

Network of Rare Blood Disorder Organizations

**Conference on
Comprehensive Care
for Rare Blood Disorders**

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Friday, February 3

Medical/Scientific Programme

Welcome & Opening Remarks

Silvia Marchesin, Conference President

The Conference on Comprehensive Care for Rare Blood Disorders brought together 150 patients, physicians, clinicians and allied healthcare professionals from across Canada, the U.S., U.K., Germany, Italy and Sweden to share their experiences of diagnosis, treatment and care. “The vision of better care for patients can become a reality only if all parties work together—collaboration is essential,” stated Conference President Silvia Marchesin. “Patient groups and health professionals need to work together to overcome barriers and find solutions to support comprehensive care for rare disorders.”

Session 1 – Hereditary Angioedema: Past, Present and Future

Chair: Tom Bowen, Clinical Professor of Pediatrics and Medicine, University of Calgary

Canada is some 20 years behind Europe in its standard of care for rare blood disorders, stated chair Tom Bowen. He thanked the participants who had come from abroad to share their knowledge and expertise. Only recently has Canada focused on hereditary angioedema and the challenges related to treatment. An international conference held in October 2003 saw the launch of the immune deficiency, blood disorders and hereditary angioedema clinics, and a challenge was brought forward to establish comprehensive care clinics across the country. Since then, HAE has received concerted attention from medical associations, and was the focus of the September 2004 issue of the *Journal of Allergy and Clinical Immunology*.

C1 Inhibitor Deficiency: Genetics, Diagnostic Algorithm, Attack Triggers, Attack Prevention

Dr. Marco Cicardi, University of Milan, Italy

Hereditary angioedema (HAE) always involves urticaria, a superficial swelling of skin due to transient plasma leakage that affects more than 30 per cent of the general population, said Dr. Marco Cicardi, of the University of Milan and San Giuseppe Hospital in Milan, Italy. However, HAE also involves a blood vessel leakage deeper in the skin, and may also affect the upper respiratory and gastrointestinal tracts. It can be difficult to distinguish between the different types of HAE, Dr. Cicardi noted. His talk focused on diagnosis and management of HAE.

The primary task with HAE is to try to identify the trigger. Angioedema can be brought on by a medication or food allergy; most of the time patients are able to recall the onset of angioedema after consuming certain foods or drugs. When the patient cannot identify the cause of the angioedema, it is rare for the physician to be able to do so. If the patient responds to antihistamines, it is likely to be an allergic reaction. But if the angioedema does not respond to antihistamines, it may suggest one of three possibilities:

- Angioedema related to the use of angiotensin-converting enzyme inhibitors
- Angioedema due to hereditary C1 inhibitor deficiency
- Idiopathic non-histaminergic angioedema

Most angioedema unresponsive to antihistamines are mediated by bradykinin release; however, there are many different types of angioedema that still need to be better defined.

Angioedema due to C1 inhibitor deficiency is a rare autosomal dominant disorder that affects both women and men. The C1 inhibitor is active in the complement and contact systems, and coagulation and fibrinolysis pathways. Angioedema due to C1 inhibitor deficiency is associated with mutations within one of its two alleles.

Patients with HAE are screened for C1 inhibitor gene mutation using fluorescence-assisted mismatch analysis (FAMA), direct sequencing and PCR sequence analysis. In the majority of cases, about 85 per cent, mutation in the C1 inhibitor gene is single-based and results in decreased levels of C1 inhibitor, known as type 1 HAE. About 15 per cent of cases involve type 2 HAE, which is characterized by normal levels but decreased function of C1 inhibitors; this cannot be detected by FAMA but can be determined by scanning the C1 inhibitor gene for mispairings and mutations or via direct sequencing.

Mutations in the C1 inhibitor gene may include block of transcription; transcription of abnormal mRNA; translation of non-secreted proteins; and secretion of dysfunctional C1 inhibitors. These different effects raise different issues. For example, non-secretion of proteins in some situations may cause disease or cell degeneration. With both type I and type II HAE, mRNA is significantly and similarly reduced in patients. Identifying the mechanisms underlying reduced mRNA levels, and finding a way to remove such downregulations, could possibly lead to a cure, he suggested.

HAE can be lethal, mostly due to upper airway obstruction leading to asphyxiation. Even when HAE has been diagnosed, delay in administering treatment can be fatal. Emergency treatment can involve invasive intubation or tracheotomy. In the majority of cases, angioedema presents itself in the first decade, with close to 90 per cent of patients showing symptoms by their second decade. About 30 per cent of patients with HAE experience more than 12 attacks monthly, translating into 75 days of disability per year.

Criteria for diagnosing angioedema caused by C1 inhibitor deficiency include major symptoms such as noninflammatory subcutaneous angioedema, recurrent abdominal pain and recurrent laryngeal edema; family history; and laboratory analysis.

There are several areas of primary prevention for HAE:

- Infection may worsen the disease; infected teeth and other foci of infection, which may activate the complement, should be sought and treated.
- Eradication of *Helicobacter pylori* may be effective in reducing abdominal attacks.
- Patients and physicians should be advised that infections should be treated promptly.
- Patients and physicians should be advised that estrogen may exacerbate HAE symptoms.
- Angiotensin converting enzyme (ACE) inhibitors need to be avoided because of their effects on the kallikrein-bradykinin pathway.
- Angiotensin-II receptor antagonists may be used with caution in patients with C1 inhibitor deficiency.

Treatment of HAE comprises short- and long-term prophylaxis, and therapy for acute attacks. Long-term prophylactic treatment is indicated for patients with many harmful and disturbing edema episodes (more than one attack per month or disability for more than five days per month) and more than one episode of severe abdominal pain or edemas per year. Long-term prophylaxis options include antifibrinolytic agents, attenuated androgens and plasma-derived C1 inhibitor. Antifibrinolytic agents, however, have side effects such as nausea, diarrhea, muscle cramps and increased thrombotic risk.

Long-term therapy with attenuated androgens also comes with risks of depression, liver tumours, peliosis hepatis, hemorrhagic cystitis, polycythemia, weight gain and arterial hypertension. Monitoring of long-term therapy using androgens should include a yearly exam, with a full count of blood cells, liver enzymes and lipids, urinalysis, and hepatic ultrasounds. Long-term prophylaxis is also possible with C1 inhibitor; however, access to C1 inhibitor for treating acute attacks should be optimized.

Short-term prophylaxis using danazol can be given to patients when they may be at risk for angioedema (e.g., dental care, endoscopic investigations, endotracheal intubation). C1 inhibitor is useful in emergency situations when there isn't time to administer danazol to control the symptoms, he concluded.

People with hemophilia develop antibodies to the factors they are lacking, a participant noted. Does this happen with C1 inhibitors? Dr. Cicardi replied that while some patients have antibodies to C1 inhibitors, they are not caused by treatment. These patients are unresponsive to danazol, possibly because they cannot produce enough C1 inhibitors to overcome the catabolism of the drug. Antibody formation against C1 inhibitors is associated with the development of lymphoma. "The symptoms are exactly the same but the treatment is more complicated," he said. Patients may benefit from chemotherapy, which can eradicate antibodies and even reverse C1 inhibitor deficiency.

Safety and Efficacy of C1 Inhibitor in Airway and Abdominal Events in HAE

Dr. Konrad Bork, Johannes Gutenberg University, Germany

Treatment with C1 inhibitor concentrate has been available in Germany since 1973, with pasteurization introduced in 1985, stated Dr. Konrad Bork of the Department of Dermatology of Johannes Gutenberg University, in Mainz, Germany. C1 inhibitor concentrate is manufactured by ZLB Behring and marketed under the name Berinert P for the treatment of acute HAE attacks, including laryngeal edema, facial swelling and severe abdominal attacks.

Treatments for acute HAE attacks comprise C1 inhibitor concentrate, fresh frozen plasma, tranexamic acid and danazol. Prophylaxis is recommended in oral surgery. C1 inhibitor is known to work in the treatment of abdominal attacks, however, objectivating its efficacy is a challenge. The standard procedure for establishing efficacy is through a randomized double-blind clinical trial, but this is difficult to perform with HAE because the occurrences and attack triggers are unpredictable. In addition, during acute attacks, patients may suffer from extreme pain, vomiting or diarrhea that prevent them from traveling to seek help. "Therefore, the participation rate in a clinical trial would be a biased dataset, of patients having less severe attacks," he noted.

Dr. Bork described a retrospective clinical study comparing untreated attacks to attacks treated with C1 inhibitor concentrate in the same individuals. Between 500 and 1,000 units of C1 inhibitor concentrate are needed to treat acute attacks, with about two hours between administration of therapy and the onset of relief. C1 inhibitor concentrate is effective for treating both moderate and severe pain attacks, and reducing side effects such as vertigo, vomiting and diarrhea. Pain scores and HAE symptoms are much improved with early treatment.

C1 inhibitor concentrate is highly effective for treating abdominal pain attacks related to HAE, substantially improving all symptoms and shortening the duration of the attacks considerably. C1 inhibitor concentrate is also effective in relieving the symptoms of laryngeal edema, he concluded.

Double-Blind, Placebo-Controlled Studies in HAE

Dr. Michael Frank, Duke University Medical Center, U.S.A.

Hereditary angioedema affects people in unusual and difficult ways, stated Dr. Michael Frank, Professor of Medicine and Immunology at Duke University Medical Center in the U.S. All three complement pathways (lectin, classical and alternative pathways) are affected by C1 inhibitor deficiency. Patients with HAE also tend to have low C4 and C2 inhibitors, which is used for diagnostic purposes.

Dr. Frank began his study of HAE in the early 1970s, after encountering a patient with HAE who had a total respiratory obstruction and needed an emergency tracheotomy. Little was known about the disorder and how to treat it. The medical team decided to try treatment with epsilon amino caproic acid (E-ACA), a plasmin inhibitor. However, it was very difficult to tell whether it was having a therapeutic effect, so the team undertook the first double blind study of E-ACA. The trial was designed for a relatively small number of patients, in which each patient served as their own control. In the 28-day trial, patients on the course of E-ACA therapy rarely had attacks while those taking a placebo continued to have attacks. "It was very clear that this drug was very effective," Dr. Frank stated. The team observed that patient C1 and C3 inhibitors levels remained the same, however, attacks quickly abated with use of E-ACA. However, E-ACA is fairly toxic, particularly to the muscles. In Europe, tranexamic acid (cyclized E-ACA) offers lower toxicity, but is not available in the U.S.

Hereditary angioedema occurs with equal incidence in males and females, but symptoms become far worse at puberty. The disease is made much more severe by estrogen. With pregnancies, HAE is much improved in the third trimester of pregnancy, but can be severe about a week after delivery. A double blind progesterone trial found patients treated with progesterone felt better, but it did not change the frequency of attacks.

A study using danazol, which inhibits the production of estrogen, yielded incredibly striking results, Dr. Frank reported. The use of large doses of danazol (600mg/day) led to large increases in C4 inhibitors and increased C1 inhibitor levels to normal ranges. Danazol side effects include weight and hair loss, muscle aches and pains and muscle enzyme abnormality, but most patients do not want to stop therapy because it is very effective.

Interferon-gamma has been found to raise C1 inhibitor levels and reduce the frequency of attacks; however, it is also highly toxic.

C1 inhibitor in animal trials have been shown to be very effective in preventing ischemia, a partial or total blockage of blood vessels, and reperfusion injury, a condition in which the restoration of circulation results in oxidative damage from the oxygen rather than restoration of normal function. C1 inhibitor was effective for treating myocardial ischemia in rats and markedly decreased damage from liver ischemia reperfusion.

There are few reports of C1 inhibitor use to prevent ischemia and reperfusion in humans; however, Dr. Frank reported that following failed coronary angioplasty, three patients treated with a bolus of C1 inhibitor followed by infusion recovered.

C1 inhibitor may also have applications in cardiopulmonary bypass and corrective surgery of neonatal congenital cardiac defects. He described a study in which he and colleagues tested whether plasma levels of C1 inhibitor may be decreased in children undergoing cardiopulmonary bypass. The hypothesis was that C1 inhibitor would inhibit the complement and other pathways, and therefore reduce the inflammatory response to

cardiopulmonary bypass in neonates and reduce organ damage post-bypass. The researchers believe that C1 inhibitor improves pulmonary function and reduces capillary leak syndrome, and that further investigation is needed on other differential effects on cardiac function. “C1 inhibitor will be very useful in some of the other illnesses where inflammation is a big feature of the disease,” he concluded.

Dr. Marco Cicardi asked whether C1 inhibitor might be used for prophylaxis or only acute attacks. Prophylaxis trials are harder to do because it is difficult to prove the connection between the treatment and the absence of attacks, Dr. Frank said. However, HAE lends itself to double blind studies because patients who have very clear attacks are given a drug that stops the attacks act as their own control.

