



ORIGINAL ARTICLE

US Hemophilia Treatment Center population trends 1990–2010: patient diagnoses, demographics, health services utilization

J. R. BAKER,* B. RISKE,† J. H. DRAKE,‡ A. D. FORSBERG,§ R. ATWOOD,¶ M. VOUTSIS** and R. SHEARER†

*Center for Comprehensive Care & Diagnosis of Inherited Blood Disorders and Department of Pediatrics, University of California Los Angeles, Orange, CA; †Hemophilia and Thrombosis Center, University of Colorado Health Sciences Center, Denver, CO; ‡Gulf States Hemophilia and Thrombophilia Center, University of Texas Health Science Center at Houston, Houston, TX; §New England Hemophilia Center, UMass Memorial Hospital, Worcester, MA; ¶Winston-Salem, NC; and

**Mount Sinai Regional Comprehensive Hemophilia Treatment Center, Mount Sinai School of Medicine, New York, NY, USA

Summary. For several decades, US government agencies have partially supported regional networks of Hemophilia Treatment Centers (HTC). HTC multidisciplinary teams provide comprehensive and coordinated diagnosis, treatment, prevention, education, outreach and surveillance services to improve the health of people with genetic bleeding disorders. However, national data are scarce on HTC-patient population trends and services. The aim of the study was to examine national trends over the past 20 years in patient diagnoses, demographics and health services utilization among the Health Resources and Services Administration (HRSA) and Centers for Disease Control and Prevention (CDC)-supported HTC network. Diagnoses, demographics and health services utilization data from 1990 to 2010 were aggregated from all HTCs using the Hemophilia Data Set (HDS). From 1990 to 2010, the

HTC population grew 90% from 17 177 to 32 612. HTC patients with von Willebrand's disease increased by 148%, females by 346%, Hispanic patients by 236% and African Americans by 104%. Four thousand and seventy-five deaths were reported. From 2002 to 2010, annual comprehensive evaluations grew 38%, and persons with severe haemophilia on a home intravenous therapy programme rose 37%. In 2010, 46% of patients were less than 18 years vs. 24% for the general US population. The Hemophilia Data Set documents the growth and diversity of the US Hemophilia Treatment Center Network's patient population and services. Despite disproportionate deaths due to HIV, the HTC patient base grew faster than the general US population. The HDS is a vital national public health registry for this rare-disorder population.

Keywords: haemophilia, public health, registries, trends

Introduction

Over the past 20 years, US residents with genetic chronic bleeding disorders have obtained an array of health services from the national network of regionally organized Hemophilia Treatment Centers (HTC) [1,2]. All Hemophilia Treatment Centers

(HTC) in the US, in collaboration with the Health Resources and Services Administration (HRSA) and the Centers for Disease Control and Prevention (CDC), annually collect and report aggregate data to assess population and service characteristics. However, national examinations of longitudinal trends of the US HTC-patient population and services utilized are scarce. Such analyses are important for public health planning and evaluation. This is the first report of demographics, health services and mortality among the US HTC network from 1990 through 2010.

National haemophilia registries are found in other countries including Sweden, [3] the United Kingdom [4–6] and Canada [7,8]. Medical registries are systematic compilations of delineated demographic and health

Correspondence: Judith R. Baker, MHSA, Federal Hemophilia Treatment Centers/Region IX, UCLA Department of Pediatric Hematology/Oncology, 10833 Le Conte Blvd., A2-410, Los Angeles, CA 90095, USA.

Tel.: +310 794 6264; fax: +310 206 0288;

e-mail: judithbaker@mednet.ucla.edu

Accepted after revision 25 June 2012

datasets that are organized in central databases for predetermined purposes and which describe persons with particular health attributes. Registries can contain a wealth of data on the long-term clinical outcomes. In the US, early attempts at haemophilia registries were primarily state based [9,10] or centre specific [11]. In 1972, the Heart and Lung Institute/National Institute of Health conducted a study on the use of human blood and blood products that included a pilot of haemophilia treatment in the US [12]. That pilot estimated a prevalence of 25 500 individuals with factor VIII (FVIII) (haemophilia A) or factor IX (FIX) (haemophilia B) deficiency who were treated in 1970 and/or 1971. Over 90% of the patients were under the age of 25 years. Over 95% of all physicians responding to the survey cared for less than 10 patients. Those authors noted the importance of patient volume to developing and improving treatment skills.

