

WY Au 區永仁
 Vincent Lee 李偉生
 Bonnie Kho 許紫珊
 Alvin SC Ling 凌紹祥
 Desmond Chan 陳振榮
 Eric YT Chan 陳日東
 Godfrey CF Chan 陳志峯
 Winnie WW Cheung 張永慧
 CW Lau 劉靜華
 CY Lee 李靜賢
 Rever CH Li 李澤荷
 CK Li 李志光
 SY Lin 連錫營
 Vivien Mak 麥慧敏
 Lina Sun 孫偉芬
 Kris HF Wong 黃鴻勳
 Raymond Wong 王紹明
 Jeffrey Yau 丘炳華
 HL Yuen 袁煦樑

Key words

Factor VIII; Hemophilia A; HIV infections;
 Mutation; Survival rate

Hong Kong Med J 2011;17:189-94

Department of Medicine, Queen Mary Hospital

WY Au, FHKAM (Medicine)

WWW Cheung, FHKAM (Medicine)

Department of Paediatrics, Prince of Wales

Hospital

V Lee, FHKAM (Paediatrics)

CK Li, FHKAM (Paediatrics)

Department of Medicine, Pamela Youde

Nethersole Eastern Hospital

B Kho, FHKAM (Medicine)

Department of Paediatrics, Princess Margaret

Hospital

ASC Ling, FHKAM (Paediatrics)

Department of Paediatrics, United Christian

Hospital

D Chan, FHKAM (Paediatrics)

Department of Paediatrics, Kwong Wah Hospital

EYT Chan, FHKAM (Paediatrics)

Department of Paediatrics, Queen Mary Hospital

GCF Chan, FHKAM (Paediatrics)

Department of Medicine, Tuen Mun Hospital

CW Lau, FHKAM (Medicine)

Department of Paediatrics, Caritas Medical

Centre

CY Lee, FHKAM (Paediatrics)

Department of Paediatrics, Tuen Mun Hospital

RCH Li, FHKAM (Paediatrics)

Department of Medicine, United Christian Hospital

SY Lin, FHKAM (Medicine)

Department of Medicine, Princess Margaret Hospital

V Mak, FHKAM (Medicine)

Department of Paediatrics, Pamela Youde

Nethersole Eastern Hospital

L Sun, MRCPaed

Department of Medicine, Queen Elizabeth Hospital

KHF Wong, FHKAM (Medicine)

J Yau, FHKAM (Paediatrics)

Department of Medicine, Prince of Wales Hospital

R Wong, FHKAM (Medicine)

Department of Paediatrics, Queen Elizabeth

Hospital

HL Yuen, FHKAM (Paediatrics)

Correspondence to: Dr WY Au

Email: auwing@hotmail.com

Objective To provide a synopsis of current haemophilia care in Hong Kong.

Design Retrospective survey.

Setting All haematology units of the Hospital Authority in Hong Kong.

Patients All patients with haemophilia A and haemophilia B.

Results To date, there were 222 mild-to-severe haemophilia patients (192 type A, 30 type B) under regular public care in Hong Kong (43% were considered severe, 33% moderate, and 24% mild), which gave a crude prevalence of 6.8/100 000 male inhabitants. A total of 12.8 million units of Factor VIII and 3 million units of Factor IX were prescribed annually. This amounts to 1.83 units of FVIII per capita of the population, which is comparable to that of other developed countries. Leading causes of mortality were human immunodeficiency virus-related complications (10 cases) and cerebral bleeding (2 cases). The life expectancy of patients with severe haemophilia in Hong Kong is improving; currently the oldest patient is 60 years old. Such improved survival may be due to enhanced factor availability, prompt treatment of bleeding episodes at home, safer factor products, and better antiviral treatment. Primary prophylaxis is the accepted standard of care for severe and moderate cases, and "Factor First" has become hospital policy. However, 12 patients continue to present treatment challenges, due to the documented presence of factor inhibitors. In all, 28, 100, and 14 cases respectively were positive for human immunodeficiency virus, hepatitis C virus, and hepatitis B virus; the youngest patients with the corresponding infections being 28, 13, and 22 years old. Comprehensive care with dedicated physiotherapy, surgical support, and radionucleotide synovectomy may reduce morbidity further.