HAE Therapeutic Options and Clinical Trials

Dr. Bruce Zuraw, University of California, San Diego

Dr. Bruce Zuraw was unexpectedly unable to attend the conference; chair Tom Bowen presented his paper in his stead.

The standard of healthcare for hereditary angioedema in the richest country of world, the United States, is not up to speed and there is clearly a medical need for double blind trials, according to Dr. Bruce Zuraw, Professor of Medicine at the University of California, San Diego. In Canada, unlicensed products for replacement therapy can be obtained through the country’s Special Access Programme.

Until recently, there was only a single, unlicensed replacement therapy option available. However, there are currently four double blind control trials underway in Canada; the new clinical landscape includes plasma-derived C1 inhibitor, DX-88, HOE-140 (Icatibant), and recombinant transgenic human C1 inhibitor.

The standard of care around the world for the treatment of HAE is vapor-heated C1 inhibitor concentrate. A double blind trial is being conducted to meet the requirements of the U.S. Food and Drug Administration (FDA) and Health Canada.

A number of products are coming to trial:

- Germany’s ZLB Behring has developed a rabbit recombinant product, shown to be effectively virally inactivated and with an “outstanding” safety record, which will soon be coming to trial.
- A non-filtered replacement product by Lev Pharma is also coming to clinical trial.
- The product EDEMA3, which shifts therapy from intravenous to subcutaneous injection, shows great promise.

- Icatibant is demonstrating interesting possibilities for treating other disorders.

Plasma-derived C1 inhibitor replacement therapy, however, remains the gold standard for treatment, with proven efficacy and safety.

The best treatment for HAE is not yet known and it is possible that combinations of therapies are needed, depending on a variety of factors such as severity, location, timing of attack, etc. It is important to keep the needs and interests of the patient population at the forefront and continue to push to get new products licensed in North America to advance the treatment of the disorder, Dr. Frank concluded.

Participants discussed the challenges and ethical concerns related to clinical trials, which include finding enough patients to enrol in trials and the ethically questionable but unavoidable placebo-controlled trials. Many patient groups are eager for access to unlicensed products before they come out.

2006 Canadian Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema

Tom Bowen, Clinical Professor of Pediatrics and Medicine, University of Calgary

In Canada, the blood product Berinert P for the treatment hereditary angioedema is available through the Special Access Programme, with about 45 to 50 infusions per million people annually, stated Tom Bowen, Clinical Professor of Pediatrics and Medicine at the University of Calgary. However, that consumption is merely the tip of the iceberg of potential demand.

At the International Conference on Management of Hereditary Angioedema in Toronto in October 2003, a Canadian consensus was reached for the diagnosis, therapy and management of hereditary angioedema; guidelines were published in the *Journal of Allergy and Clinical Immunology* in September 2004.

A national database registry is essential in order to capture the safety and efficacy outcomes of various efforts, Bowen said. A program for comprehensive care is required to collect data.

Three assays are required to diagnose HAE: C4 protein, C1 inhibitor antigenic protein, C1 inhibitor function and C1q protein. Six provinces perform such lab analysis (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario and Quebec), but not all centres are doing all the assays required. Standardization of assays is needed.

Recommendations for a Canadian comprehensive care program include:

- Updating the consensus document with a table listing Canadian centres performing C1 inhibitor assays along with reference ranges for normal results.

- Use of different methods to assess C1 inhibitor antigenic level, C1 inhibitor function and C1q antigenic level.
- Standardization of assays to ensure quality and accuracy of laboratory diagnosis.
- Establishment of a reference centre with suitable expertise in laboratory diagnosis of HAE to support physicians and patients.
- Home self-infusion and subcutaneous care for HAE should be developed in each province and territory based on existing home therapy programs for hemophilia care and European comprehensive care models.

“We have much to learn and much to do,” Bowen said, while thanking patients for their participation in clinical trials, which is critical to the eventual licensing of products.

A participant emphasized the need to ensure access to products for home care, and a vigilant vein-to-vein tracking system that feeds into national and international registries.

Session 2 – Primary Immune Deficiency

Chair: Tom Bowen, Clinical Professor of Pediatrics and Medicine, University of Calgary

Update on Primary Immune Deficiency Diseases: Genes, Phenotypes and Diagnostic and Therapeutic Options

Hans Ochs, Professor of Pediatrics, University of Washington

Over the years, primary immune deficiency (PID) has developed into a field of its own and now counts some 140 genes that are somehow involved in the way we defend ourselves against microorganisms and disease, said Hans Ochs, Professor of Pediatrics at the University of Washington. His talk gave insight into the principles of genetics, diseases, polymorphism, and the correlation between genotypes and phenotypes.

Molecular characteristics such as genetic defects (e.g., in T-cell or B-cell receptors), polymorphic modifiers and variable phenotypes have a profound impact on making the diagnosis, genetic counseling and treatment for primary immune deficiencies. Defects lead to serious infection. It is important to recognize the enormous complexity and variability of hemoglobulins, Dr. Ochs said. “Medicine in the 21st century will be driven by recognition of the molecular basis of diseases and the genetic defects of these diseases, and will have an enormous impact on prenatal diagnosis, neonatal screening, and carrier detection.”

Therapeutic options for PID can only be determined by knowing the patient’s precise genetic defect. For example, the X-linked recessive disorder Wiskott Aldrich syndrome is

characterized by eczema, recurrent infections, abnormal B- and T-cell function, autoimmune disease, and malignancies. Other symptoms include congenital bleeding, petechii, bruises, perinatal brain hemorrhage, bloody diarrhea as infants, severe eczema, allergies, ear infections and severe pneumonia. X-link inherited thrombocytopenia (ITP) involves amino-acid mutation with platelet dysfunction and x-chromosome inactivation; treatment with neo-antigen amplifies isotype switching and switch memory cell development. Understanding the distinct molecular and genetic defects is critical to proper diagnosis and appropriate therapy. Management of PID involves early diagnosis and molecular analysis, dietary adjustment for food allergies, antibiotics and IVIG therapy.

Immune deficiency and dysregulation involving polyendocrinopathy, enteropathy and X-linked dysregulation is known as IPEX syndrome. Characterized by neonatal diabetes, hypothyroidism, enteritis, hemolytic anemia, thrombocytopenia, and dermatitis, IPEX can be fatal. IPEX syndrome is associated with mutations identified in the FOXP3 gene. FOXP3 is involved in the activation and regulation of the immune system; FOXP3 mutation is linked to the inability to maintain mRNA level, however, the mechanisms are not clear.

Registries are central to determining incidence, product usage and prognosis. The NIH has established registries for eight diseases; reaching and registering patients are key to their success. International collaboration and pooling of data is valuable for rare disorders like IPEX. Clinical studies, genetic phenotyping, and identification of modifier genes and gene polymorphism are also key to advancing diagnosis and therapy. Registries can also be established for prophylactic IVIG towards improving efficacy. It is clear that patients enjoy the convenience of subcutaneous self-infusion at home.

Session 3 – The Hemoglobinopathies

Chair: Richard Alexander Wells, Toronto Sunnybrook Regional Cancer Centre

The Prevention and Management of Hemoglobinopathies

Dr. Isaac Odame, McMaster Children's Hospital, Hamilton, Ontario

Hemoglobinopathies refer to genetic blood disorders such as sickle cell disease and thalassemia, which affect five per cent of the population globally, stated Dr. Isaac Odame, Associate Professor and Staff Hematologist/Oncologist at McMaster Children's Hospital in Hamilton, Ontario. Hemoglobinopathies are not uncommon: about 2.5 in 1,000 births involve homozygous globin disorders. In Canada, hemoglobinopathy incidence is expected to rise as the number of Canadians from ethnic minorities continue to increase. It is vital to address the health outcomes and socio-economic impacts of hemoglobinopathies, and develop prevention and management strategies.

Recent years have seen advances in the management of thalassemia and sickle cell diseases, with improved standards of care, advances in medical knowledge such as induction of hemoglobin F production, improved iron chelation therapy and hemopoietic stem cell transplantation. But despite these developments, these blood disorders continue to cause significant morbidity and early mortality. Enormous investment is required to treat hemoglobinopathies, which has a profound impact on health care systems. Prevention is the most realistic approach to minimizing the impact and costs of these disorders, Dr. Odame stated.

Prevention requires education, effective screening and carrier identification tools, genetic counseling facilities and prenatal diagnosis programs. Retrospective management involves newborn screening programs with follow-up education, treatment, counseling and monitoring. While carrier identification can be very expensive since these disorders involve over 200 mutations, prevention is still more successful than retrospective management for reducing the health and economic burdens, Dr. Odame said.

Genetic counseling must be done with careful attention to empowering families to make decisions through a clear understanding of their options (e.g. prenatal diagnosis, newborn screening, preconception or preimplantation diagnosis, not to have offspring, etc.) and limitations, and the consequences and ethical implications of their decisions.

Management of thalassemia should be carried out in the context of comprehensive care clinics, ideally with a hematology team with the expertise, knowledge and ability to treat these disorders. Blood bank support is essential. Other key components are preventive care and prophylaxis, iron chelation therapy, pain management and nutritional guidance. Improved management of thalassemia has a great impact on quality of life; iron chelation therapy helps prevent osteoporosis and better care improves fertility for patients with thalassemia.

Newborn screening and preventive care are also essential for improving the health outcomes for patients with sickle cell disease and to prevent stroke and mortality. Sickle cell patients would benefit from broader criteria for hemopoietic stem cell transplantation, Dr. Odame said.

Gene therapy, although sound in principle, requires improved safety and efficiency before it will become available.

Patients with cardiopulmonary disease or stroke risk may require chronic transfusion, which is accompanied by complications such as iron overload.

The overwhelming majority of patients with hemoglobinopathies live in developing world — the responsibility of the developed world is not just to find a way to control these disorders, but to transfer knowledge to the developing world, Dr. Odame said. The developed world enjoys high-quality care with availability of transplantation and prospects for gene therapy. In developing world, the situation is desperate — there is an

absence of effective newborn screening and carrier identification programs, and iron chelation therapy and hemopoietic stem cell transplantation are prohibitively expensive.

Iron Chelation Therapy

Dr. Paul Telfer, Department of Hematology, Royal London Hospital, U.K.

Dr. Paul Telfer of the Department of Hematology at the Royal London Hospital in the U.K. gave an overview of the consequences of transfusion iron overload, and discussed four chelation therapies, desferrioxamine, deferiprone, combination therapy, deferasirox.

Thalassemia care has advanced greatly in the last 50 years, with regular blood transfusion greatly extending life expectancy. However, chronic blood transfusion leads to the inability to excrete iron, causing iron overload and eventual toxicity in various organs including the endocrinological glands, liver and heart. Early treatment is critical to preventing complications.

Iron chelation with intravenous and subcutaneous desferrioxamine effectively removes excess iron. The treatment, however, can be difficult to administer as it involves infusion via a syringe pump into the abdominal wall or continuous infusion via a port-a-cath; adolescence can be a challenging period as patients begin to take more responsibility for their own care. Until recently, desferrioxamine was the most widely used iron chelator and considered the best treatment for iron overload.

Desferrioxamine has also shown to be effective in reversing cardiomyopathy and dramatically improving heart function.

Desferrioxamine, has brought progressive improvement survival rates. Life expectancy has improved considerably, with patients surviving into their 30s. Cardiac problems remain an issue, however, and compliance is a serious problem that has great effect on prognosis.

Side effects of desferrioxamine include skeletal dysplasia, sensorineural hearing loss, retinal toxicity, yersinia infection and osteoporosis. Skeletal dysplasia is particularly an issue with children, who should not be given high doses of desferrioxamine. Iron chelation therapy is largely unavailable and unaffordable in the developing world.

Important developments in chelation therapy include clinical studies on deferiprone, an oral iron chelator licensed in Europe for the treatment of iron overload in patients with thalassemia major in whom desferrioxamine is contra-indicated or not tolerated; deferiprone is not licensed in North America. Numerous studies show the efficacy of deferiprone in inducing iron excretion protecting the heart against the effects of iron overload.

Adverse effects of deferiprone include agranulocytosis, neutropenia, gastrointestinal disturbance, arthropathy, and zinc deficiency. Monitoring of blood counts must be done very carefully, Dr. Telfer said. Hepatic fibrosis, previously believed to be a possible side effect of deferiprone, has been largely discounted as a deferiprone side effect.