Today, the US has a national network of 129 HTC, which provide multidisciplinary comprehensive care services to over 30 000 individuals with haemophilia, von Willebrand's disease (VWD) and other inherited bleeding disorders [1]. Haemophilia is a rare (prevalent in 1/7500 males) disorder in which the individual lacks or is deficient in either clotting FVIII or FIX. People with severe haemophilia (factor level <1%) may experience bleeding usually into joints or muscles, as often as weekly. Those with moderate (1–5%) disease may experience bleeding without antecedent trauma; individuals with mild disease (>5%) do not. Haemorrhages are treated by intravenous infusions of factor concentrates either on demand (at haemorrhage onset) or prophylactically (2–3 times a week). Early recognition of bleeding onset and swift response via home infusion of factor products [13] facilitates rapid treatment, reducing morbidity and costs [14].

VWD is a common but often under-recognized condition that occurs equally in males and females and results in prolonged bleeding. VWD symptoms can range from mild to severe. The most common signs are easy bruising, frequent or prolonged nose or menstrual bleeds or prolonged bleeding after surgery, dental work or injury.

To decrease long-term complications, and reduce mortality, individuals with haemophilia, VWD and other rare bleeding disorders should be diagnosed early and their care should be coordinated by multidisciplinary specialists at HTCs [15]. The public health mission of HTCs has expanded [2]. Regional leadership guides HTCs to perform nearly all of the 10 essential public health services, with an emphasis on early access to diagnosis and treatment [16,17].

Methodology

In 1987, through an interagency agreement with HRSA, the CDC initiated funding for HTCs to

conduct HIV risk-reduction services to determine the HIV prevalence among individuals with haemophilia who were exposed to contaminated blood products, their sexual partners and children. To monitor HIV risk-reduction service delivery, in 1989 a national committee of HTC clinicians and HRSA staff established a registry, the Hemophilia Minimal Data Set (HDS). Registry data were aggregated at the HTC level in response to widespread fears that individual-level data would threaten the HIV-status confidentiality, and lead to discrimination. Since 1990, HDS data from all HTCs have been submitted annually to HRSA and CDC by the 12 regional grantee centres.

Over the years, the HDS broadened to capture more detailed demographic, diagnostic, mortality and health services data. It evolved into an electronic system to enhance data quality, by ensuring that inclusion criteria are met and purging old records. Each HTC uses a glossary that defines the data elements and outlines their proper entry to generate accurate reports. The annual HDS report includes patients who have any HTC visit type during the calendar year. Patients who die are considered 'active' for that calendar year and purged from future reports.

Individuals are considered to be 'active' only at their primary HTC. Duplication is a consistent but presumed small problem, typically occurring when patients need access to specialty services (e.g. complex orthopaedic surgery) that are offered only at another HTC. The HDS report more likely undercounts patients because it does not include those with mild disorders who commonly visit the Center every 2 or 3 years. HDS variables and definitions changed between 1990 and 2010, limiting the number of data elements that could be compared. This analysis examines trends where variable definitions were consistent.

Results

Diagnoses of HTC patients

From 1990 to 2010, the numbers of patients seen at HTCs experienced growth and change (Fig. 1). While the general US population grew 24% [18], the HTC population grew 90% from 17 177 to 32 612. Milestones were achieved in 1994 with >20 000 HTC patients, in 2000 with >25 000 patients and in 2008 with >30 000 patients. From 1990 to 2010, the HTC haemophilia population with FVIII deficiency grew by 35% from 9 805 to 13 276; and those with FIX deficiency grew by 66% from 2 531 to 4 209. Factor IX as a percent of the haemophilia patients grew from 20% in 1990 to 24% in 2010. HTC patients with VWD grew by 148% from 5 326 in 1996 to 13 239 in 2010; they now nearly equal the HTC FVIII population. The total number of HTC patients with 'Other' rare factor deficiencies (e.g. factors I, II, V, VII, X, XI

