



APEC Recommendations for Enhancing Access to Safe Therapy for Persons with Immunodeficiency and Bleeding Disorders

Introduction

Patients with bleeding disorders, such as von Willebrand or hemophilia, have conditions that disrupt their blood clotting process due to a deficiency of clotting factors or a platelet disorder¹. Immune deficiencies, such as primary Immunodeficiencies (PIDs), cause increased susceptibility to infections. Left undiagnosed or misdiagnosed, these diseases often lead to severe illness, disability, permanent organ damage or even death. Outcomes improve when patients are appropriately diagnosed and properly treated while maintaining preventive measures. In many APEC Economies, the lack of or delayed diagnosis of such disorders often impedes patients from receiving these treatments. Plasma protein replacement therapy is critically important to addressing bleeding and immune deficiency disorders, but access to these life-saving treatments can be limited. Failure to receive appropriate treatment can result in unnecessary, frequent or recurrent hospitalization, financial burden and major reduction of quality of life and life expectancy.

Bleeding disorders

Hemophilia and other bleeding disorder patients are frequent recipients of blood and blood components. As a consequence of the introduction of innovative therapies, life expectancy amongst the hemophilia community in developed economies increased from 16 years at the start of the 20th Century to 60 years in 1980, but fell to 40 years in 1994 due to contaminated product supply.² The large scale Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) infections among patients with hemophilia in the 1980s led to the development of safer factor concentrates via the introduction of good manufacturing practices and product innovation. Double viral inactivation during the manufacturing process of plasma derived concentrates greatly reduces HIV and HCV contamination risk, and with the introduction of third generation recombinant (synthetic) factors, the risk of contamination with known and unknown blood borne pathogens is eliminated.³

The economic consequences of pathogen transmission in patients with bleeding disorders have been well documented. HIV and HCV have both proved highly costly as well as highly morbid. Costs have included direct healthcare management of the disease and co-morbidities, as well as

¹ World Federation of Haemophilia <http://www.wfh.org/en/page.aspx?pid=1282> , American Society of Hematology <http://www.hematology.org/Patients/Bleeding.aspx> (Last accessed 24 November)

² Evatt BL. The tragic history of AIDS in the hemophilia population, 1982–1984. *Journal of Thrombosis and Haemostasis* 2006; 4: 2295–2301

³ Berntorp, E., "Why Prescribe Highly Purified Factor VIII and IX Concentrates?", *Vox Sang* 1996; 70: 61-68. Shapiro. *Vasc Health Risk Manag.* 2007;3(5):555-565

Grillberger L, Kreil T, Nasr S, Reiter M. Emerging trends in plasma-free manufacturing of recombinant protein therapeutics expressed in mammalian cells. *Biotechnol. J.* 2009, 4, 186–201.

indirect costs due to lost productivity, litigation, and compensation costs.⁴⁵⁶⁷⁸ By investing in safer therapy, governments can greatly reduce the risk of transmittable blood-borne infections and prevent the resulting burden of morbidity and associated costs.

In developed economies, the use of clotting factor concentrates to treat hemophilia is the gold standard. In developing economies, governments have made factors increasingly available; however, the provision of coagulation factors through the production of cryoprecipitate remains. Viral inactivation, the crucial steps to eliminate HCV and HIV viruses in donated blood and plasma, is often not implemented in the production of cryoprecipitate⁹, leaving patients exposed to higher risks of infection. In addition, a larger volume of cryoprecipitate is needed to provide the targeted amount of clotting factor, as compared to using factor concentrates. Lastly, the administration of this form of treatment can only be offered in a hospital setting, limiting the access of treatment to patients.

Because cryoprecipitate has often not undergone viral inactivation, international guidelines do not recommend its use to treat hemophilia, von Willebrand disease and other hereditary bleeding disorders, with the exception of the rare congenital bleeding disorder dysfibrinogenemia for which it is the only treatment currently available.¹⁰

Immune deficiencies

A key element to the management of patients with an immunodeficiency, such as primary immunodeficiency (PID), is for healthcare professionals to provide accurate information about the disease so that patients have access to accurate information, the appropriate medical care and choice in treatment modalities¹¹. Intravenous and subcutaneous Immunoglobulin (Ig) replacement therapies are included in the World Health Organization (WHO) Lists of Essential Medicines for the treatment of PIDs, and although Ig replacement therapy is a suitable therapy for many conditions, it should be prioritized for patients with PID as it is generally their only available treatment modality.