Combination chelation therapy with desferrioxamine and deferiprone is based on the rationale of increased efficiency through an additive or synergistic effect; improved adherence and fewer desferrioxamine infections; optimized chelation from different pools (i.e., desferrioxamine for liver iron chelation, deferiprone for heart iron chelation. Reducing the dose of individual chelators may minimize chelator toxicity. “Combination chelation is the most reliable way to get negative iron balance and decrease toxicity,” Dr. Telfer stated. Improvements for patients with cardiac disease have also been observed, with significant improvement in mortality.

Deferasirox (marketed as Exjade) is a once-daily oral iron chelator, which brings great convenience for patients. It was recently approved for licensing by the U.S. Food and Drug Administration and is awaiting approval in Europe. Randomized studies comparing deferasirox and desferrioxamine show equivalence in effects. Patients with heavy iron overload are found to require higher doses of deferasirox to reduce their iron levels or maintain iron balance. The drug is well-tolerated, however, Dr. Telfer emphasized the importance of monitoring renal function with the long-term usage of deferasirox.

The adverse effects of deferasirox are similar to desferrioxamine; gastrointestinal and dermatological angioedemas are more frequent with deferasirox but the symptoms are manageable. The frequency of important uncommon angioedema is not known because the safety population small. Indefinite use of deferasirox will likely be associated with more frequent and different transfusions.

Once-daily administration of deferasirox for a period of one year produced significant reduction in liver iron count, using 20 or 30 mg/kg, equivalent to desferrioxamine dosage. “Deferasirox appears to be a convenient, well-tolerated and effective once-daily oral iron chelator for the treatment of chronic iron overload in adult and pediatric patients receiving regular blood transfusions,” Dr. Telfer said.

Patients and physicians now have choices for iron chelation therapy, with alternatives to nightly injections of desferrioxamine:

- Deferasirox is likely to maintain acceptable iron balance in children and previously well-chelated. However, at present many patients and physicians would like to see longer-term data on efficacy and safety before switching from desferrioxamine therapy.

- Deferiprone has been shown to have an important cardioprotective effect and has an important role for patients with cardiac dysfunction. Deferiprone therapy must be carefully monitored, with systemic checking of neutrophil count.
- Combination therapy with desferrioxamine and deferiprone is the most efficacious chelation regime and should be considered in heavily iron loaded patients who have not adhered to desferrioxamine.

Further research is needed to determine if deferasirox is sufficiently effective and safe with long-term dosing, and whether it is effective in chelating heart iron. Other areas for exploration include determining the best chelation regime for preventing endocrine complications and the best combination of chelator drugs. Finally, recommendations are needed on providing safe, effective and affordable iron chelation therapy to people with thalassemia living in the developed world, he concluded.

Panel Discussion

A participant asked Dr. Telfer to elaborate on the considerable heterogeneity in organ-specific iron overload in organs. Dr. Telfer explained that iron in the heart cumulates in patients who receive regular transfusion during childhood without adequate chelation. Differences in heart and liver iron overload can also be due to recent treatment with desferrioxamine, which reduces liver iron but not heart iron.

From the patients' perspective, the model for comprehensive care therapy is superior, but the funding perspective may be different, a participant noted. How eager have provincial and federal agencies been to support the comprehensive care model? Dr. Isaac Odame explained that a comprehensive care model involving satellite centres would be more convenient and cost-saving for patients, who will not have to travel long distances for care, making it a cheaper and more convenient model.

A patient asked whether the use of vitamin C in severely iron-overloaded patients is ill-advised. Dr. Telfer replied that vitamin C not only enhances iron absorption in the heart but also increases iron in plasma, potentially causing toxicity. On the other hand, ascorbic acid is needed to mobilize the iron into a form that can be chelated. He was not aware of data concerning patients clinically encountering problems or complications if they stop taking ascorbic acid.

A participant asked whether combination therapy using desferrioxamine and deferasirox has been tried. Dr. Telfer replied that given that desferrioxamine and deferasirox seem to work in similar ways, deferasirox and deferiprone may be a more effective regime.

Lobbying for newborn screening programs at the provincial and federal levels is critical to saving and improving lives, a participant said. In addition, funding is needed to publish epidemiological data for Canada.

Noting that cardiac problems can be reversed with appropriate chelation, a participant asked whether there is potential for reversing iron-overloaded pituitary glands. Unfortunately, endocrinological damage appears to be irreversible, Dr. Telfer replied.

A participant asked about efforts to get pharmaceutical companies to reduce antiretroviral drug costs to make them accessible to the developing world. Dr. Telfer replied that iron chelation drugs are not on the World Health Organization list of essential drugs. Work needs to be done to get iron chelation therapy classified as essential drugs; better epidemiological data is needed about sickle cell and thalassemia globally, with calculations of the global health burden of these disorders compared to other diseases. Iron chelation is not cheap and is a lifelong course of therapy. Patient groups and healthcare organizations need to get together to develop a strategy on access to iron chelation.

Patients need to keep well-informed about standards of treatment and new forms of treatment. Good patient-physician communication is critical; physicians must be thoroughly versed on treatment standards and complications, and patients must take responsibility for keeping a record of their care.

Patient groups must be involved in planning their care and developing protocols for treatment and comprehensive care, emphasized Tom Bowen. Dr. Odame added that funding agencies listen to patients, not physicians. In Ontario, the inclusion of patient groups in advocacy for newborn screening programs was successful, he noted.

Comprehensive Care Programme

Introductory Session

Welcome

Eric Stolte, Canadian Hemophilia Society

The Conference on Comprehensive Care for Rare Blood Disorders represents an exciting time in Canada, with nine partner organizations coming together to work towards providing comprehensive care that will dramatically change the lives of Canadians, stated Eric Stolte, president of the Canadian Hemophilia Society. “Small numbers can produce amazing results, especially in partnership,” he stated.

The Canadian Hemophilia Society (CHS) is an example of how a small group of people changed the nation, he said. The CHS was founded in Montreal in 1953. Within 15 years, chapters had been established in every province but it was 25 years before the first

Canadian conference on comprehensive care for hemophilia took place, in Winnipeg in 1978. “And 25 years later, we’re still working hard within our community to see comprehensive care become something that’s accessible and secure across the country — it’s still very fragile in many places,” Stolte said.

Yet he asserted that comprehensive care has been proven to save lives and healthcare costs, and allows people to have productive lives and contribute to society. Hemophilia is a rare blood disorder that affects 3,000 people across Canada. Stolte noted that in the 1980s the hemophilia community was devastatingly affected by tainted blood, but galvanized their efforts to testify about their experiences and see a safer blood system in the country. “A small group of volunteers changed the entire blood system in Canada,” he said.

The comprehensive care model holds promise for a productive future for people with rare blood disorders, Stolte stated, while underlining that strong alliances between medical professionals and patients, partnering organizations and sponsors will be key to seeing quality comprehensive care become a reality that will benefit people across country.

A Vision of Comprehensive Care for Rare Blood Disorders

Silvia Marchesin, Conference President

The vision for comprehensive care for rare blood disorders is the result of the coming together of nine organizations, said Conference President Silvia Marchesin. The nine founding members of the Network of Rare Blood Disorder Organizations are:

- Aplastic Anemia and Myelodysplasia Association
- Canadian Hemophilia Society
- Canadian Hereditary Angioedema Society
- Canadian Immunodeficiencies Patient Organization
- Canadian Organization for Rare Disorders
- Canadian Porphyria Society
- Canadian Sickle Cell Society
- Thalassemia Foundation of Canada
- Sickle Cell Society of Ontario

The vision came out of an international conference in October 2003, hosted jointly by the Canadian Hemophilia Society (CHS) and Canadian Hereditary Angioedema Society (CHAES) and organized principally by Jeanne Burnham of the Canadian Hereditary Angioedema Society and Tom Bowen of the University of Calgary. A consensus emerged at the conference supporting the concept of a specialized system for blood immunology and comprehensive care for all rare blood disorders. “The idea had been floating around a long time but this was the first time I saw a coherent list of what was possible,” Marchesin said. “It was the beginning.”

David Page of the CHS undertook consulting leaders of the blood disorder organizations about working together to create a network. With a one-year National Volunteer Health Organization Sector Development Grant from Health Canada, the Network of Rare Blood Disorder Organizations (NRBDO) was established in 2004. The network is managed by the CHS.

The network's objectives are to:

- Create an active network of volunteers and encourage permanent relationships and an exchange of knowledge about issues and challenges for other disorders;
- Raise awareness and knowledge about key areas: patient registries, specialized care centres, tracking of rare blood and blood products, and the need for active adverse reaction reporting and post-market surveillance;
- Share existing successful models on comprehensive care, in particular the CHS;
- Facilitate the development of organization policies on key issues;
- Create permanent links to remain connected after funding has ended; and
- Encourage research.

At the end of the first year, network members identified some common issues and determined that its focus for the next year must be comprehensive care. "Exceptionally, the Public Health Agency offered NRBDO a grant for a second year, perhaps because they realized the opportunities involved and the momentum of the network," Marchesin said.

The vision of comprehensive care is broadly based on an approach developed in the 1970s for hemophilia and other disorders, with healthcare professionals, patients and families contributing to the development of model. "The baseline was that care of rare blood disorders is less than optimal in some parts of Canada, yet optimal care is good for patients, their families and society as a whole," Marchesin said. Canada has the knowledge, expertise and resources to provide optimal care for people with rare inherited bleeding disorders, but commitment is needed to advance the vision of comprehensive care.

NRBO Working Hypothesis on Comprehensive Care for Rare Blood Disorders

David Page, Canadian Hemophilia Society

David Page, Director of Programs and Communications with the Canadian Hemophilia Society (CHS), described a number of characteristics that the Network of Rare Blood Disorder Organizations identified as essential for a comprehensive care system Canada:

Designated provincial programs: All provinces must designate provincial programs with dedicated budgets for comprehensive care. These designated programs will mandate specialized centres for diagnosis, treatment and care. "The nine associations believe that these blood disorders are far too rare to be decentralized for management by regional or

local health authorities,” Page said. “Provinces are trying to regionalize, but we believe that would lead to unequal and suboptimal quality of care.”

National patient registries: Database registries are essential to promote high-quality, evidence-based medicine. Registries also help attract new resources for novel therapies and measuring patient outcomes. However, there is a lack of resources to develop and maintain registries. The Canadian Hemophilia Registry was established in 1980s.

Self/family administration of therapeutics: Home therapy for hemophilia has been practiced for some 30 years. Comprehensive care must include training for patients and families. “Hemophilia is the vanguard of the self-infusion revolution and the movement away from hospital to self-care,” Page said. “We need a health system that provides support and training to patients with rare blood disorders and their families.”

Patient/family involvement: Beyond patients and their families, patient associations are indispensable. “Patient associations must be involved in the design of a comprehensive care system —politicians will listen to them,” Page said.

Portability and national standards: People with rare blood disorders must be able to move around for work, education, etc., and have access to the same quality of care.

Decentralization: A good comprehensive care program must be decentralized, since people with disorders are not confined to large cities. Treatment and service must be provided in the home community, Page emphasized. Outreach is key.

Multidisciplinary care: Beyond drug therapy, people with blood disorders need education so that they can contribute to their own care; with home therapy, the level of education and knowledge must be much higher than for those who put their faith in hospitals, he noted.

Aggressive maintenance and early intervention: Early diagnosis and prompt treatment are shown to improve quality of life and survival.

Comprehensive care: Comprehensive care involves diagnostic services, education therapies, nursing evaluation, genetic counseling, psycho-social evaluation and services, laboratory, monitoring of blood products, home infusion training, allied medical specialist services, outreach, referral services, case management, program coordination, research, and coordinated hospital and emergency room care. Patients, families, physicians, nurses, social workers, and specialized professional services are all involved. “Investing more in comprehensive care would also optimize the use of high-cost products,” Page noted.

Program evaluation: Without evaluation and accountability, standards are unproductive. Evaluation and accreditation should be conducted regularly by qualified peers, based on measurable standards.

National collaboration: Blood disorder communities are too small and rare to act in isolation or opposition. Strong links between patient organizations and healthcare professionals and among healthcare teams are essential.

Blood borne pathogen surveillance: Blood borne pathogens are not limited to HIV, HBV and HCV. In the last 30 years, a new blood borne agent has emerged yearly, from vCJD to the West Nile Virus, and Hepatitis E and G. “Not all are pathogenic or cause disease — but we don’t know unless there is monitoring and surveillance. A key role of comprehensive care is to monitor for adverse reactions and conduct systematic blood borne pathogen surveillance,” Page said.

Research: A national network is needed to measure health outcomes and conduct research into improved therapies.

There is a lot of flexibility built into the notion of comprehensive care to accommodate regional and geographic differences, Page said. A variety of comprehensive care centres are needed, from urban centres that deal with a single disorder to rural comprehensive care centres that may need to cover a combination of diseases.