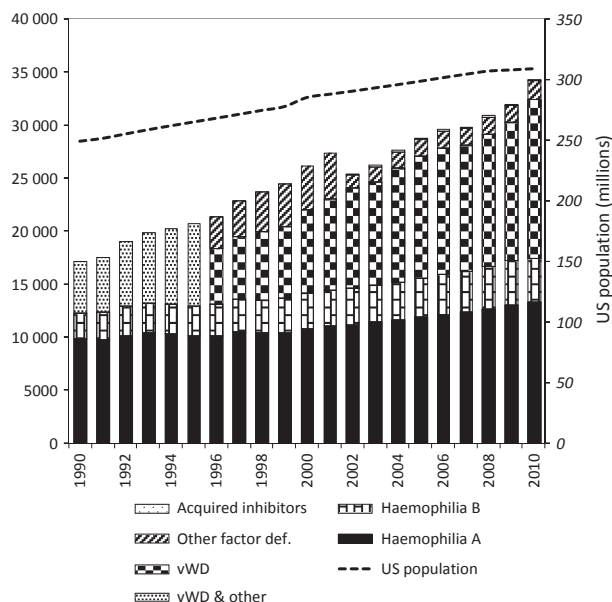


Fig. 1. US Haemophilia treatment center patient population by diagnosis 1990–2010.

and XIII) grew by 43% from 1 237 in 2002 to 1 772 in 2010. These factor deficiencies have extremely low prevalence in the general population.

Starting in 2002, disorder severity was collected, and appeared to remain constant. Roughly half of all HTC haemophilia patients had 'severe' disorder, 20% had moderate haemophilia and 30% were classified with mild deficiency. The severity of the VWD HTC population also appeared to remain steady. Approximately 85% of HTC patients with VWD had Type 1 (mild), about 13% had Type 2 (moderate) and about 3% Type 3 (severe).

Patients infected with HIV remain an important, although declining population: from 4 508 in 1990 to 1 264 in 2010. No new cases of treatment-related HIV have been reported since the mid-1980s. The decline in the number of HIV patients is related to significant mortality, before effective HIV medications became available in the mid-1990s.

Gender

The female HTC population grew 346%, from 2 288 in 1990 to 10 201 in 2010 (Fig. 2). In 2010, females comprised 31% of all HTC patients, up from 13% in 1990. Beginning in 2002, the dataset included diagnoses by gender. Females with VWD (>8 100 in 2010) now represent nearly 80% of the female HTC population. While females consistently represented about 7% of the HTC haemophilia VIII and FIX population between 2002 and 2010, their absolute numbers grew by 62% during that interval to 1 165 individuals in 2010. During each year of that time period, females

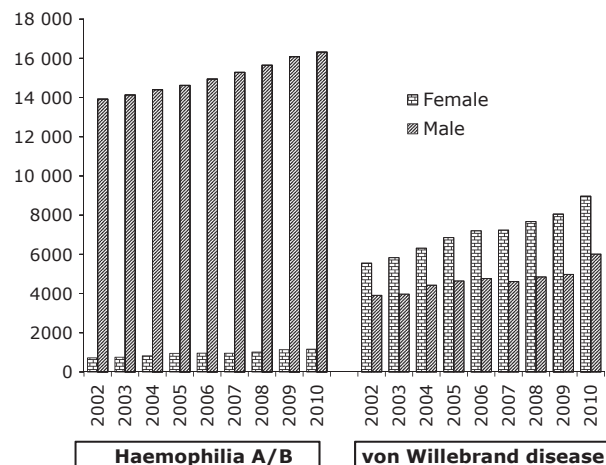


Fig. 2. US Haemophilia treatment center patients: haemophilia and von Willebrand's disease by gender 2002–2010.

with VWD outnumbered males, with 60/40 females to males. Approximately 45% of HTC patients with VWD under the age of 13 were female whereas closer to 70% of HTC patients with VWD over the age of 13 were female.