Conclusion A multidisciplinary approach can further improve the future care for haemophilia patients in Hong Kong.

Introduction

Hereditary haemophilia is a form of congenital bleeding tendency caused by deficiency of coagulation factors. Haemophilia A and B, caused by deficiency in coagulation factor (F) VIII and IX, are X-linked recessive conditions. There are currently 222 patients with mild-to-severe haemophilia (all male) in Hong Kong under the care of the Hospital Authority. This is the closest to a regional registry¹ and gives a crude prevalence of 6.8/100 000 male inhabitants. This is similar to rates in China and worldwide, which range from 6.6 ± 4.8 to 12.8 ± 6 , the variations are mainly due to the recognition of mild cases.^{2,3} In this article, we update the comprehensive care available to these patients.⁴ Patients with acquired haemophilia due to autoimmune antibodies,⁵ rare factor deficiencies (including FV/VIII combined deficiency),⁶⁻⁸ and von Willebrand disease⁹ are not covered in this review.

Demography

In all seven clusters of the Hospital Authority, patients with haemophilia are cared for by either adult or paediatric units according to age.⁴ The ratio of haemophilia A to haemophilia B patients is 6.4 to 1. Disease severity is classified according to clotting factor activity into severe (<1 IU/dL), moderate (1-5 IU/dL), and mild (>5-40 IU/dL). In our cohort,

香港血友病治療的現況概覽

- 目的** 提供香港血友病治療概覽。
- 設計** 回顧性問卷調查和年度資料更新。
- 安排** 香港醫院管理局轄下醫院的血液學部門。
- 患者** 所有甲型和乙型血友病患者。
- 結果** 直至2011年1月為止，共222名（甲型192名、乙型30名）輕微至嚴重血友病患者於公立醫療機構接受常規治療；其中43%屬嚴重、33%屬中等、24%屬輕微病例），而總現患率為每100 000男性居民有6.8人。據統計，醫院每年為患者注射共1280萬個單位的第八凝血因子，以及300萬個單位的第九凝血因子。換言之，第八凝血因子的人均注射量為1.83個單位，數字與其他已發展國家相若。患血友病的主因包括與愛滋病毒相關的併發症（10宗病例）和腦出血（2宗病例）。近年香港嚴重血友病患者的壽命有所改善，最長的是60歲。這或與凝血因子供應量上升、患者在家出現腦出血時能作即時治療、凝血因子產品較以往安全，以及較佳的抗毒治療有關。初步的預防性因子注射是中等至嚴重病例的可接受治療標準，而以凝血因子作優先治療選擇也是現時醫院的治療政策。對愛滋病毒、丙型肝炎病毒和乙型肝炎病毒呈陽性反應的病例依次有28宗、100宗和14宗；而受上述病毒感染的最年輕患者分別為28歲、13歲和22歲。然而，12名患者在治療過程中出現因子抑制物，因此血友病治療仍為醫務人員帶來挑戰。特定物理治療、外科治療和放射性核素滑膜切除術的合作，有助進一步減低患病率。
- 結論** 跨部門合作有助進一步改善對香港血友病患者的治療。

the corresponding ratio of cases was 43%, 33% and 24% (Fig a). Most patients were aged from 1 to 55 years; with 27% aged younger than 18 years. Several factors affect the case prevalence (Fig b). Genetic counselling and prenatal diagnosis can prevent some severe familial cases, but de-novo mutations also occur. The prevalence of severe haemophilia in persons aged 0 to 30 years has actually been stable at 4-6/100 000 male inhabitants. Premature death in severe cases (due to bleeding and transfusion-related viral infections) leads to falling prevalence with increasing age. However, with more adequate factor usage, improved viral safety of factors and better treatment of human immunodeficiency virus (HIV)¹⁰ and hepatitis C virus (HCV) infections, younger patients with severe (and moderate) haemophilia may have normal life expectancy. Mild-to-moderate cases may be diagnosed later in life. Our youngest mild case is now aged 5 years, and the prevalence of mild haemophilia shows no apparent variation with age.