The principles of comprehensive care were put together by patients and medical advisors in the Network of Rare Blood Disorder Organizations, stated Conference President Silvia Marchesin. The conference’s objective would be to look at what works and what doesn’t in Canadian and international models, and develop a consensus that the network can take to federal and provincial healthcare policy decision-makers to improve care for Canadians with rare blood disorders.

Panel Discussion

Networking with other groups is an indispensable part of comprehensive care, a participant said. It is critical to recruit effective members, and to lobby. “There’s nothing like a variety of groups and numbers to help in lobbying,” he added.

The NRBO comprises nine diverse organizations representing different diseases and with their own specific challenges, but collectively there are many common and overlapping issues, Marchesin noted. As a network, the organizations have drafted a vision for comprehensive care nationally. At the same time, researchers, clinicians, physicians and patient organizations are also coming together to share experiences, advocate and push initiatives forward.

Partnership among patient groups and physician and clinical care groups is of utmost importance, a participant said. Whatever the disorder, every treating centre should have a strong connection with the patient society, he said. Patient organizations should be visiting hospitals and actively reaching out to educate physicians, he added.

A strong and supportive relationship between physicians and patient organizations, with the patient at the centre of the comprehensive care circle, is key to the success within each clinic, Marchesin concurred. However, she also noted some of the challenges rare disorder organizations face in increasing awareness of their disorders, such as geography and a limited volunteer base. “We need ideas about how to get the awareness out.”

The Canadian Sickle Cell Association coordinates a sickle cell satellite clinic in the Montreal Children’s Hospital, along with a monthly parent support group, a participant said. Newly diagnosed patients referred to the hospital are always given information on the support available from the association. She added that the umbrella organization very much needs funding in order to reach people across the country with sickle cell disease. The challenge remains that while most of the organizations are national, there may not be chapters in all provinces, Marchesin said. So there is significant representation in some cases and less in others.

The best way to find patients with rare blood disorders is to follow the blood product, a participant. “It’s the common thread,” she said. She advised organizations to visit infusion nurses who dispense the products, who tend to be willing to share information and learn about disorders.

Patients are critical in the development of comprehensive care for rare blood disorders, a participant said. “Governments listen to the patients, and when the patients and doctors are on the same page, there is at least a chance of accomplishing what needs to be accomplished.”

Another participant emphasized, “The only way this will work is if we all work together — physicians, patients and their organizations and the pharmaceutical companies who bring new products to market. We may have different points of view but we must work together.” He urged participants to think of the big vision, debate the issues, and arrive at some consensus on comprehensive care for rare blood disorders.

Saturday, February 4

Comprehensive Care Programme

Welcome and Conference Objectives

Silvia Marchesin, Conference President

Conference President Silvia Marchesin welcomed participants, noting that the audience represented an impressive gathering of patients and their families, patient organizations, physicians, clinicians and other healthcare professionals, and representatives from industry and government. All share an interest in the vision for a comprehensive care program that would include database registries, comprehensive care clinics and other necessary support for Canadians with rare disorders.

The Network of Rare Blood Disorder Organizations (NRBDO) involves nine patient organizations from across Canada, and is coordinated by the Canadian Hemophilia Society (CHS) under the direction of David Page. The network was founded two years ago and is funded by a National Volunteer Development Organization grant from Health Canada. In its second year, the NRBDO has focused on one issue common to all the groups: comprehensive care. The vision of comprehensive care is based on the successful CHS model of comprehensive care clinics across Canada.

Marchesin reviewed the characteristics that NRBDO considers essential for a comprehensive care program:

- Provincial designation
- National registries
- Self/family administration therapies
- Patients involvement
- Portability
- Decentralization
- Multidisciplinary
- Core services
- Comprehensive care team
- National collaboration
- Blood borne pathogen surveillance
- Research

The objective of the conference would be to test this vision against Canadian and international models, and develop a practical model for comprehensive care for rare blood disorders to put forward to provincial health authorities, Marchesin concluded.

Session 1 – Current Canadian and International Models of Comprehensive Care

Chair: Tom Alloway, Past President, Canadian Hemophilia Society

The Impact of Comprehensive Care on Morbidity and Mortality in Hemophilia

Dr. Bruce Evatt, Atlanta, GA

Comprehensive care is truly effective in reducing morbidity and mortality, stated Dr. Bruce Evatt, who spoke of its proven benefits in the treatment of people with hemophilia. The distinguished hematologist, whose major accomplishments include identifying AIDS as a blood-borne disease affecting people with hemophilia and blood-transfusion patients, emphasized that lack of treatment is the most dangerous risk for people with hemophilia.

This is evident in the tremendous difference in quality of life between those living in developed and developing countries, he noted. In the poorest countries, people with hemophilia suffer joint damage, are often bedridden, and rarely live beyond 19 years of age. In contrast, people with hemophilia living in developed countries have had increasing life expectancy since the development of blood transfusions during the Second World War and the subsequent use of fresh frozen plasma in patients. Hemophilia associations are established throughout the world, with the primary purpose of increasing blood drives to provide blood product medical treatment.

The 1960s and 1970s saw rapid progress with the development of cryoprecipitates and concentrates that greatly improved the capacity of patients to be treated by physicians. Patients and physicians gradually formed an alliance to develop the concept of comprehensive care. Comprehensive care greatly improved life expectancy, which increased further until the 1980s.

The hemophilia comprehensive care program is based on a preventive care approach and the concept of home care, with organized specialized care delivery, integrated multidisciplinary teams, education and training of patients, and a coordinated network of centres for care and early management of bleeds.

Dr. Evatt noted that even poor countries that do not have access to the sophisticated treatment products of the developed world have achieved remarkable benefits from comprehensive care, experiencing an almost fivefold increase in life expectancy. Comprehensive care is also shown to dramatically reduce hospital stays and joint bleeds, leading to considerably improved lifestyles and employability for people with hemophilia, Evatt reported. Children with hemophilia are now able to engage in activities from soccer to rock-climbing, without the joint problems that previously impeded them.

However, the arrival of HIV, Hepatitis C (HCV) and Hepatitis B (HBV) in the 1980s had a devastating impact on the hemophilia community and led to a major push by hemophilia associations for safer blood products. The development of heat-treated products in 1985 eliminated the risk of HIV infection through blood products.

Nonetheless, there continues to be a push by industry based upon the demand of hemophilia associations to improve the safety of blood products. The introduction of viral inactivation technology in the 1990s eliminated the risk of HCV infection through products. But with hospitalization and death rates higher among patients not visiting comprehensive care centres, policymakers awoke to the fact that continued funding for comprehensive treatment centres was essential and treatment could not be left to private practice alone.

The specialized medical team approach brought significant improvement, including reduced hospital visits and life-threatening complications. Patients were educated and trained in home care and treatment of their disease and had easy access to expert treatment for emerging issues. But as home treatment became more common, clinics became less visible to medical institutions and complacency among patients also led to a decline in patient advocacy, Evatt said. In fact, a 2000 survey by the U.S. National Hemophilia Foundation found that physicians in hemophilia treatment centres were only spending about 20 per cent of their time taking care of patients. Staff were found to be spending about 69 per cent of their time on hemophilia care, but patient visits had dropped to 5.2 patients per week.

This has compelled hemophilia comprehensive care clinics to change the nature of their care delivery in order to maintain the expertise in hemostasis and thrombosis needed to increase the survival of patients with rare blood disorders and to reduce their morbidity. Women with von Willebrand's disease are being incorporated into clinics, as are thrombophilia patients; a concerted effort is being made to advocate for comprehensive care as the standard of care for the management for all rare blood disorders.

The World Federation of Hemophilia (WFH) experience has highlighted a number of critical issues that must be considered for other comprehensive care models:

1. A long-term approach is essential to accommodate changes in comprehensive care over time as successful therapy reduces patient dependency on the clinic.
2. Comprehensive care must be more than just administration of therapeutic products; it must encompass healthcare education.
3. Programs must be sustainable and tailored to resources, which must come from government.
4. The current care system must be modified.
5. There must be strong advocacy from patient organizations.
6. Strong leadership in physician organizations is needed.
7. Alignment with other patients amplifies effect with politicians.

WFH suggests steps in five different areas:

Essential components for comprehensive care include government support for the management of chronic diseases, access, availability and affordability of treatment products, sufficient medical expertise, knowledge of the regulatory process, and strong patient organizations. Long-term plans with clear goals and objectives and coalitions between health care providers and patients are critical to successful care of chronic disorders and rare blood disorders, he concluded.

The Canadian Network of Comprehensive Care Centres for the Treatment of Bleeding Disorders

Prof. Jerry Teitel, Medical Director, Adult Hemophilia Program, St. Michael's Hospital, Toronto

Julia Sek, Provincial Hemophilia Coordinator, Ontario

The evolution of hemophilia therapeutics in the 20th century led to the ability to deliver comprehensive care, began Jerry Teitel, Medical Director of the Adult Hemophilia Program at St. Michael's Hospital in Toronto, in an overview of the development of hemophilia treatment centres in Canada. In the 1970s, the advent of lyophilized factor VIII concentrates and active prothrombin complex concentrates (PCC) enabled home management of the disorder and better quality of life. The 1980s, however, brought transfusion-transmitted infections, a disaster that continued until the development of high-purity factor VIII concentrates in the 1990s. More recently, the introduction of plasma protein free factor VIII concentrates has brought reassurance to the hemophilia community of the safety of blood products.

Hemophilia comprehensive care clinics feature teams of specialized medical expertise, including hematologists, rheumatologists and specialists in coagulation and transfusion, infectious diseases, nursing, dentistry, physiotherapy, social work, genetic counseling, and data management. Another key component is home-based self-infusion of clotting factor concentrates, which has liberated people with hemophilia from clinics.

The experience and evolution of hemophilia care is instructive for other rare blood disorders, Teitel said. The first comprehensive hemophilia clinic was established at the Montreal Children's Hospital by Dr. Hanna Strawczynski, a pioneering physician whose studies demonstrated that home management led to earlier and better treatment and better school attendance, which translates into better employment opportunities and more productive citizens. Subsequent clinics arose in Canada in following years, initiated by different mechanisms: the CHS, local physicians or local ministries of health. There are currently 25 clinics located in university and community hospitals in 21 cities, with both adult and pediatric units. These centres provide care to almost 6,000 patients, including people with rare blood disorders. Teitel noted that one of the challenges Canada faces in

terms of comprehensive care is the size of the country. There are also variable funding models for clinic infrastructure across the provinces.

In addition to the community and university hospitals where they are located, key partners in hemophilia care in Canada are advocacy organizations such as the CHS and professional associations associated with hemophilia care (i.e., physicians, nurses, physiotherapists, and other healthcare professionals specializing in hemophilia care); national regulators (i.e., Health Canada), and blood product providers (i.e., Canadian Blood Services and Héma-Québec); provincial ministries of health; and manufacturers of clotting factor concentrates.

The mission of the Association of Hemophilia Clinic Directors of Canada (AHCDC) is to ensure excellent care for people with congenital blood disorders. The AHCDC establishes and maintains registries; promulgates standards of care and guidelines; collaborates on research and survey studies; shares information; and develops strategies with partners. In 1998, the AHCDC and CHS consensus conference in Winnipeg yielded the following important messages:

- Standards of comprehensive care should be delivered according to national standards; care is now approaching standards in various provinces and nationally.
- Hemophilia comprehensive care programs should be officially designated, and recognized by provincial ministries, which should provide core services.
- Accreditation and review of programs are essential; comprehensive care clinics should be accountable for all clotting factor concentrates distributed.
- Comprehensive care programs must be supported by provincial ministries of health.

Hemophilia is a rare disease that is fatal if not treated and requires intense and multidisciplinary care by a team of physicians and nurses, social workers, physiotherapists, and other specialists, stated Julie Sek, Provincial Hemophilia Coordinator for the province of Ontario. “Effective care will decrease future healthcare costs, increase quality of life and lower morbidity,” she said. Effective disease management improves patient outcomes and decreases disability, hospitalizations, emergency room visits, days lost at school, healthcare costs, and mortality.

Following the vision put forward at the 1998 consensus conference, a steering committee was formed in Canada for the development of hemophilia comprehensive care standards at both the provincial and national levels. Membership included people with hemophilia, healthcare professionals, CHS, Canadian Blood Services, and provincial government representatives.

Comprehensive care is the preferred method by which to ensure that people with inherited bleeding disorders have access to effective and expert healthcare, Sek asserted. “The provision of high-quality care for individuals and families affected by disorders will improve patient outcomes and optimize resource utilization.”