Race/ethnicity

Bleeding disorders occur in individuals of all race and ethnic backgrounds. This is reflected in the US HTC network. In 2010, 71% of HTC patients were White, 13% Hispanic, 9% Black and 7% 'Other.' This represented slightly lower proportions of minorities as compared with the 2010 U.S. population of 64% White, 16% Hispanic, 13% Black and 6% 'Other' [18]. However, from 1990 to 2010, the numbers of HTC Hispanic and Black patients grew by 236% and 104% respectively (compared to a 76% increase for White and 71% for 'Other'). The number of Hispanic HTC patients exceeded the number of Black HTC patients in 1996, with that trend persisting.

Age

Between 1990 and 2010, the HTC patient base <13 years rose 82%, from 5 441 in 1990 to 9 873 in 2010. HTC patients aged 13+ years increased by 98% from 11 470 in 1990 to 22 739 in 2010. Starting in 2002, the HDS age categories expanded to better quantify age-related access to care and for adolescent transition planning. From 2002 to 2010, the number of HTC infant and toddler patients (ages 0–2) rose 2% to 1 271; HTC paediatric patients aged 3–12 grew 14% to a total of 8 602. Teenage HTC patients (ages 13–17) grew by 27% to 5 102; post high school (ages 18–21) patients grew 59% to 3 576, young adults (ages 22–24) increased by 68% to 1 913 and adults (>24 years) grew 31% to 12 148. Compared with the

general US population, the current HTC patient base remains young. In 2010, 46% of HTC patients were <18 years of age vs. 24% for the US [18].

Health services utilization

From 2002 to 2010, specialty laboratory testing at HTCs for diagnostic evaluations rose 38% from 6 842 to 9 432. The number of individuals obtaining an annual comprehensive exam conducted by at least three members of the multidisciplinary team grew 33% from 12 701 to 18 296. HTC patients with severe haemophilia on a home intravenous therapy programme rose 37%, from 4 742 to 6 166. In 2010, 77% of HTC patients with severe haemophilia, 51% with moderate and 21% with mild haemophilia used home intravenous therapy (growing respectively from 70%, 43% and 14% in 2002). Home intravenous therapy grew in the severe VWD population from 39% in 2002 to 46% in 2010.

Mortality

From 1990 to 2010, HTCs reported a total of 4 705 patient deaths (Fig. 3). Annual numbers of deaths rose from 300 in 1990 to a high of 436 in 1994. Mortality then dropped each year through 1997 ($n = 191$), hovered between 157 and 185 and dropped below 150 in 2005 where it remained with 126 deaths reported in 2010. Causes of death were reported beginning in 1993; the definitions were refined in 2002. The numbers and proportions of HIV-related

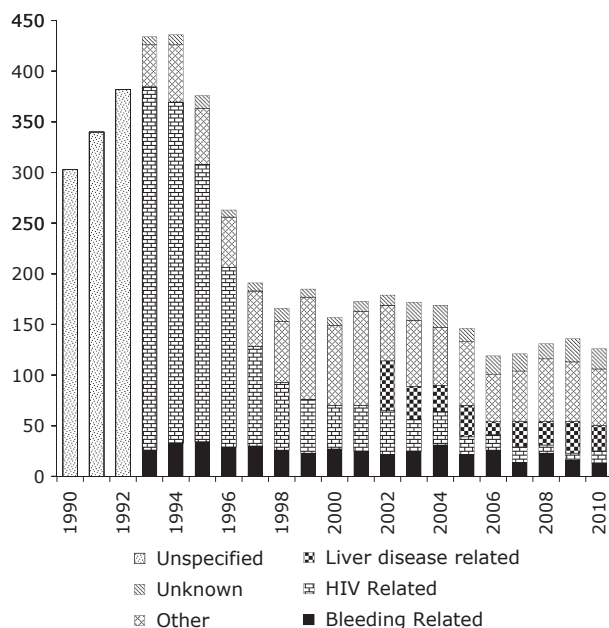


Fig. 3. US Haemophilia treatment center patients: mortality by cause 1990–2010.

deaths fell from a high of 358 in 1993 (representing 83% of all deaths) to a low of eight in 2008 (6% of all deaths). Bleeding was implicated in the deaths of 445 individuals between 1993 and 2010; annual average of 25 (range 6–22%). Liver disease-related mortality was reported in 256 cases from 2002 to 2010 (annual average of 28). ‘Other causes not specified’ were implicated in 514 deaths since 2002 (annual average of 57).