Factor replacement

Both FVIII and FIX concentrates are available as specialist items under Hong Kong's public health care at no additional cost to patients. Before 1992, both imported plasma products and non-virally inactivated local plasma products (eg fresh frozen plasma or cryoprecipitate) had been used for haemophilia treatment. Since 1992, high-purity FVIII and FIX concentrates became available from CSL (Australia) using Hong Kong donor plasma. Factor concentrate is the only recommended form of factor replacement for most haemophiliacs. The local blood has very low intrinsic risk for viral contamination. Multiple viral inactivation steps further reduce the estimated risks of hepatitis B virus (HBV), HCV, and HIV infection, by 12.6, 9.8, and 20 logs respectively.¹¹ At \$450 per vial, the cost of FVIII (250 units) and FIX (500 units) vials for haemophilia patients remain a top budget item. In the year 2009, a total of 12 804 750 units of FVIII and 3 049 000 units of FIX were prescribed. This translates to population factor use of 1.83 units of FVIII per capita, which is within affluent country standards (1.1-2.8 units per capita), and almost identical to factor consumption levels in Korea, Japan, and Singapore.¹² Recombinant products are only available as a patient-paid item, and are only used by a small minority of young patients. Their local costs are 5-to-10-fold those of plasma products, but the relative risks of HBV, HCV, and HIV from recombinant products are negligible.

Prophylactic factor infusion (2-3 times per week, weight-adjusted from childhood) is now the standard of care in many countries.¹³ This policy prevents joint damage and allows normal lives for haemophiliacs. In the long run, it saves factor consumption and money by preventing bleeding complications and surgery due to long-term substandard care.¹⁴ There is also productivity gain from normal joints, and an improved lifestyle and lifespan.^{15,16} For very young kids, venous access may make starting prophylaxis difficult. For some patients with very difficult venous access, central venous catheters were inserted temporarily. Early fears of increased risks due to the development of inhibitors were mostly unsubstantiated. A survey of local patients showed that 57 local patients (34% of all severe-to-moderate cases, aged 2 to 36 years) are receiving prophylactic treatment. The remainder receive on-demand therapy.

Inhibitors

The prevalence of inhibitors in Chinese haemophilia patients has been reported to be comparable to average rates worldwide.¹⁷ In these patients the treatment of bleeding is problematic, since they may be refractory even to high-dose factor replacement, which might also trigger a rebound in inhibitor

titre due to an anamnestic response. Despite their very high costs, both bypass agents (Factor Eight Inhibitor Bypass Activity and recombinant activated Factor seven [Novoseven])¹⁸ are freely available for treating these patients. There were 12 such patients with inhibitors in Hong Kong, one of whom has haemophilia B. Their factor deficiency was severe in eight patients, moderate in three and mild in one, and their peak inhibitor levels ranged from 3 to 116 Bethesda Units. The cumulative proportion of patients with severe-to-moderate deficiency with inhibitors was 8.5%. The reported cumulative figure in western countries varied from 7.5 to 30%, depending on frequency of testing and cohort inclusion criteria.^{13,19}

Notably, inhibitors were not detected in the cohort of local Hong Kong patients on regular prophylaxis. The experience with immune tolerance treatment is very limited. In three patients, low-dose regimens with steroids have been tried, one of whom achieved eradication of antibodies to FVIII.