The development of guidelines required data collection, evidence from practice and research, collaboration of consumers and healthcare providers, and resources. The Canadian Hemophilia Assessment and Resource Management System (CHARMS) was created to collect data from sources such as infusion records, and clinic surveys and reports are being conducted nationally in collaboration with CHS or provincially. The evidence-based recommendations subsequently put forward by the AHCDC and CHS has led to the development of best practices and clinical practice guidelines. One of the challenges, Sek noted, is that governments sometimes regard home care programs as belonging to a “different envelope.” Education is required that self-infusion is self-administered healthcare.

Canada’s comprehensive care program for hemophilia is an excellent model of integrated health delivery, with an interdisciplinary healthcare team dedicated to the prevention and management of bleeding. However, it has some shortcomings, Sek said. There is a lack of provincial budgeting for the hemophilia program, and securing physiotherapy and social work hours for people with hemophilia is a constant battle. There is also a national shortage of hematology residents with an interest in hemophilia care and coagulation, resulting in very limited and inconsistent staffing resources to deliver highly complex care. Subspecialty services are also very limited and inconsistent.

Sek suggested the provincial hemophilia coordinator should be implemented federally. “Given the high cost of clotting factor concentrates, this is a unique opportunity to track utilization and responsible management.”

The current restructuring of Health Canada allows for advocacy for orphan and new programs, she noted. “This is a great opportunity for us to bring our story to the table and advocate for needs.”

The major challenge that remains is that inherited blood disorders are rare, but demands on resources are constant. Sek noted that there is growing demand for services across regions, yet a lack of dedicated funding.

The benchmark set by hemophilia treatment centres for comprehensive care is in the interest of Canadian society and its healthcare system, with shown benefits such as improved overall health, accountability for the tracking and management of factor concentrate use — a program for integrated healthcare driven by patient needs, Sek concluded.

A Patient's Perspective on the Difference in Quality of Life Before and After the Introduction of Comprehensive Care

David Page, Canadian Hemophilia Society

Through pictures, David Page, Director of Programs and Communications at the Canadian Hemophilia Society, showed the sharp contrast in quality of life for people with hemophilia with and without comprehensive care. He recalled how as a child, before the introduction of comprehensive care, he missed one day out of three of school — spending the equivalent of one month out of 12 in hospital. While developed countries have made considerable progress in recent decades, he noted that developing countries lack comprehensive care and people with hemophilia suffer conditions that have not been seen in the developed world for many decades.

Chronic disorders have an effect on the entire family, he added, noting the challenge of providing for the family unit when trying to provide medical care for patients.

Safe clotting factor concentrates in the late 1980s onward have greatly improved quality of life; however, Page emphasized that the advances could not have been possible without comprehensive care. For example, the CHS organizes camps where children are trained in self-infusion; children as young as four and five have learned the many steps involved in infusion (mixing products, sterilizing syringes, etc.). Comprehensive care must also involve a specialized medical team. Nurses and physiotherapists are essential members of the team. In Quebec, funding for physiotherapists for hemophilia treatment has been cut, a shortsighted measure since the savings in salaries for physiotherapists will be nullified given the substantially larger costs that will be incurred for the extra care for joint rehabilitation due to insufficient physiotherapy, he concluded.

The Network of Care Centres for Primary Immune Deficiency (PID) in the U.K.

Prof. Carrock Sewell, Path Links Immunology/University of Lincoln, U.K.

Networking is an essential aspect of the work of immunologists in the U.K. given their scarcity in numbers in the country, said Dr. Carrock Sewell of Path Links Immunology and the University of Lincoln in the U.K. He gave a presentation that highlighted some of the distinct features of the U.K. model.

Immunology centres are dispersed throughout the U.K.; immunologists also run the laboratories and some centres are run by a single consultant. The U.K. Primary Immune Deficiencies Network was formed in 1999 as multidisciplinary network of specialists who treat immune diseases as defined by the government department of health. Its activities include a national meeting; accreditation and approval of immunology centres; establishment of consensus guidelines and standards; advocacy with government and health organizations; and education and awareness of primary immune deficiencies.

Members include nurses, physicians and scientists involved in the care or research of patients with PID. While the network has very close links with the patient organizations, it functions as “the technical arm.” The network is overseen by three executive officers (a chair, secretary and treasurer), with working groups formed for each function undertaken.

U.K. PIN’s first five years have been funded by a block grant from the immune globulin manufacturer BPL; the network is currently developing a business sponsorship plan for its future administration. Funds support administration, training and accreditation activities, and staff exchanges. Standards are established by consensus and compliance is rigorously scrutinized through peer and self-assessment. The network also holds a national immunology forum every two years, where a range of stakeholders including physicians, consultants, nurses and trainees come together to learn the latest information and vote on different issues.

The network has developed standards in six domains:

- Organization of centres
- Staffing of centres
- Facilities (outpatient facilities, infusion rooms, office space, library)
- Clinical care (documentation, protocols and procedures)
- Home therapy standards (training)
- Audit, education and management (compliance, quality, research)

Dr. Sewell outlined some of the lessons learned. The network initially set some of the standards far too high; minimum standards that have some flexibility are more practical. In addition, the network’s initial funding model, with free membership, was impractical.

There have been many successes. Widespread involvement of all centres in the U.K.; practical minimum standards; effective communications; and minimal bureaucracy have been the network’s pillars of success.

The network is now looking ahead to new funding and accreditation arrangements, refining its guidelines by continuous review, and greater sharing of its information with others, he concluded.

The Network of Care Centres to Treat Hereditary Angioedema in Italy

Dr. Marco Cicardi, University of Milan, Italy

Hereditary angioedema is a very young disease, stated Dr. Marco Cicardi of the University of Milan and San Giuseppe Hospital in Milan, Italy. Hemophilia, by comparison, began to be treatable with therapy at the end of the 19th century, but hereditary angioedema (HAE) does not have such a long history and has been somewhat ignored, he said.

There is little on HAE in the literature historically, with the first solid reference to HAE found at the end of 1900 by a physician in Naples. The physician described a man with the symptoms of HAE, giving a very precise and comprehensive description of the disease. Another article from an Italian medical journal describes how a physician gave an emergency tracheotomy at home to his son, who was suffering with HAE and about to die from it.

To most physicians, HAE is an obscure disease, but Dr. Cicardi emphasized that it is a very important disease. “People can die and suffer, so there is very good reason to treat these patients and try to give them the best possible care.” Diagnosis of HAE has been improved by interactions with hemophilia researchers in Italy, and the hemophilia model remains an important reference point, he added.

An HAE patient support group was established in 1980 and has assisted considerably in expanding knowledge, understanding and diagnosis of the disease in Italy. Finding and correctly diagnosing people with HAE is of primary importance and remains the biggest challenge. One successful initiative that reached a good number of new patients involved a simple poster at hospital entrances and in emergency rooms outlining the three major symptoms of HAE: aphasia, acute abdominal attacks, and angioedema of the face.

Italy has seen a progression in the diagnosis of HAE, with a rising number of patients. Still, many remain undiagnosed and can go untreated for 10 or 15 years. Healthcare is provided regionally in Italy but patients with HAE are sent to specialized centres for the treatment of rare diseases. Travel distances present significant obstacles to patients.

In the mid-1990s, the Italian government developed a network of specialized centres specifically for the treatment of rare diseases. However, more recently, healthcare funding has been drastically reduced and patients are being asked to pay part of the expenses for their drugs, hospital visits, etc. “When you have a chronic disease, this is a big problem because frequent visits and specialist access are required.” At the end of the 1990s, a network of rare diseases was established, encompassing about 300 rare diseases including HAE. Patients with these diseases were given a medical card from their local authority giving them access free of charge to healthcare services and treatment related to their disease. This has worked fairly well but Dr. Cicardi said the next step should be the creation of centres to take care of each disease. Each region should have experts on HAE, he emphasized, and it is important keep the patients connected to a specialized centre.

More recently, efforts have been made to build up referring centres in Italy, staffed by physicians who can provide correct diagnosis of HAE. These physicians are available around the clock for calls from patients. There are also outpatient clinics for regular follow-up. “Patients have been doing fairly well for last few years because they can always find a physician who has experience with HAE.” Physicians are accessible by mobile phone 24 hours a day, which is important not only for patients but for physicians as well, he concluded.

Comprehensive Care for Aplastic Anemia

Dr. Vikas Gupta, Princess Margaret Hospital, Toronto

Aplastic anemia is a very rare disorder, with an incidence of about 2 per million annually in Europe and North America and incidence about three to fourfold higher in developing countries, stated Dr. Vikas Gupta, of the Princess Margaret Hospital in Toronto. He gave an overview of treatment strategies and clinical issues for the disease.

There are no well-designed epidemiological studies for aplastic anemia in Canada, though estimates for North America are about 60 to 70 cases annually. However, some researchers suggest that cases of aplastic anemia may be somewhat higher in Canada because of the diverse immigrant population from China and India. A study in British Columbia found an incidence of 1.7 per million among Caucasian children, and an incidence of 7.3 per million among children from southeast Asian or east Indian origin. Since the majority of patients are born in Canada, it is possible that there is a gene predisposition to aplastic anemia. A recent study in Thailand, one of the largest epidemiological studies on aplastic anemia, also suggested that the disorder is likely related to genetic predisposition and is about three to four times higher in the Asian population.

At the Princess Margaret Hospital in Toronto, an adult program sees from 10 to 12 adult patients with acquired aplastic anemia. The program provides continuity of care for pediatric patients with congenital acquired aplastic anemia reaching adult age. Treatment consists of bone marrow transplant or immuno-suppressive therapy.

The aplastic anemia registry demonstrates that the outcome of bone marrow transplants for patients improved significantly, with survival of people around age 20 of between 80 to 85 per cent, and around 75 per cent for patients 30 years of age. For patients over 40 years of age, survival drops to 50 per cent.

The European bone marrow transplant group includes more than 2,500 patients. The outcome for immune disorder aplastic anemia has improved, with survival rising from 50 per cent to nearly 85 per cent. "This improvement in survival has come from improvement in the supported therapies for aplastic anemia, in the form of better transmission practices and the better avail of products," Dr. Gupta said.

Optimum delivery of quality care has one of the most important impacts on patients with aplastic anemia, particularly the care they receive before they receive bone marrow transplant or immuno-suppressive therapy. Early diagnosis and appropriate support and therapy to prevent infection and bleeding conditions are key. Another highly important part of support care is appropriate transfusion support to prevent alloimmunization, bleeding complications, and platelet refractoriness. Studies have shown that risk of graft rejection in aplastic anemia patients is high, particularly with bone marrow transplant.

Major effort is spent on patient education. A designated nurse is involved in education about the disease, teaching patients how to identify infection and bleeding, coordinating a support group, and serving as a primary point of contact for advice.

Prevention and treatment of the infection is essential; patients with severe aplastic anemia can face life-threatening health conditions. Survival following bone marrow transplant is affected by the number of transfusions, whether patients had an active infection before transplant, and refractoriness to platelet infusion.

Psychological support for patients, their families and friends is essential. It is important that everyone have an understanding of the chronic nature of the disease and the fact that response to immuno-suppressive therapy can be slow. In the U.K., designated social workers help patients with aplastic anemia sort out complex issues related to employment, insurance problems, etc.

Following bone marrow transplant or immuno-suppressive therapy, patients must be monitored for long-term complications, from clonal disorders to secondary malignancies and bone complications.

Approaches to improve outcomes for patients with aplastic anemia who receive bone marrow transplant or immuno-suppressive therapy include new protocol designs to address the problem of graft rejection for patients who receive bone marrow transplants and new protocols using minimal therapy to minimize regimen-related toxicity, he concluded.

The Network of Comprehensive Care Centres to Treat Thalassemia and Sickle Cell Disease

Dr. Paul Telfer, Royal London Hospital, U.K.

Prevalence of hemoglobinopathies in England at the end of 2003 consisted of 644 diagnosed patients with thalassemia, and an estimated 10,000 people with sickle cell disease, stated Dr. Paul Telfer of the Royal London Hospital in the U.K. Data from the national neonatal screening shows that in 2004-05, among 400,000 births, 250 infants had sickle cell disorders (1 in 1,600 births) and 16 infants were born with thalassemia (1 in 25,000 births).

The UK Thalassemia Register, created in 1967, was formally reactivated in 1992 with funding from Wellcome Trust and later the U.K. Thalassaemia Society (1997-2003). However, it has been difficult to find funding to maintain the register. In addition, there are now much more stringent regulations regarding the need for individual consent for the register, making data collection much more difficult.

England is an ethnically diverse country. Thalassemia is not seen in the Caucasian population, but is more common in Mediterranean, particularly Cypriots, Asian and

Southeast Asian groups. However, patients are distributed around the country and although there are centres of excellence where a large number of patients are treated for particular diseases, about 50 per cent are treated in smaller clinics. Treatment is not being primarily managed in large centres and care may suffer as result, Dr. Telfer said, adding that survival has been shown to depend on the degree of expertise and the size and sophistication of the centres where patients being treated.