Discussion

This descriptive examination of trends from the US Hemophilia Treatment Center network’s Hemophilia Data Set from 1990 to 2010 characterizes growth and diversity in the bleeding-disorder populations obtaining HTC care, increased health service utilization, reduced mortality and changes in the primary cause of death. Despite disproportionate loss of life due to the HIV epidemic, starting in the 1980s, the HTC patient-base expansion outpaced the growth of the general US population.

The major driver of the HTC population increase was in persons with VWD, particularly females [19]. By 2010, the number of HTC patients with VWD nearly equalled the number with haemophilia. The surge in female patients is concurrent with focused outreach and education – by HTCs and consumer organizations – in response to recognized need [20,21]. The female HTC population may continue to grow secondary to national VWD recommendations promulgated by the National Heart Lung and Blood Institute [21], the American College of Obstetrics and Gynecology [22] and Healthy People 2020 [23]. The gender differences in the age trends among HTC VWD patients may be understood in the context of VWD being a symptom-driven diagnosis. Bleeding in boys with VWD may be prompted primarily by the typical childhood physical-activity injuries that boys outgrow, whereas menses are the more common bleeding symptom of affected girls.

Individuals with the rarest factor deficiencies also comprise an important and growing group of patients. The extremely low prevalence of these disorders poses particular public health challenges [24,25]. Therapies for these individuals are not often available.

Minority patients served at HTCs increased, particularly Hispanics, raising demands for HTC Spanish speakers. Yet, these data suggest that Hispanics and African Americans remain under represented. Research is needed to understand differences in minority utilization of HTCs, which could help design interventions.

The US HTC population remains largely paediatric; why relatively fewer adults obtain HTC care is not clear. From 1990 to 2010, HTC growth was similar among patients under and over the age of 13 years.

Yet in 2010, nearly half of the US HTC patients were still <18 years of age (vs. 24% for the US population). A significant cohort of adult patients died of HIV and hepatitis C, resulting in a slightly age-skewed population. The progressive nature of musculoskeletal disease, prior to the recent widespread adoption of prophylaxis treatment, may lead adult patients to prioritize obtaining care from orthopaedics, hepatology and infectious disease specialists who, while affiliated with HTCs through communication and referral for care management, are typically located in separate clinics. The authors posit that the rise of Medicaid-managed care and commercial insurance policy changes may also restrict HTC access, more so for adults than for children, because most states offer special insurance programmes for children with catastrophic conditions.

HTC health service utilization grew between 2002 and 2010, noted by the increases in diagnostic evaluations, annual comprehensive examinations and home i.v. therapy. Obtaining accurate diagnosis is the first step to determining appropriate treatment. The dearth of hospitals' coagulation laboratory capacity sometimes necessitates sending out samples to reference laboratories, increasing the delays and accuracy due to mishandling fragile biologic materials. [26] Most HTCs have coagulation labs, further illustrating the comprehensiveness of their care.

The rise of HTC patients who obtained an annual comprehensive evaluation (33%) outpaced the overall HTC population growth (28%). This is noteworthy not only given the emerging literature, which documents the benefits of team-based care for vulnerable populations [27], but because HTC growth was driven by individuals with VWD, most of whom are diagnosed with the mild form of the condition, which typically does not require an annual HTC visit. The annual comprehensive visit is the hallmark of HTC care. It includes individual (and often family) consultations with the core team: haematologist, nurse, social worker and physical therapist plus other specialists as needed. This team assesses physical, social, emotional and financial status; devises a coordinated care plan in conjunction with the patient/family, with a focus on disease prevention and cost reduction for the next year. It is modified as needed and shared with the primary care practitioner and other specialists.