Musculoskeletal damage

Prevention and treatment of musculoskeletal damage is the cornerstone for haemophilia care.²⁰ The prevalence, extent, and severity of joint damage in local haemophilia patients are not well documented. This is due to insufficient patient and

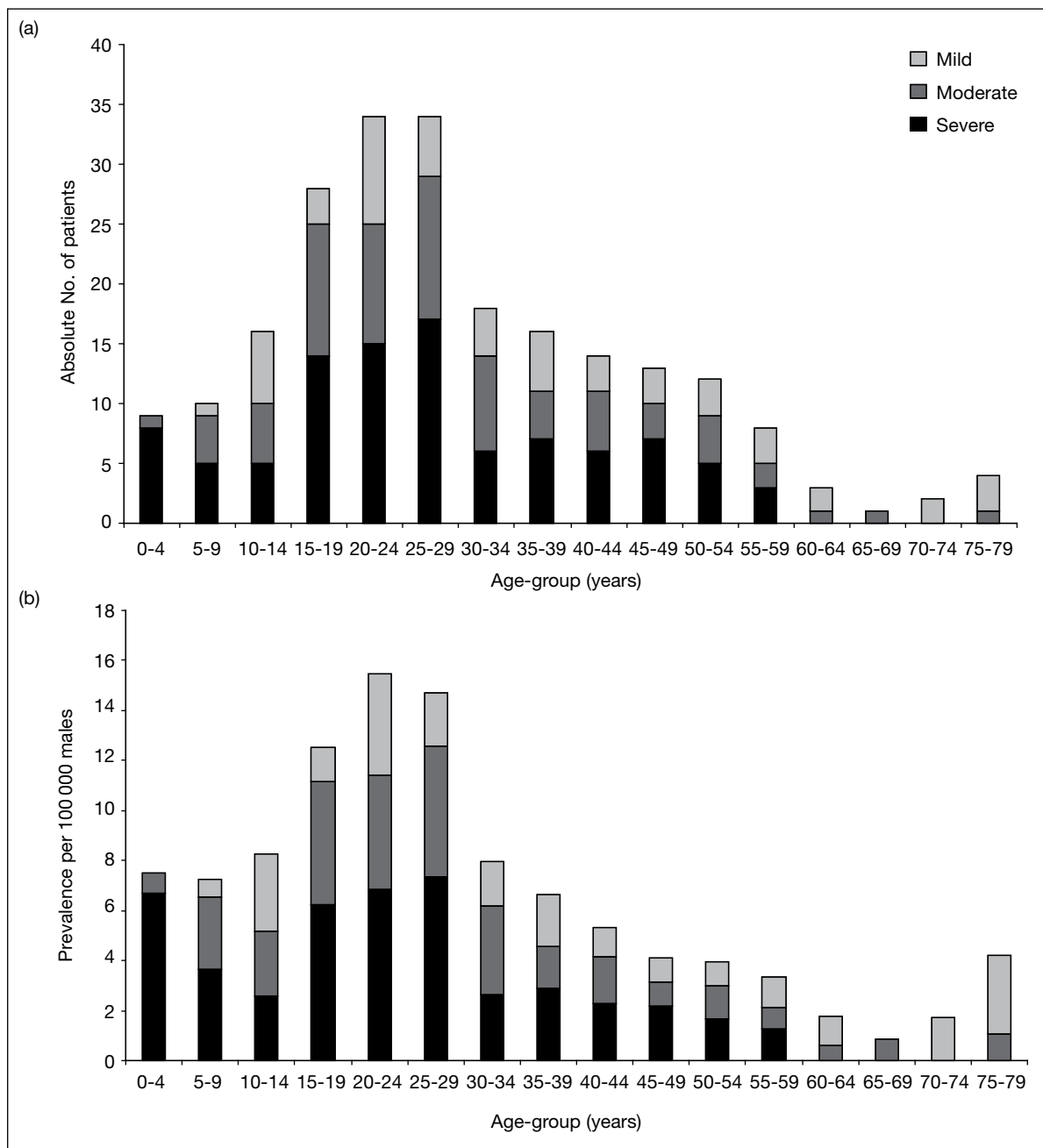


FIG. (a) No. of patients and (b) case prevalence of patients in different age-groups by disease severity

doctor enthusiasm and a shortage of dedicated physiotherapists and radiologists. In 2010, a regional specialist physiotherapy programme was launched in all clusters, in line with the China National Comprehensive Care Project in haemophilia.² A comprehensive joint assessment score for both paediatric and adult patients was adopted, both in Hong Kong and in mainland China.²¹ Regular exercise (after appropriate factor replacement) is also important, with a view to prevent osteoporosis and fractures later in life.²² Joint assessments and scoring by plain X-rays, ultrasonography, computed tomography, and magnetic resonance imaging are also emerging in Hong Kong and China.^{23,24}