Another important aspect of thalassemia treatment and care is the U.K. Thalassaemia Society (UKTS), an extremely active organization that collaborates with thalassemia specialists on treatment and care, and providing information and support to patients. It has been involved in funding early trials of deferiprone; developing an Asian awareness campaign; pioneering the “patient-held record,” which documents important clinical information and personal results; and pushing for national standards of thalassemia care. Other initiatives include the thalassemia register and networking among small clinics and centres of excellence. He reported that there has been a small improvement in outcome and mortality from iron overload which has decreased significantly since 2000.

Improved survival rates in the U.K. are also attributed to disposable deferoxamine infusers; treatment using deferiprone in combination with deferoxamine; T2 cardiac MRI; and national register referrals to centres of excellence.

While national health centres provide free treatment for all thalassemia patients in the U.K., continual reorganization in the way healthcare is delivered has thwarted delivery of care, Dr. Telfer said. Furthermore, hemoglobinopathies are not a high priority because the number of patients are relatively low.

On other hand, the government has invested substantially into improving services and patient choice, informing and involving patients in care, and improving access to services, including social services. According to Dr. Telfer, key objectives should include:

- A national hemoglobinopathy screening program linked to antenatal and neonatal diagnosis. “Ethically and morally, a national screening also implies the need for national standards of care,” Dr. Telfer said. National standards of thalassemia care were developed and published in June 2005 supported by the U.K. department of health, National Health Service, and medical colleges.
- A working group involves collaboration among the UKTS and health professionals, with input from ministries of health and public health.
- Performance indicators and health outcome measurements drawn from national service frameworks would help ensure fair access to effective delivery of healthcare.

- A network of care involving regional specialist centres and local clinics, where patients can get regular transfusion and monitoring rather than having to travel long distances for basic standards of care.

Some particular issues include communication and staffing. How specialist centres communicate with local, clinical and primary care professionals, and patients and their families is critical. There is also a lack of trained specialists, particularly hematologists to staff the specialized centres, and a need to designate specialists for thalassemia medical requirements, transitional care and psycho-social support. Inspection and accreditation of centres, creation of a central registry of patients and outcomes, and linking up with standards for sickle cell disease are also essential, he concluded.

Panel Discussion

Funding for national database registries is an abomination across the world and the issue of consent has further stymied progress, observed Tom Bowen. National and provincial agencies somehow need to be persuaded about the wisdom of the registry and solve the consent issue.

Dr. Bruce Evatt reported that the extensive databases in the U.S. are largely financed out of the Centers for Disease Control (CDC), and for the most part were a response to demands by the hemophilia population and advocacy groups for a database to truly examine the state of hemophilia treatment and care and set up a monitoring system to ensure that patients not face another epidemic. While consent may be an issue, Dr. Evatt noted that about 90 per cent of people with hemophilia agree to be in the database. “It provides them with a service that allows them to have their blood monitored each year, and if new diseases emerge the CDC can quickly assess whether it’s an important issue for the hemophilia population. It provides reassurances to the community as well as supplies important data that justifies continued funding of centres,” he said. Databases are critical because they provide outcome-based data in support of the better outcomes shown with comprehensive care.

Dr. Sewell expressed some reserve with national databases. “Keep it simple and allow individual centres to run their own databases. A database does not have to be expensive to answer simple useful questions.” Important epidemiological questions can be answered without needing to go to any great expenditure.

A participant noted that the average number of visits to hemophilia treatment centres is five patients per week, and asked if this was the general experience in terms of comprehensive care for hemophilia in Canada and the U.S. Furthermore, how might organizations deal with the challenge of convincing provincial governments that comprehensive care is needed for primary immune deficiencies and hereditary angioedema? Dr. Evatt replied that the figure of five visits per week is pretty consistent

across the United States. “But that’s what happens when patients get in such a good state of care—most patients coming in were for routine visits,” he said. He added that outcomes data has demonstrated that patients who went to their own physicians for routine care but maintained a connection with a hemophilia treatment centre had as good an outcome as those who went to hemophilia treatment centres all the time. “Association of training at hemophilia treatment centres for patients and access to experts made the difference. But if patients had no connection to care, adverse conditions went up.”

He noted the challenge of maintaining clinics when they demonstrate low frequency of visits. However, he emphasized that when comprehensive care clinics are taken away, there is an increase of morbidity and mortality. The current struggle is how to maintain the clinics as part of a successful healthcare delivery system.

Dr. Jerry Teitel said the issue is a matter of how a visit is defined, and shows the importance of keeping statistics through registries. Julia Sek underlined that at least 40 per cent of the comprehensive care work is done on the telephone; in Ontario, this is counted in statistics. Telephone calls are triaged to hemophilia physicians, nurses, physiotherapists, and social workers. The key issue is the reduced number of patient visits and hospitalizations. Self-infusion is preventing up to 2,000 visits a month in hospitals, she reported.

David Page stated that five patient visits per week is a sign of success; lack of visits is not a sign of failure but rather that things are working.

The issue arises when a clinic is competing for hospital space, and the hospital does not want to reserve clinic space for five visits a week, Dr. Evatt said. “It’s a constant battle as much with bean counters as with the fact that this is successful.”

A participant asked about patient representation in the accreditation process. Patient involvement is key at all levels of accreditation, Dr. Sewell said. In an accreditation visit, all stakeholders — patients, nurses, physicians, and a range of specialists — should be interviewed, he added.

The network was created to answer a demand for blood products to treat rare disorders, a participant noted. Perhaps more initiative should be put into blood drives and drawing blood donors. It was noted for instance that Canadian sources meet only 25 per cent of the demand for IVIG products.

Tom Bowen suggested that much like “Doctors Without Borders,” there could be clinics without walls. “The virtual clinic must come,” he said, pointing to the geographical expanse of Canada as well as provincial jurisdiction as two issues that can be overcome virtually. In the virtual clinic, there are fewer patient visits but many outpatients self-infusing at home. The key is to work with clinics and provinces to find the virtual experts on primary immune deficiencies or hereditary angioedema.

Dr. Sewell noted that blood results can be done over a computer system, and in one case he advised a family via videoconferencing. Patients can continue to see their own physicians but have access to expertise and support in the comprehensive care centres.

In many areas of the U.S. there are no comprehensive care centres, Dr. Evatt noted, describing trips up to Alaska to set up a clinic, where local physicians are responsible for care but able to call on the expertise at the comprehensive care centres. Ultimately, it should be the responsibility of the Canadian government to provide funding, he said.

Monitoring and ensuring quality and accessibility to comprehensive care centres are critical, a participant said. Once minimum standards are established, “eternal vigilance” is required by patient organizations to remain on top of the latest issues and developments.

Patient organizations are critical for maintaining care for populations because of the pressure they put on governments, Dr. Evatt said. “Research is an important part of that but we need to balance the translation of research into good care. The biggest challenge is that once times become good, patient visits drop off dramatically, but we need continued zeal to push for activities that the health system needs.”

Session 2 – The Challenge of Self/Family Care in the Context of Rare Blood Disorders

Chair: Tina Morgan, President, Canadian Immunodeficiencies Patient Organization

Support for the Safe, Effective Use of Self-Infusion in Hemophilia

Julia Sek, Provincial Hemophilia Coordinator, Ontario, Canada

Self-infusion, under the direction of the comprehensive healthcare team, is key to the independence and autonomy of people with hemophilia and is the cornerstone of hemophilia care, stated Julia Sek, Provincial Hemophilia Coordinator in Ontario.

Findings have shown that when product is administered at home, treatment is given sooner after the onset of bleeding, which brings significant benefits. Self-infusion results in fewer days away from school or work; improved quality of life; decreased disability due to prompt treatment; decreased emergency room visits; and increased independence and autonomy. With prophylaxis and treatment, youth today can participate in a increased variety of physical activity, such as rock climbing and whitewater rafting, which their grandparents would never have dreamed of doing.

It must be clear, however, that self-infusion must involve a close relationship between the patient and clinics and medical professionals. Self-infusion is complex, involving some 36 steps. Good venous access is essential. Key concerns include patients who delay seeking assessment and management, and the ability to track efficient and responsible use

of expensive products. Another concern is the lack of experience of health professionals such as emergency room and clinic staff, who do not get important practical experience in hemophilia treatment.

Children with hemophilia receive education and training on self-infusion at a summer camp, where peer learning and influence is highly effective. Self-infusion education must be comprehensive, going beyond IV skills to information about the disease and identifying bleeds, completing important paperwork, etc.

A self-infusion program should include information on product storage and disposal, instructions on keeping infusion logs and essential information on achieving better outcomes. A contract would ensure that everyone knows what is involved in the program. The responsibility of the healthcare team is to demonstrate how infusion logs bring meaning to patient care and the management of their disease and self-infusion (e.g., dosage, time of treatment, etc.). Medical professionals with expertise in hemophilia treatment also need to be available for consultation with families by phone.

Collaboration among all stakeholders (i.e., people with hemophilia, community organizations, blood services, and government) is essential.

Technology is helping in the collection of patient data, particularly through the Canadian Hemophilia Assessment and Resource Management System (CHARMS), which documents patient logs, inventory and other meaningful information that help blood product providers with managing products effectively (e.g., product recalls). PDAs may also bring about better adherence for patients who do not keep paper logs on self-infusion.

Most eligible patients in Canada with severe hemophilia are enrolled in a self-infusion program, with 85 per cent of factor concentrates used in homes, Sek concluded.

A Patient's Perspective on Self-Infusion in the Treatment of Hereditary Angioedema

Peggy Adomatis, Canadian Hereditary Angioedema Society

Peggy Adomatis described her journey living with angioedema, a disorder she has had all her life but which was only diagnosed in 1998. She has been self-infusing since 2000. "I have earned a lot about my self, and the medical profession, and that we have to engage in one's own healthcare." She was trained in self-infusion and treats herself at home, under the direction of the hemophilia clinic. Learning how to self-infuse was not easy; however, Adomatis reported that she has gotten very proficient. "I would not go back to life without self-infusion," she stated.

One challenge is that when patients experience bad abdominal pain and vomiting, they cannot self-infuse due to nausea and pain. It is important to find a way to alleviate these

symptoms so that the patient can then self-infuse. Education of family members is also critical.

The Challenges in Implementing Self/Family Care in the Treatment of Hereditary Angioedema

Dr. Bruce Ritchie, University of Alberta, Director, Dr. John Akabutu Centre for Bleeding Disorders

There are no barriers to implementing self/family care for the treatment of hereditary angioedema if a proper infrastructure is in place, said Dr. Bruce Ritchie of the University of Alberta. While some treatment products are not approved in Canada, they can be obtained through the Special Access Programme, he noted.

Without a proper infrastructure, patients would not be able to get products, and there would be no support for home therapy and no tracking and surveillance of product use. Essential components for a solid infrastructure include:

- A clinic with a dedicated staff trained in the treatment of the disorder and self-infusion.
- A clinic network to facilitate tracking and surveillance, set standards and undertake research on better treatment and care for patients.
- Collaboration among all stakeholders (i.e., nurses, physiotherapists, social workers, physicians, governments, industry and patients) on improvement of treatment.

Standards must be developed based on research and surveillance. Minimum standards set the bar for clinics and funding. It is essential to convince governments to provide secure financial support for clinics. The CHARMS database provides important clinical outcomes such as the prevention of hospital admissions and surgery, and also allows clinics to remain in control of their data. Patients generally consent to the surveillance program because it can detect emerging blood-borne pathogens and improve science and treatment. Communication and vigilance is key, he concluded.

The Challenges of Self/Family Care in the treatment of Hemoglobinopathies

Howard Leung, Past Vice-President, Thalassemia Foundation of Canada

Hemoglobinopathy is an inherited blood disorder in which the patient is unable to make normal hemoglobin, stated Howard Leung, in a presentation on behalf of Josie Sirna of the Thalassemia Foundation of Canada. It is the single most common gene disorder in the world, commonly found in the “Malaria Belt.” Two of the most common hemoglobinopathies are thalassemia and sickle cell disease.

Thalassemia treatment in noncomplicated care entails red blood cell transfusions coupled with specialist care and diagnostic tests in hospital. Iron chelation therapy places the overall burden of care with the patient, who must prepare the medication and inject it subcutaneously, and transfuse products over 10 to 12 hours with a battery-operated pump. Usually, the most difficult time comes when patients reach their teenage years and test their limits and develop social circles beyond the family.

The prognosis for people with thalassemia has improved considerably over the past 20 years, with patients reaching educational, career and family milestones previously unimaginable, including having healthy children. Iron chelation therapy has contributed to the improved prognosis.

