf](http://www.mhpa.org/_upload/MHPA%20Hemophilia%20Issue%20Brief%20final%20082113.pdf). Accessed February 17, 2015.
- Globe DR, Curtis RG, Koerper MA; HUGS Steering Committee. Utilization of care in haemophilia: a resource-based method for cost analysis from the Haemophilia Utilization Group Study (HUGS). *Haemophilia*. 2004;10(suppl 1):63-70.
- Tencer T, Friedman HS, Li-McLeod J, Johnson K. Medical costs and resource utilization for hemophilia patients with and without HIV or HCV infection. *J Manag Care Pharm*. 2007;13(9):790-798.
- Bohn RL, Avorn J, Glynn RJ, Choodnovskiy I, Haschemeyer R, Aledort LM. Prophylactic use of factor VIII: an economic evaluation. *Thromb Haemost*. 1998;79(5):932-937.
- Fredericks M, Pyenson B, Iwasaki K. An Actuarial Study of Hemophilia: Implications for Commercial and Medicaid Managed Care Plans. New York, NY: Milliman, Inc; October 24, 2013. <http://www.milliman.com/uploadedFiles/insight/2014/Hemophilia-actuarial-study.pdf>. Accessed February 17, 2015.
- White GC 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J; Factor VIII and Factor IX Subcommittee. Definitions in hemophilia. Recommendation of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost*. 2001;85(3):560.
- Online Mendelian Inheritance in Man (OMIM). <http://www.omim.org/>. Accessed January 4, 2015.
- Aledort LM, Haschemeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med*. 1994;236(4):391-399.
- Löfqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients—a long-term follow-up. *J Intern Med*. 1997;241(5):395-400.
- Franchini M, Tagliaferri A, Mengoli C, Cruciani M. Cumulative inhibitor incidence in previously untreated patients with severe hemophilia A treated with plasma-derived versus recombinant factor VIII concentrates: a critical systematic review. *Crit Rev Oncol Hematol*. 2012;81(1):82-93.
- National Hemophilia Foundation. MASAC Recommendation Concerning Prophylaxis (Regular Administration of Clotting Factor Concentrate to Prevent Bleeding). November 4, 2007. <http://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendation-Concerning-Prophylaxis>. Accessed January 25, 2015.
- Nerich V, Tissot E, Faradji A, et al. Cost-of-illness study of severe haemophilia A and B in five French haemophilia treatment centres. *Pharm World Sci*. 2008;30(3):287-292.
- Roth DA, Kessler CM, Pasi KJ, et al. Human recombinant factor IX: safety and efficacy studies in hemophilia B patients previously treated with plasma-derived factor IX concentrates. *Blood*. 2001;98(13):3600-3606.
- Konkle BA. Clinical challenges within the aging hemophilia population. *Thromb Res*. 2011;127(suppl 1):S10-S13.

## Reports

21. Carlsson KS, Högård S, Lindgren A, et al. Costs of on-demand and prophylactic treatment for severe haemophilia in Norway and Sweden. *Haemophilia*. 2004;10(5):515-526.
22. Gringeri A, Mantovano L, Scalone L, Mannucci PM; The COCIS Study Group. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. *Blood*. 2003;102(7):2358-2263.
23. Ullman M, Hoots WK. Assessing the costs for clinical care of patients with high-responding factor VIII and IX inhibitors. *Haemophilia*. 2006;12(suppl 6):74-79; discussion 79-80.
24. Shapiro A, Pipe S, Geraghty S, et al. Hemophilia and managed care: partnering to achieve cost-effective care. *Am J Pharm Benefits*. 2011;3(5):248-255.
25. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Healthcare expenditures for males with haemophilia and employer-sponsored insurance in the United States, 2008. *Haemophilia*. 2012;18(2):268-275.
26. Teitel J. Inhibitor economics. *Semin Hematol*. 2006;43(2, suppl 4):S14-S17.
27. National Hemophilia Foundation. Fast Facts. <https://www.hemophilia.org/About-Us/Fast-Facts>. Accessed January 4, 2015.
28. Berntorp E, Spotts G, Patrone L, Ewenstein BM. Advancing personalized care in hemophilia A: ten years' experience with an advanced category antihemophilic factor prepared using a plasma/albumin-free method. *Biologics*. 2014;8:115-127.
29. Siddiqi AA, Ebrahim SH, Soucie JM, Parker CS, Atrash HK. Burden of disease resulting from hemophilia in the U.S. *Am J Prev Med*. 2010;38(4 suppl):S482-S488.
30. National Hemophilia Foundation. HIV/AIDS. <https://www.hemophilia.org/Bleeding-Disorders/Blood-Safety/HIV/AIDS>. Accessed February 17, 2015.
31. Gouw S, van der Bom J, Ljung R, et al. Factor VII products and inhibitor development in severe hemophilia A. *N Engl J Med*. 2013;368(3):231-239.
32. Franchini M. The modern treatment of haemophilia: a narrative review. *Blood Transfus*. 2013;11(2):178-182.
33. Liras A, Segovia C, Gaban AS. Advanced therapies for the treatment of hemophilia: future perspectives. *Orphanet J Rare Dis*. 2012;7:97.