The earliest joint damage in haemophilia is in the soft tissue, for which prevention is better than cure. By the time bone changes are evident, care is already suboptimal and the damage may already be irreversible. However, surgery, local radionucleotides and secondary prophylaxis can halt further damage and provide functional restoration.²⁵ All operative options (osteotomy, fusion, joint replacement) are available in three tertiary centres (Queen Mary Hospital, Prince of Wales Hospital, and Queen Elizabeth Hospital). With adequate use of factors, surgical risks are acceptable in Chinese haemophilia patients.^{26,27} There is no local registry of the total number and types of joints replaced. Radionucleotide synovectomy (Yttrium/Rhenium) is a new standard of care for progressive arthropathy,²⁸ particularly in conjunction with secondary factor prophylaxis.^{13,29} Expertise is available in three tertiary centres, but so far only 10 patients (9 haemophilia A cases and 1 haemophilia B case with inhibitor) have been treated with Yttrium in Hong Kong. All had knee injections, except for one who received bilateral ankle treatment.

Infections

The epidemic of HIV infection due to tainted imported factor products remained a dark chapter in the history of haemophilia care worldwide.³⁰ In Hong Kong, a total of 10 patients died of HIV-related complications; while 28 are alive on antiviral therapy. These included mainly older patients (age 28-52 years), and except for one FIX-deficient case, all had haemophilia A. Anti-retroviral treatment and the management of HIV-related infections and complications are under the care of the Department of Health, separate from haemophilia care. With optimal antiviral combination therapy, the CD4 counts in most patients are at normal levels and their prognosis has improved vastly.³¹

The prevalence of HCV infection is even higher. The local prevalence of HCV carriage in blood donors is only 0.01%, but HCV antibody screening of blood products only started in 1993.

Hence, previous use of imported factor products and local plasma products resulted in a high HCV antibody prevalence of 45% (100 cases; age range, 13 to 79; median age, 38 years). The distribution of serotypes follows local prevalence.³² Treatment with a combination of pegylated interferon and ribavirin yields clearance rate from 53 to 67%,^{33,34} depending on the viral load and serotype. Up to 25% may have viral recrudescence, and lifelong follow-up for viraemia, hepatitis and hepatic tumour seems prudent. The use of fibroscan may help assess liver damage, since biopsy is not without risks in haemophiliacs.³⁵ The carriage rate of HBV (6.5%, 14 cases; age range, 22-62; median age, 40 years) was not different from that in other age-matched locals. In Hong Kong, universal HBV vaccination of newborns began in 1988, and it is doubtful whether any older carriers are transfusion-related. Interestingly, two local patients with HCV-related non-resectable hepatocellular carcinoma (HCC) received living donor liver grafts and were cured of both HCC and haemophilia. Better control of HIV viral load also slowed the activity of the nearly inevitable concomitant HCV infection.³⁶

Mortality

A total of 12 haemophilia patients have died in Hong Kong in the past 18 years. Except two patients with cerebral haemorrhage, all of them were HIV positive. Fulminant sepsis was the cause of death in nine of the cases, and HCV-related cirrhosis contributed to two other HIV deaths.³⁶ The same pattern is seen in developed economies; where HIV-related deaths and end-stage liver diseases are the overwhelming causes of death.^{37,38} Up to 50% of patients were certified dead before reaching the medical ward and hospital proper. One HIV-negative patient died from intracranial haemorrhage in Mainland China. Education and training of patients and family members on early and appropriate home therapy is the most important first-line defense against morbidity and mortality. The availability of factors in the accident and emergency department, and the issuance of a "Factor First" policy at initial triage screening appears to reduce the pain, damage, bleeding, and possibly mortality of haemophilia patients coming to hospital for help.