Sometimes the side effects of thalassemia, such as congestive heart failure and diabetes resulting from iron overload, can be more difficult to deal with than the thalassemia itself. Still, Leung said it is important that patients “try to be normal.” The teenage years are challenging, as patients strive to fit their health needs into busier schedules (juggling school, work and social activities), gain independence and take responsibility for their healthcare from parents.

Funding for treatment remains a challenge. The cost of medication for iron chelation therapy is more than \$20,000 per year per patient, with neither federal or provincial government willing to assume the costs. “We’re caught in the middle,” he said.

The Swedish Experience with Subcutaneous Self-Infusions at Home of IgG by Children and Adults with Primary Immunodeficiencies

Ann Gardulf, Karolinska Institutet, Sweden

The Swedish experience with self-infusion of immunoglobulin (IgG) is long, dating back to the 1980s, said Ann Gardulf of the Department of Laboratory Medicine at the Karolinska Institutet in Sweden. She gave an overview of the costs and benefits of home therapy self-infusion.

The implementation programs for home self-infusion of IgG for children and adults suffering from primary antibody deficiencies results in improved health and quality of life. Studies also show that funding care for patients with primary immunodeficiencies brings substantial indirect cost savings in terms of social and healthcare services.

Subcutaneous IgG replacement therapy is demonstrated to significantly improve quality of life and allow patients to be employed and lead productive lives. Patients have been responsive to subcutaneous self-infusion, and report improved health and greater independence, freedom and flexibility with home treatment. Moreover, patients feel they can contribute to their own well-being. Self-infusion also reduces emotional distress and

negative impacts on school, work, travel and social activities. The first step, however, is to find, diagnose and treat people with primary immunodeficiencies.

In Sweden, it is estimated that switching from intravenous hospital treatment to home therapy would reduce healthcare costs by more than \$10,000 per year per patient; with 1,300 patients in Sweden with primary immunodeficiencies, this would bring cost reduction in the order of more than \$13 million annually. Home therapy has been shown to reduce patient-borne costs by half in Sweden. A recent cost analysis in Germany showed that switching 60 per cent of its patients from intravenous to subcutaneous therapy could bring \$17 to \$77 million euros in savings. An economic analysis of cost savings through home therapy in the U.S. or Canada is strongly recommended.

In Sweden, about 50 to 60 patients are educated and trained annually in self-infusion at a clinic in Stockholm staffed by physicians and nurses specialized in infectious diseases and immunology. They are educated on the importance of regular treatment, handling and preventing infections, and identifying adverse reactions. Self-care is the central concept. More than 500 patients self-infuse at home then go to clinics bi-annually for medical follow-up.

Gardulf noted the minimal cost implications of home therapy and self-infusion:

- There are no increased cost in terms of space and staffing.
- In Sweden, one syringe pump is paid for by the society, and lasts five to 10 years.
- Infusion products and equipment cost the same whether it is done at home or in hospital.
- Expensive infusion equipment is not necessary.

Ultimately, she noted, cost savings is not the main motivation for the upwards of 80 per cent of Swedes who opt for self-infusion — rather, increased quality of life is a key factor.

Panel Discussion

A participant asked whether subcutaneous treatment is as effective as intravenous. Subcutaneous infusion is known to be very safe, stable provide good protection against severe infections, Gardulf said.

Dr. Ritchie noted that CHARMS is well set up for the tracking of products once they leave hospital. A participant asked how CHARMS got around privacy and confidentiality issues. There are major challenges related to legislation on privacy protection and freedom to information, with no simple answers, Dr. Ritchie said.

A bone marrow transplant specialist stated that nurses have identified a group of patients who do not enjoy home therapy and asked how to not compel them to have therapy

against their will. Introducing new families to experienced ones helps show home therapy successes, Julia Sek said. Home therapy “gives you independence that you have no idea you had lost until you get it back,” said Peggy Adomatis. “Where I go, my stuff comes with me. I count on me and that’s fine.”

A participant expressed concern that the Canadian model is shifting costs to patients who simply cannot bear the cost of drug. Howard Leung stated that desperol is covered as part of the hospital program for thalassemia, though at his hospital, care is capped at 99 patients. Silvia Marchesin noted that not all disorders have drug coverage.

Patient organizations need to work with hospital administrators to prove the savings gained in decreased hospital staffing and reduced pressure on the medical daycare unit, Sek said.

Services need to be more uniform across the various disorders, a participant said.

A participant asked if self-infusion comes with a lower incidence of infectious disease among patients not going into the hospital for treatment. Gardulf replied that in her clinical experience, being at home is beneficial because patients are not as exposed to sick children or adults in waiting rooms. Certainly, patients report feeling better with home therapy, she said.

Session 3 – Transition from Pediatric to Adult Care

Chair: Riyad Elbard, Thalassemia Foundation of Canada

A Patient’s Perspective on the Challenge of the Transition from Pediatric to Adult Thalassemia Care in Toronto

Riyad Elbard, Thalassemia Foundation of Canada

People with thalassemia face challenges on an individual level, but also as part of the thalassemia population as a whole, said Riyad Elbard of the Thalassemia Foundation of Canada. Thalassemia is no longer a childhood disease, with life expectancy rising due to advances in medicine and transfusion therapy. Iron chelation therapy and the upcoming oral chelation, collaboration and research, education and advocacy have together extended life expectancy for people with thalassemia into adulthood.

However, adults are currently treated in pediatric units because of lack of budget and funding. This brings some advantages, such as access to experienced and committed hematologists and comprehensive care. There is also more immediate access to information on new research and medications, as well as interaction with other thalassemia patients. On the other hand, disadvantages include being treated as children by pediatric professionals; a lack of understanding of adult issues; and decentralized care,

which sometimes forces a patient to travel to a different hospital for specialty services such as endocrinology or cardiac specialists.

The adult care program, for its part, is confronting challenges itself. Programs for rare diseases are low priority for hospitals, and the adult thalassemia program is insufficiently funded. Comprehensive care is not available for adult thalassemia patients, and there is variation in treatment among clinics across Canada. “Transition from pediatric care to adult care is a challenge, especially when transition programs do not exist,” he said. At his hospital the program is capped at 99 patients and physician hours are limited to two clinic days. The program does not provide infusion pumps. There is a lack of expertise available in emergency units, while the backlog of patients in pediatric clinics is unacceptable. Patient monitoring and support is inadequate and complications are not monitored.

A transition program, adult care, more research and an advanced blood bank in the Toronto area is needed, Elbard said. Currently, the morbidity and mortality for people with thalassemia is that they do not live past their fourth decade due to the complexity of patient needs and deteriorating provision of care, he said.

Facilitating the Transition from Pediatric to Adult Care in Thalassemia, Sickle Cell Anemia and Hemophilia

Dr. Molly Warner, McGill University Health Centre

The transition from pediatric to adult programs is inevitably difficult for patients and families alike, said Dr. Molly Warner, Associate Director of the Hemophilia and Thalassemia Programs at the McGill University Health Centre in Montreal, in an overview of programs for thalassemia, hemophilia and sickle cell disease.

Transition care is a process that attends to medical, psychological, social, educational and vocation needs of adolescents as they move from adolescent to adult care. There are many challenges for the patients, healthcare providers and the healthcare system. Patients have described feeling abandoned in the adult milieu. They are afraid to leave behind the medical team that has been treating them for many years, and many are afraid of a lack of knowledge in the receiving team about their doses, narcotics and care.

There are many challenges faced by the healthcare provider. Adult physicians tend to feel more comfortable with older patients. Time constraints and lack of knowledge, supports and resources compound the challenges. Adjunct healthcare providers available in pediatric centres are not available in adult centres.

The McGill University Health Centre has thalassemia and hemophilia clinics housed in the intensive ambulatory care centre, and a new sickle cell program. The outpatient facilities are staffed by well-trained nurses.

The thalassemia program has 45 patients, the equivalent of one and a half full-time nurses, two hematologists, a hepatologist, and social workers and physiotherapists whose primary patients are people with hemophilia. All patients get blood transfusions and chelation therapy at the Montreal Children's Hospital. Pumps for chelation therapy are provided by the hospital foundation. Desperol was previously supplied by the hospital but has recently come under hospital formulary; patients pay up to \$70 monthly and government covers the rest of the costs.

There are now 300 to 400 patients in the hemophilia program, which also attends to people with rare blood disorders. There are two full-time hemophilia nurses onsite, a hepatologist, physiotherapist, social worker, clerical support and a part-time data keeper. Patients visit the clinics every six months and collect their coagulation products at the hospital blood bank or regional hospital. Ambulatory care is provided to all patients but adults may need to be admitted to an adult hospital if further investigation is required.

The sickle cell program differs because there is a very large population with sickle cell in Montreal, which cannot be accommodated in the ambulatory care centre. A few years ago, it was decided to develop a transition care and adult program at the Royal Victoria Hospital in Montreal. Medical professions began preparing patients and families several years prior to transfer and prepared a chart summary with the patient's clinical details for the new treaters.

At the adult site, a sickle cell nurse attends to the outpatient population. Protocols for emergency room patients and a list of patients are readily available, so that staff are ready to greet the new patients. Nurses and medical resident staff have been educated in the management of patients with sickle cell disease and pain crisis. The medical staff then meet with patients, families and the pediatric team to review pertinent points of medical care. Patients and families get a tour of the adult site with the sickle cell nurse, to familiarize them with the site before their first visit. The centre sees about 70 to 80 patients in transition annually.

The biggest hardship for patients is going to the hospital emergency room, which can be very busy and sometimes hostile. It is important to ensure that they get rapid care and put on pain control protocols, Dr. Warner said.

A Family's Perspective on the Transition from Pediatric to Adult Care for a Child with Severe Combined Immune Deficiency

Libby Tough, Canadian Immunodeficiencies Patient Organization

Severe Combined Immune Deficiency (SCID) represents a whole new world for the medical community, with the few children who have survived SCID as pioneers, said Libby Tough, the parent of a child with SCID from Alberta. She has a healthy son, 17, and a daughter, Megan, 16, who received a MUD bone marrow transplant for SCID. Although currently enjoying really good health, there are many challenges along the way.

Next year, Megan will be required to move to an adult patient ward. “This scares me mostly because we’ve been lucky to have a private room and now we’ll be going to medical chairs. This will expose her to infections from other patients there getting antibiotics. Also, we’ll be starting over with physicians and nurses with minimal experience with SCID.”

As an adult, hospital staff will be required to speak directly to Megan, but she noted that Megan, while 16, is about 14 socially, having missed so much school over the years that she has been unable to keep up with peers her age. She is very shy and expects her mother to speak for her, even about how much pain she is feeling.

Megan has begun to take responsibility for her own medications at home mornings and nights, but is not ready to self-administer IVIG. Education on her medical history and how it will affect her in the future is ongoing, along with potential problems and avoiding exposure to infectious diseases.

Subcutaneous immunoglobulin is an exciting prospect for improving Megan’s condition and the family is eagerly awaiting its approval.

One concern is keeping the treatments at no cost to the family. “It’s an essential lifesaving treatment,” Tough said. Treatment in hospital is provided at no cost, and so should be for subcutaneous immunoglobulin too.

The association is working with Dr. Bruce Ritchie of the Dr. John Akabutu Centre for Bleeding Disorders in Alberta to set up comprehensive care in the province to monitor and ensure quality care in the outpatient setting, with education and training for subcutaneous treatment. Home infusion is essential to limit exposures to infection, she emphasized.

While the hope is that Megan will one day join the workforce, Tough worried about whether she would be able to keep up with it.

Panel Discussion

Julia Sek commended Dr. Molly Warner’s work in transitional programs for hemophilia. Transition needs to begin way before patients leave the pediatric clinic. Some transition programs offer group education sessions for new families and also connect them with experienced families. She encouraged Libby Tough and her daughter to join a youth support group so that they won’t feel so isolated. Tough replied that there is only one other SCID patient in Edmonton; Megan is part of a support group in the U.S.

Support, sharing of experiences and financial resources are needed to develop transition programs, a participant said.

A participant from Seattle said that he has not experienced problems in switching patients from one clinical environment to another. In Seattle, all patients receive local primary care and are treated as adult patients in a hematology clinic. Patients are treated at the children's hospital until age 21 — age 16 is too early for the transition, he expressed. Transition programs need to be more adaptable to patients.

A participant said that she and her mother struggled through her adolescence and though she appeared to be ready to handle the transition to an adult hospital, it was a struggle. Only now, at age 25, is she starting to feel comfortable, she added.

It is important for families to have information such as patient logs and summaries and physician letters on hand at the time of transition, a participant said.