Medically supervised home i.v. therapy is the standard of care for severe bleeding disorders [13]. It provides rapid haemorrhage treatment or prevention, and when administered prophylactically can avert or reduce joint damage [28]. The growth in home i.v. programme utilization demonstrates HTC commitment to help patients and families obtain competency in chronic disease management, an essential element of the Chronic Care Model [29].

Mortality declined and causes of death changed, likely related to improved therapies and approaches. No new transmission of HIV or hepatitis C infections through contaminated blood products occurred since 1987. The fall of HIV-related deaths was expected after the mid-1990s introduction of disease-modifying therapy. Liver disease-related mortality was expected in a small, but steady number of persons. Bleeding-related death remained relatively modest, despite HTCs caring for significant numbers of patients with clinically severe disorders [15]. Since 2002, most mortality was related to 'Other' causes, warranting investigation to determine trends amenable to intervention.

There are several limitations to this retrospective study. First, aggregate data is not amenable to statistical analyses that require individual-level data. Second, while a glossary defining the data elements was used, no third party audit was conducted to determine fidelity to the definitions across 129 HTCs over 20 years. Third, data collection was initially performed manually, increasing the possibility of patient omission, duplication or misclassification. In recent years, most HTCs used a computerized database that includes validation checks to enhance data quality. Patients, particularly those with mild disease, may not meet the inclusion criteria, inadvertently resulting in undercount. These data reflect only US HTC network trends and may not be generalizable outside this network. However, using 2010 US Census data, the nearly 14 000 males with haemophilia in this network represents approximately 70% of the estimated 20 000 US residents with haemophilia FVIII and FIX deficiency, based on the age-adjusted prevalence rate of 13.4/100 000 males with these disorders [24].

Conclusion

The Hemophilia Data Set documents the growth and diversity of the US Hemophilia Treatment Center Network's patient population over the past two decades. The major sources of growth were among traditionally under-represented (e.g. Hispanic and African American) and under-recognized (female) populations, documenting increased access among those more vulnerable to experiencing poor health outcomes. The US HTC network provides comprehensive, patient centred and coordinated multidisciplinary prevention, diagnosis, treatment, surveillance, research, education and outreach services to US residents in all states and several territories. The HDS registry provides valuable information on the majority of the US population diagnosed with inherited bleeding disorders. It can serve as an important instrument in national public health planning and evaluation initiatives to improve health outcomes and health care delivery for

individuals who have rare and under-recognized genetic bleeding disorders.

Acknowledgements

The authors are grateful for the dedication of the US Hemophilia Treatment Center network staff that collected these data, the Regional Coordinators for data management and CDC staff who collated the HDS in the earlier years. Preliminary versions of these data were presented at the 1st and 2nd National Conferences on Blood Disorders and Public Health in 2010 and 2012, Atlanta, GA; at the 2011 American Thrombosis and Hemostasis Network Summit, Chicago IL; and at the HRSA 2011 Hemophilia Data Summit, Alexandria, VA.

Authorship

Ms. Baker, Riske, Forsberg and Mr. Drake designed the study. Ms. Baker and Mr. Drake acquired the data. Mr. Drake and Mr. Shearer analysed the data. Ms. Baker, Riske, Forsberg, Voutisis, Mr. Drake and Atwood interpreted the data and wrote the manuscript. Ms. Baker provided overall direction.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