Social challenges

The bleeding risks, frequent fixed contractures, and damaged joints prevent many haemophilia patients from undertaking vigorous exercise and other challenging activities. Parental fear may transfer to haemophiliac children, leading to harmful protective behaviour and social seclusion.³⁹ Actually, light exercise should be encouraged and muscles around damaged joints must be strengthened. Moreover,

with appropriate factor replacement, a patient with haemophilia is no different from any other normal person. For patients adhering to prophylactic treatment, their joints can be completely normal. Haemophilia patients are therefore encouraged to take up normal lives and careers and families should avoid overprotecting their haemophiliac children.⁴⁰ The Patient Association (www.haemophilia.org.hk) serves to voice views and safeguard their well-being. Improved prognosis means that patients can have a normal life expectancy. There is a major role for parents, families, and caregivers in helping to move haemophilia patients from paediatric to adult care (and to geriatric care in due time).^{41,42} Since care models for paediatrics are not the same as in the adult set-up, uncoordinated transition can produce unnecessary anxiety and suffering for patients, families, and even caregivers. Such transfer is relevant, however, since adult medical complications may be better screened and managed by adult medicine physicians. The transition of care to an adult unit also facilitates the psychological progression for independent self-care. From a family perspective, patient families are also urged to take part in prenatal diagnosis and screening whenever there is a risk of passing the haemophilia gene to offspring. Genetic screening for carrier status should be extended to close female relatives, before they become pregnant. In one study in Southern Chinese, up to 35% of the molecular defects are unknown; hence linkage analysis on amniocentesis or chorionic villi sampling will be needed for some local families.⁴³

Conclusions

The future of haemophilia care in Hong Kong is bright.

There are many unmet needs however, especially with increasing age and patient life expectancy. Emerging problems in adult haemophilia patients (renal failure, osteoporosis, cardiovascular morbidity) noted in other developed countries are also likely to surface in Hong Kong. There is also much need to improve genetic counselling, physiotherapy, and patient/family education. Experience from Europe and America indicates that dedicated multidisciplinary haemophilia units—with better coordination between specialists in haematology, laboratory medicine, physiotherapy, orthopaedic surgery, nursing, medical social service and dentistry—improves patient care and satisfaction.⁴⁴⁻⁴⁶ Locally, in each of the seven clusters within Hong Kong, dedicated personnel are being identified and a critical mass of expertise is being established. Dialogue between the patient population and caregivers is also continuously improving. Such a multidisciplinary approach can improve the care of haemophilia patients and their families in Hong Kong.

Acknowledgements

The authors would like to thank the Working Group on Transitional Care of the Coordinating Committee in Internal Medicine and Coordinating Committee in Paediatrics, Hospital Authority for its support and endorsement, Dr Hiu-fai Ho and Ms Andrea Leung of Queen Elizabeth Hospital for the coordination of emergency medicine and physiotherapy care respectively, Dr Cheuk-kwong Lee of Hong Kong Red Cross Blood Transfusion Services on data on viral safety, Mr William Chui for factor usage data, and Prof Man-chiu Poon of World Federation of Hemophilia for his constructive advices.