⁴Tencer T, Friedman HS, Li-McLeod J, *et al.* Medical Costs and Resource Utilization for Hemophilia Patients With and Without HIV or HCV Infection. *J Manag Care Pharm.* 2007;13(9):790-98

⁵ Hess G, Kondo K, Curry A. The cost effectiveness of plasma/albumin-free factor VIII. [Poster]. Presented at: the XXVII International Congress of the World Federation of Hemophilia. Vancouver, Canada; May 21-25, 2006b

⁶ Kennelly JM, Tolley KH, Ghani ACH, Sabin CA, Maynard AK, Lee CA. Hospital costs of treating haemophilic patients infected with HIV. *AIDS* 1995, 9(7);787-793

⁷ Scitovsky AA, Rice DP, "Estimates of the Direct and Indirect Costs of Acquired Immunodeficiency Syndrome in the United States, 1985, 1986, and 1991," *Public Health Reports (January-February 1987):* 5-17

⁸ Heemstra HE, Zwaan T, Hemels M, *et al.* Cost of severe haemophilia in Toronto. *Haemophilia* 2005;11:254-260

⁹ World Federation of Haemophilia, Guide for the assessment of clotting factor concentrates. www.wfh.org (Last accessed 24 November).

¹⁰ World Federation of Hemophilia, *Guidelines for the Management of Hemophilia*, 2012 www.wfh.org; National Hemophilia Foundation, *MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders*, 2015; Keeling, D. *et al.*, "Guideline on the selection and use of therapeutic products to treat hemophilia and other hereditary bleeding disorders", *Haemophilia* (2008), 14, 671-684

¹¹ Primary immunodeficiencies – Principles of care. IPOPI, www.ipopi.org
http://www.ipopi.org/uploads/media/news/Expert%20recommendations%20Mgt%20of%20PID_FINAL.pdf

Recommendations

In working toward the goals of the APEC Blood Supply Chain 2020 Roadmap, APEC economies may be guided by the following recommendations to enhance access to safe plasma protein replacement therapy, significantly reducing or eliminating pathogen transmission risk and enabling an efficient use of blood products. The recommendations include:

1. To improve laboratory diagnosis and assist healthcare personnel to standardize the early identification of patients with plasma protein deficiency. Accurate diagnosis is the first step in treatment.
 - a. Create a national training requirement at medical, nursing and therapist schools to allow better understanding of immune deficiencies and bleeding disorders and their symptoms, including training on quality/Good Manufacturing Practices (GMP) standards for blood and blood products to hospitals, doctors, medical and nursing schools.
 - b. Identify laboratory training and funding priorities.
 - c. Linking actions between different specialties and levels of health care.
2. To set standards of care for plasma protein replacement therapy in line with international guidelines.
3. To select plasma protein derived products with a strong and proven safety record. Plasma protein derived products should be manufactured under GMP standards, from collection of plasma (including donor selection criteria), to processing (type and number of validated viral inactivation steps) and distribution.
4. To select clotting factor concentrates for hemophilia treatment based on evidence, prioritizing products with a strong and proven safety record as preferred therapy.
 - a. To limit the use of cryoprecipitate for treating bleeding disorders to life threatening emergencies when protein concentrates are not available.
 - b. When selecting plasma derived clotting factor concentrates, give preference to products which have undergone suitable steps of viral inactivation during the fractionation process, thereby significantly reducing pathogen transmission risk.
5. To include an educational curriculum about bleeding disorders and immune deficiencies in medical and nursing schools to strengthen the recognition of symptoms and improve access to laboratory testing, including training on quality/GMP standards for blood products to hospitals, doctors, medical and nursing schools.
6. To establish treatment coverage policies based on evidence and in partnership with all stakeholders, including medical societies, hospitals, patient groups, and manufacturers.



These coverage policies should ensure access to effective, safe and affordable plasma-derived products.

7. To establish and regulate robust quality systems to optimize the safety of the blood supply.