- 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**: 1910–6.
- Hoots WK. Comprehensive care for hemophilia and related inherited bleeding disorders: why it matters. *Curr Hematol Rep* 2003; **2**: 395–401.
- Larsson SA. Life expectancy of Swedish haemophiliacs, 1831–1980. *Br J Haematol* 1985; **59**: 593–602.
- Cumming IR, Cumming AM, Redding OM *et al.* A computerized database for haemophilia patient records. *Clin Lab Haematol* 1992; **14**: 9–17.
- Saad S, Rowley G, Tagliavacca L, Green PM, Giannelli F. First report on UK database of haemophilia B mutations and pedigrees UK Haemophilia Centres. *Thromb Haemost* 1994; **71**: 563–70.
- O'Connor GI, Temperley IJ. A database for a National Haemophilia Centre. *Clin Lab Haematol* 1996; **18**: 195–200.
- Walker I. Survey of the Canadian hemophilia population. *Can J Public Health* 1991; **82**: 127–9.
- Walker I, Pai M, Akabutu J *et al.* The Canadian Hemophilia Registry as the basis for a national system for monitoring the use of factor concentrates. *Transfusion* 1995; **35**: 548–51.
- Eyster ME, Lewis JH, Shapiro SS *et al.* The Pennsylvania hemophilia program 1973–1978. *Am J Hematol* 1980; **9**: 277–86.
- Jubelirer SJ, Ohgren LC, Haddy L, Stevenson M, Rogers JS, 2nd. West Virginia State Hemophilia Program. *W V Med J* 1985; **81**: 259–61.
- Eyring EJ, Bjornson DR, Close JR. Management of hemophilia in children. *Clin Orthop Relat Res* 1965; **40**: 95–112.
- Cooper T. Summary Report: NHLI's Blood Resource Studies. Department of Health Education, and Welfare. Bethesda, MD; 1972.
- Teitel JM, Barnard D, Israels S, Lillicrap D, Poon MC, Sek J. Home management of haemophilia. *Haemophilia* 2004; **10**: 118–33.
- Soucie JM, Symons J, Evatt B, Brettler D, Huszti H, Linden J. Home-based factor infusion therapy and hospitalization for bleeding complications among males with haemophilia. *Haemophilia* 2001; **7**: 198–206.
- Soucie JM, Nuss R, Evatt B *et al.* Mortality among males with hemophilia: relations with source of medical care. *Blood* 2000; **96**: 437–42.
- Centers for Disease Control and Prevention. National Public Health Performance Standards Program. Available at <http://www.cdc.gov/nphsp/essentialServices.html>. Accessed January 11, 2011.
- National Research Council. The Future of Public Health. The National Academies Press, Washington, DC; 1988.
- U.S. Census Bureau: State and County QuickFacts. Data derived from Population Estimates, American Community Survey, Census of Population and Housing, State and County Housing Unit Estimates, County Business Patterns, Nonemployer Statistics, Economic Census, Survey of Business Owners, Building Permits, Consolidated Federal Funds Report. Last Revised: Tuesday, 17-Jan-2012 16:42:01 EST.
- U.S. Department of Health and Human Services, Health Resources and Services Administration. Women's Health USA 2009.
- Byams VR. Women with bleeding disorders. *J Womens Health (Larchmt)* 2007; **16**: 1249–51.
- Nichols WL, Hultin MB, James AH *et al.* von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia* 2008; **14**: 171–232.
- Committee on Adolescent Health Care and Committee on Gynecologic Practice. ACOG Committee Opinion no. 451: Von Willebrand disease in women. *Obstet Gynecol* 2009; **114**: 1439–43.
- U.S. Department of Health and Human Services. *Office of Disease Prevention and Health Promotion*. Healthy People 2020. Washington, DC. Available at <http://www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=4>. Accessed July 23, 2012.
- Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States The Hemophilia Surveillance System Project Investigators. *Am J Hematol* 1998; **59**: 288–94.
- Shapiro AD, Soucie JM, Peyvandi F, Aschman DJ, DiMichele DM. UDC Rare Bleeding and Clotting Disorders Working Group and the European Network Rare Bleeding Disorders Database Knowledge and Therapeutic Gaps: A public health problem in the rare coagulation disorders population. *Am J Prevent Med* 2011; **41**(Suppl 4): S324–31.
- Shahangian S, Stankovic AK, Lubin IM, Handsfield JH, White MD. Results of a survey of hospital coagulation laboratories in the United States. 2001. *Arch Pathol Lab Med* 2005; **129**: 47–60.
- Lemieux-Charles L, McGuire WL. What do we know about health care team effectiveness? A review of the literature *Med Care Res Rev* 2006; **63**: 263–300.
- 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**: 535–44.
- Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. *Health Aff* 2001; **20**: 64–78.