References

1. Evatt B. World Federation of Hemophilia: guide to developing a national patient registry. *World Federation of Hemophilia* 2005;1:1-22.
2. Poon MC, Luke KH. Haemophilia care in China: achievements of a decade of World Federation of Hemophilia treatment centre twinning activities. *Haemophilia* 2008;14:879-88.
3. Stonebraker JS, Bolton-Maggs PH, Soucie JM, Walker I, Brooker M. A study of variations in the reported haemophilia A prevalence around the world. *Haemophilia* 2009;16:20-32.
4. Ling SC, Chan GCF, Shing MK, et al. Children and adolescent patients with hemophilia in Hong Kong: an epidemiological and clinical review. *Hong Kong J Paediatrics* 2006;11:13-9.
5. Au WY, Lam CC, Kwong YL. Successful treatment of acquired factor VIII inhibitor with cyclosporin. *Haemophilia* 2004;10:98-100.
6. Au WY, Lam CC, Cheung WC, Kwong YL. Two novel factor X gene mutations in a Chinese family with factor X deficiency. *Ann Hematol* 2004;83:304-6.
7. Au WY, Lam CC, Chan EC, Kwong YL. Two novel factor VII gene mutations in a Chinese family with factor VII deficiency. *Br J Haematol* 2000;111:143-5.
8. Au WY, Cheung JW, Lam CC, Kwong YL. Two factor XI mutations in a Chinese family with factor XI deficiency. *Am J Hematol* 2003;74:136-8.
9. Zhang L, Li H, Zhao H, Zhang X, Ji L, Yang R. Retrospective analysis of 1312 patients with haemophilia and related disorders in a single Chinese institute. *Haemophilia* 2003;9:696-702.
10. Arnold DM, Julian JA, Walker IR; Association of Hemophilia Clinic Directors of Canada. Mortality rates and causes of death among all HIV-positive individuals with hemophilia in Canada over 21 years of follow-up. *Blood* 2006;108:460-4.
11. Intragam P product information. CSL Bioplasma website: www.csl.com.au/docs/840/200/PT374001001,0.pdf. Accessed Jan 2011.
12. Stonebraker JS, Brooker M, Amand RE, Farrugia A, Srivastava