34. Research Center for Health Technology Assessment. Assessment of the clinical and economic impact of Advate in prophylactic and treatment of hemophilia A patients. *Italian J Public Health*. 2012;9(4, suppl 2):S1-S50.
35. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357(6):535-544.
36. Petrova G, Tachkov K, Georgieva S, Dimitrova M. Humanistic and economic aspects of haemophilia treatment in Bulgaria. Comparison between two therapeutic approaches: prophylactic vs. on-demand treatment. *Biotechnology & Biotechnological Equipment*. 2014;28(3):576-582.
37. Auerswald G, von Depka Prondzinski M, Ehken B, et al. Treatment patterns and cost-of-illness of severe haemophilia in patients with inhibitors in Germany. *Haemophilia*. 2004;10(5):499-508.
38. Colombo G, Di Matteo S, Mancuso M, Santagostino E. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. *Clinicoecon Outcomes Res*. 2011;3:55-61.
39. Fischer K, Pouw ME, Lewandowski D, Janssen MP, van den Berg HM, van Hout BA. A modeling approach to evaluate long-term outcome of prophylactic and on demand treatment strategies for severe hemophilia A. *Haematologica*. 2011;96(5):738-743.
40. Salinas-Escudero G, Galindo-Suarez RM, Rely K, Carrillo-Vega MF, Muciño-Ortega E. Cost-effectiveness analysis of prophylaxis vs. "on demand" approach in the management in children with hemophilia A in Mexico. *Bol Med Hosp Infant Mex*. 2013;70(4):290-297.
41. World Federation of Hemophilia. WFH Guidelines for the Management of Hemophilia. July 2012. <http://www.wfh.org/en/resources/wfh-treatment-guidelines>. Accessed February 17, 2015.
42. Bensen-Kennedy D. Bringing new therapy options to the hemophilia community. *Thromb Res*. 2013;131(suppl 2):S15-S18.
43. Shapiro AD. Long-lasting recombinant factor VIII proteins for hemophilia A. *Hematology Am Soc Hematol Educ Program*. 2013;2013:37-43.
44. Baker JR, Crudder SO, Riske B, Bias V, Forsberg A. A model for a regional system of care to promote the health and well-being of people with rare chronic genetic disorders. *Am J Public Health*. 2005;95(11):1910-1916.
45. Aledort LM, Coates J. Can managed care support hemophilia in the 21st century? *Am J Hematol*. 2005;79(2):171-173.
46. Soucie JM, Nuss R, Evatt B, et al. Mortality among males with hemophilia: relations with source of medical care. The Hemophilia Surveillance System Project Investigators. *Blood*. 2000;96(2):437-442.
47. Soucie J, Symons J 4th, Evatt B, et al; Hemophilia Surveillance System Project Investigators. Home-based factor infusion therapy and hospitalization for bleeding complications among males with haemophilia. *Haemophilia*. 2001;7(2):198-206.
48. American Pharmacists Association. Specialty Pharmacy. <http://www.pharmacist.com/specialty-pharmacy>. Accessed January 25, 2015.
49. The Lewin Group, Inc. *National Hemophilia Foundation: Strategic Summit Report*. October 2012. <http://www.hemophilia.org/sites/default/files/article/documents/HemophiliaSummitFinalReportOct2012.pdf>. Accessed February 17, 2015.
50. EMD Serono. *EMD Serono Specialty Digest*. 8th ed. 2012. <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=15229>. Accessed February 17, 2015.
51. Gilbert A, Tonkovic B. Case report of specialty pharmacy management of hemophilia. *J Manag Care Pharm*. 2011;17(2):175-176.
52. National Hemophilia Foundation. MASAC Recommendations Regarding Standards of Service for Pharmacy Providers of Clotting Factor Concentrates for Home Use to Patients with Bleeding Disorders. 2008. <http://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendations-Regarding-Standards-of-Service-for-Pharmacy-Providers-of-Clotting-Factor-Concentrates-for-Home-Use-to-Patients-with-Bleeding-Disorder#sthash.RTNldP0U.dpuf>. Accessed January 25, 2015.
53. Zhou ZY, Riske B, Forsberg AD, et al. Self-reported barriers to hemophilia care in people with factor VIII deficiency. *Am J Prev Med*. 2011; 41(6, suppl 4):S346-S353.
54. Iowa Hemophilia Advisory Committee. *Report to the Governor and General Assembly 2009*. [https://www.idph.state.ia.us/adper/common/pdf/legis/2009\\_hemophilia.pdf](https://www.idph.state.ia.us/adper/common/pdf/legis/2009_hemophilia.pdf). Accessed February 17, 2015.
55. Epstein J, Xiong Y, Woo P, Li-McLeod J, Spotts G. Retrospective analysis of differences in annual factor VIII utilization among haemophilia A patients. *Haemophilia*. 2012;18(2):187-192.
56. California Healthcare Foundation. The Medi-Cal Prescription Drug Benefit: An Overview. December 2009. <http://www.chcf.org/publications/2009/12/the-medical-prescription-drug-benefit-an-overview>. Accessed February 17, 2015.
57. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Health care expenditures for Medicaid-covered males with haemophilia in the United States, 2008. *Haemophilia*. 2012;18(2):276-283.