- A. A study of reported factor VIII use around the world. *Haemophilia* 2009;16:33-46.
13. Carcao M, Lambert T. Prophylaxis in haemophilia with inhibitors: update from international experience. *Haemophilia* 2010;16 Suppl 2:16S-23S.
 14. O'Mahony B, Noone D, Tolley K. An introduction to key concepts in health economics for hemophilia organizations. *World Federation of Hemophilia* 2010;1:3-20.
 15. Richards M, Williams M, Chalmers E, et al. A United Kingdom Haemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. *Br J Haematol* 2010;149:498-507.
 16. Escobar MA. Health economics in haemophilia: a review from the clinician's perspective. *Haemophilia* 2010;16 Suppl 3:29S-34S.
 17. Wang XF, Zhao YQ, Yang RC, et al. The prevalence of factor VIII inhibitors and genetic aspects of inhibitor development in Chinese patients with haemophilia A. *Haemophilia* 2010;16:632-9.
 18. Hedner U, Lee CA. First 20 years with recombinant FVIII (NovoSeven). *Haemophilia* 2011;17:e172-82.
 19. van der Bom JG, ter Avest P, Van den Berg HM, Psaty BM, Weiss NS. Assessment of incidence of inhibitors in patients with haemophilia. *Haemophilia* 2009;15:707-11.
 20. Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. *HSS J* 2009 Nov 17. Epub ahead of print.
 21. Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. *Haemophilia* 2006;12:518-25.
 22. Iorio A, Fabbriani G, Marcucci M, Brozzetti M, Filippini P. Bone mineral density in haemophilia patients. A meta-analysis. *Thromb Haemost* 2010;103:596-603.
 23. Yu W, Lin Q, Guermazi A, et al. Comparison of radiography, CT and MR imaging in detection of arthropathies in patients with haemophilia. *Haemophilia* 2009;15:1090-6.
 24. Ng WH, Chu WC, Shing MK, et al. Role of imaging in management of hemophilic patients. *AJR Am J Roentgenol* 2005;184:1619-23.
 25. Wiedel J, Sally S, Geraghty S, Funk S. Joint replacement surgery in hemophilia. *World Federation of Hemophilia* 2010;5:1-10.
 26. Gao ZX, Qiu GX, Weng XS, et al. Perioperative management in hemophilic arthropathy [in Chinese]. *Zhonghua Wai Ke Za Zhi* 2008;46:809-12.
 27. Sun TZ, Lü HS, Guan ZP. Total knee arthroplasty and perioperative management of hemophilic arthritis [in Chinese]. *Zhonghua Wai Ke Za Zhi* 2007;45:708-11.
 28. Rodriguez-Merchan EC, Quintana M, De la Corte-Rodriguez H, Coya J. Radioactive synoviorthesis for the treatment of haemophilic synovitis. *Haemophilia* 2007;13 Suppl 3:32S-37S.
 29. Brecej J, Bole V, Benedik-Dolnicar M, Grmek M. The co effect of prophylaxis and radiosynovectomy on bleeding episodes in haemophilic synovitis. *Haemophilia* 2008;14:513-7.
 30. Lee SS, Wong KH, Dickinson AJ. Haemophilia and HIV infection in Hong Kong. *AIDS Care* 1996;8:365-72.
 31. Katsarou O, Touloumi G, Antoniou A, Kouramba A, Hatzakis A, Karafoulidou A. Progression of HIV infection in the post-HAART era among a cohort of HIV+ Greek haemophilia patients. *Haemophilia* 2005;11:360-5.
 32. Wong DA, Tong LK, Lim W. High prevalence of hepatitis C virus genotype 6 among certain risk groups in Hong Kong. *Eur J Epidemiol* 1998;14:421-6.
 33. Zhang RF, Sun HQ, Huang Q, et al. Efficacy and safety of pegylated interferon alpha-2a therapy for chronic hepatitis C in HIV-infected patients with haemophilia. *Haemophilia* 2009;16:502-7.
 34. Au WY, Lam CC, Liu CL, Yuen MF. Hepatitis C virus infection in adult Chinese hemophilia patients negative for the human immunodeficiency virus: treatment results with interferon and ribavirin. *Int J Hematol* 2005;82:259-61.
 35. Yeo WT, Tan LK, Dan YY, Wai CT. Delayed bleeding after liver biopsy: a dreaded complication. *Singapore Med J* 2008;49:76-80.
 36. Tatsunami S, Mimaya J, Shirahata A, et al. Current status of Japanese HIV-infected patients with coagulation disorders: coinfection with both HIV and HCV. *Int J Hematol* 2008;88:304-10.
 37. Darby SC, Kan SW, Spooner RJ, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood* 2007;110:815-25.
 38. Tagliaferri A, Rivolta GF, Iorio A, et al. Mortality and causes of death in Italian persons with haemophilia, 1990-2007. *Haemophilia* 2010;16:437-46.
 39. van der Net J, Vos RC, Engelbert RH, van den Berg MH, Helder PJ, Takken T. Physical fitness, functional ability and quality of life in children with severe haemophilia: a pilot study. *Haemophilia* 2006;12:494-9.
 40. Lineberger HP. Social characteristics of a hemophilia clinic population. A survey and literature review. *Gen Hosp Psychiatry* 1981;3:157-63.
 41. Franchini M, Tagliaferri A, Mannucci PM. The management of hemophilia in elderly patients. *Clin Interv Aging* 2007;2:361-8.
 42. Breakey VR, Blanchette VS, Bolton-Maggs PH. Towards comprehensive care in transition for young people with haemophilia. *Haemophilia* 2010;16:848-57.
 43. Chan V, Pang A, Chan TP, Chan VW, Chan TK. Molecular characterization of haemophilia A in southern Chinese. *Br J Haematol* 1996;93:451-6.
 44. Evatt BL, Black C, Batorova A, Street A, Srivastava A. Comprehensive care for haemophilia around the world. *Haemophilia* 2004;10 Suppl 4:9S-13S.
 45. Colvin BT, Astermark J, Fischer K, et al. European principles of haemophilia care. *Haemophilia* 2008;14:361-74.
 46. Grosse SD, Schechter MS, Kulkarni R, Lloyd-Puryear MA, Strickland B, Trevathan E. Models of comprehensive multidisciplinary care for individuals in the United States with genetic disorders. *Pediatrics* 2009;123:407-12.