A participant recounted that her daughter was recently diagnosed but is in denial of her condition; she does not want to discuss her medication or need for proper rest and wants to be normal. She suggested that teenagers should be put in touch by e-mail or other means to share their experiences and support each other.

Dr. Molly Warner said that her sickle cell patients once transitioned began to recognize each other in the adult hospital and have formed a support group.

Comprehensive care programs are essential to provide not only treatment and monitoring, but also psychosocial support, a participant said.

Session 4 – National Patient Registries

Chair: Silvia Marchesin, Aplastic Anemia Myelodysplasia Association of Canada

A Patient's Perspective on the Problems of Attracting Clinical Research Trials in Canada in the Absence of Patient Registries

Silvia Marchesin, Aplastic Anemia and Myelodysplasia Association of Canada

Increasing numbers of people are dealing with bone marrow failure in the form of myelodysplasia, but there is no coordinated record on who the patients are, stated Silvia Marchesin, Past President of the Aplastic Anemia Myelodysplasia Association of Canada.

She told participants about a patient who was able to take part in an eight-week trial of a new drug, which was effective in raising his hemoglobin and energy levels. Once the trial ran out, however, he was forced to pay out of pocket about \$18,000 annually for his medication. The patient can no longer afford the medication and now receives blood transfusions. He then developed iron overload from the numerous blood transfusions. He would be a good candidate for deferasirox (Exjade), however it is not yet available in

Canada even though it has received FDA approval. “It’s sad that a farmer who worked for his whole life supporting us now spends his savings on medication. It’s an example of the lack of options for clinics trying to treat myelodysplasia.”

Creation of a patient registry would provide insight on patient demographics and the benefits they gain from certain treatments, she concluded.

The Benefits of National Patient Registries for Rare Disorders

Tom Bowen, Professor of Pediatrics, University of Calgary

The treatment of rare disorders requires a virtual “clinic without walls,” said Tom Bowen of the University of Calgary, which asserting that oral immunotherapy, long available in Europe, must be made available in North America. Health Canada, the Public Health Agency of Canada, Canadian Institutes of Health Research and provincial health ministers must together umbrella comprehensive treatment programs and databases for rare disorders. “It can be done and it must be done for the sake of our patients,” he said. The access to care and survival curve for rare disorders in rural areas must be the same as for people in urban areas.

The Network of Rare Blood Disorder Organizations brings patients to the table for input on how the model should work. Patients have to led the way.

Database registries developed over the years include the International Bone Marrow Transplant Registry and the Canadian Bone Marrow Transplant Registry, which includes a pediatric registry. Survival curves have improved and these outcomes are attributed to comprehensive care. Bowen noted that the hemophilia model includes a blood product tracking systems that could be adapted for other rare disorders. These databases provide important information of the number of infusions and costs yearly.

Another issue is how much product is sufficient; funding agencies say products are costing too much, whereas industry says there is not enough profit. But Bowen said the big problem is compliance, not overuse. Another issue is identifying the best method, frequency and duration of treatment for both intravenous and subcutaneous infusion. Database registries provide key information on dosage and compliance.

The goals of a database registry are to provide prevalence estimates and define demographics and good and bad treatment outcomes. There are various models around the world. Vigilance is essential for all blood products and there should be a single standard for all programs. International registries are valuable because learning is much faster and richer when working as an international group, he added.

The Canadian Hemophilia Registry

Dr. Irwin Walker, Director, Canadian Hemophilia Registry

The Canadian Hemophilia Assessment and Resource Management Information System (CHARMS) is a clinic-based computer system capable of storing all data related to hemophilia care and exporting selected data as required, explained Dr. Irwin Walker, Director of the Canadian Hemophilia Registry.

Each of the 25 hemophilia treatment clinics has a CHARMS computer and access to the Canadian Hemophilia Registry. Clinics export information on patients; the data is assigned proxy ID numbers and a file is created with information such as diagnosis, date of birth, external identifier, sex, status, etc. Clinics can then update the files with each visit. The CHARMS network is directly linked to Health Canada and pharmaceutical companies for serious adverse events reporting.

In 1990, there was a recognized need for updating the system, but it was put on hold during the 1992 HIV and HCV investigation and for a time, data stopped being collected. In 1998, von Willebrand's disease (vWD) was incorporated in the registry and in 2002, the Rare Inherited Bleeding Disorders Registry (RIBDR) was incorporated.

Health Canada, Canadian Blood Services and the Canadian Hemophilia Society were tremendously collaborative with the database. International organizations including the World Federation of Hemophilia and the World Health Organization highlighted the issue of providing access to treatment for people in developing countries. Registries are a top priority in all countries, he emphasized. Also, twinning programs between hemophilia treatment centres in the developed and developing world have helped bridge the divide. However, relationships with pharmaceutical companies and ministries of health and hospitals are not uniformly good.

Key challenges include avoiding duplication and maintaining an accurate status on each patient. There are also many concerns including contact with mild disorders, the review of policies to improve the usefulness of the registry for research, manual maintenance, data sharing agreements (i.e., confidentiality and access), and future stewardship.

Dr. Walker highlighted some key achievements: facilitating research directly and indirectly, providing anonymous ID numbers, administrative tasks, political tasks, providing information for compensation and assistance programs for HIV, linkages with the WFH, and improved credibility.

The CHARMS database tracks blood products, documents genetic mutation, and patient information. Concentrates are tracked to monitor quality assurance on patient infusion records, to manage recalls, recognize reactions, record trends in utilization, manage shortages, and minimize wastage, particular the prevention of expiration.

However, Dr. Walker worried that hemophilia might be a victim of its own success. With the advent of home therapy, hematological residents can go through a residency and yet not see a single bleed. With changeover of staff and little hospital treatment, fewer and fewer staff are informed about hemophilia.

It is critical that patients keep diaries on their care, so that researchers can learn from their experiences. Patient diaries are an important part of the tracking system. In Canada the product comes from Canadian Blood Services and goes to hospitals and treatment centres, which dispense the products to patients. Hospitals and patients are both expected to log each time the product is used; a discrepancy is followed up with a phone call to the patient. The hospital tracking log was found to be 90 per cent reliable, while patient logs were 50 per cent reliable.

Walker gave participants a demonstration of the “EZ-Log” handheld device, a palm pilot with a barcode scanner for each time product is infused; information is then sent off electronically. Nurses receive the information automatically and healthcare professionals and patients can get access to the diaries electronically. The device records the reason for infusion; reason for bleed; bleed location; product; dosage; time of bleed and time of factor use; remarks (e.g., adverse reactions).

Panel Discussion

Dr. Sewell suggested that the database might include another data field where patients can indicate how involved they would like to be:

- 0 – Don’t want to be in research
- 1 – Don’t mind a questionnaire
- 2 – Don’t mind questionnaire or blood sample
- 3 – Would consider therapy if proposing something new

This means that researchers can know in advance by looking at the database how many patients would be willing to participate in different ways, thereby facilitating research. Dr. Walker replied that the idea was to have a database that documents which research projects patients are participating in, and whether consent was secured.

The registry is an exciting concept, but who will pay for it? Tom Bowen acknowledged that no one wants to pay for the database. While Health Canada had kindly agreed to support database registry development several years ago, the emergence of unanticipated viral diseases led Health Canada to focus its funding on viruses. The NRBDO must request secure funding — databases cannot be set up otherwise, he said. Provincial and federal groups need to come together and fund databases as partners. Patients must lead the demand for a national effort to create database registries, as was done in the U.S. with the NIH Consortium.

Silvia Marchesin stated that the patient groups associated with the NRBDO unanimously support the creation of database registries supported by Health Canada and provincial health agencies. At the same time, she noted that if other countries are introducing registries, such as the U.S. or the European Society of Immunodeficiencies (ESID), there is no reason for Canada to recreate the work. Existing databases can also be augmented with any number of diseases, she added.

Sweden has had large national registries supported by government for a number of years, remarked Ann Gardulf. It has been interesting to know how many of the patients treated do survive. She recommended that databases include a capacity to capture patient viewpoints, which would be a useful outcome for clinical research. Quality of life must be the standard of care, Bowen said.

It is extremely important to begin documenting how many patients there are for each rare disorder, or it won't be possible to describe the problem, patient demographics, and the magnitude of task, Dr. Walker said, adding that this could be achieved with a relatively basic database.

Sunday, February 5

Session 5 – Effective Collaboration

Chair: Lucia Celeste, President, Canadian Hereditary Angioedema Society

A Patient's Perspective on the Problem of Delayed Diagnosis for Primary Immune Deficiency

Tina Morgan, President, Canadian Immunodeficiencies Patient Organization (CIPO)

Tina Morgan, of the Canadian Immunodeficiencies Organization (CIPO) gave a personal account of her lifelong experience with the disorder. Returning to her mother for her early medical history, Morgan told of contracting pneumonia at six weeks of age. The next three years were marked by a number of infections resulting from intramuscularly administered penicillin; a family physician would come to the house to treat her. As the first 10 years of childhood passed, she became better able to get rid herself of infections. However, she was unhappy to miss about a month of school each term. She contracted the typical childhood diseases, as well as skin eruptions, bladder and joint infections, and sinus infections.

In her teenage years, Morgan experienced continual chest infections that became increasingly severe the older she became. In her late teens, chronic diarrhea became a difficult issue, and at one time she weighed less than 80 pounds. She was misdiagnosed with a number of disorders; in the early 1980s, her immunoglobulin I levels were measured using newly developed techniques and she was told she had Cron's Disease. This later proved to be a false diagnosis. She continued to be treated for a number of infections.

In the second and third decades of her life, asthma was deemed to be her biggest issue, though she had never had difficulty with her airway before. During this time she also had two pregnancies. Although Morgan had had measles as a child, titre levels measured as part of prenatal screening told a different story and the physician would not believe that she was not contagious. Morgan was told she could not serve customers until her pregnancy was over because he could not administer immunization. At the end of her second pregnancy, her child became infected when her amniotic sac became infected but within a week he was fine. Chronic infections including diarrhea, yeast and sinus infections, and persistent cough continued. Penicillin was the antibiotic treatment during this period.

Between the ages of 30 to 40, Morgan had a bout of chicken pox and bronchitis, until she was finally diagnosed with primary immunodeficiency disorder (PID). "My blood levels were no different when I was finally diagnosed from 20 years earlier," she said.

When patients present with infections, more attention needs to be paid to medical history, she continued. Prenatal testing can catch many patients with primary immunodeficiency disorder. On one occasion, she was administered steroids, which caused her first septic infection. Steroids should not be given to treat chronic or acute infections, she said. In addition, no live vaccines should be given to children under six years of age or to patients with a history of infections without screening for PID.

PID patients see respiratory, gastro-intestinal and obstetrics specialists, Morgan noted, adding that targeted screening would catch a lot of patients. Finally, she urged healthcare professionals, “If you think a patient should be tested for HIV, then please screen for PID.”

**Research Opportunities for Patients with Rare Blood Disorders:
Perspectives of the National Cancer Institute of Canada Clinical Trials Group and
the Canadian Bone Marrow Transplant Group**

Dr. Stephen Couban, Queen Elizabeth II Health Sciences Centre, Halifax

Clinical trial organizations such as the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) and the Canadian Bone Marrow Transplant Group (CBMTG) are essential components of the research to improve the diagnosis and treatment of rare blood disorders, stated Dr. Stephen Couban, of the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia. He gave an overview of the two groups and the research opportunities within each group, particularly related to aplastic anemia and myelodysplasia.

Data from the CBMTG shows that for the last three years, there were approximately 20 to 30 transplants each year, while transplants related to myelodysplasia ranged from 40 to 50 each year. These represent a relatively small proportion of the 1,200 transplants done in Canada.

The CBMTG is a non-profit organization whose membership includes all the transplant centres in Canada, of which there are about 25, and more than 200 bone marrow transplant patients. The CBMTG mission is to improve the safety and efficiency of transplants in Canada through clinical trials and laboratory research, and partner with other organizations and clinical trial groups to facilitate research on uncommon and rare diseases. Studies on haploidentical transplant for patients with hemoglobin malignancies (including myelodysplasia), the use of cyclovir and IVIG to prevent CMV infection show promise.

Dr. Couban reported that the CMBTG recently completed a relatively large study comparing standard therapy (i.e., stem cells from bone marrow) and therapy using stem cells from peripheral blood. The key finding was that patients treated with stem cells from peripheral blood had significantly better overall survival. This is leading to significant change in practice.

The CBMTG is in the process of trying to initiate three more studies, on patients undergoing bone marrow, transplant and antibody allogeneic transplant.

The CBMTG has completed some clinically important research in transplantation including in patients with myelodysplasia and aplastic anemia. “Clearly the challenge for us is to be more effective and have more studies available.”

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) is divided into different areas of cancer by disease site: breast, lung, gastrointestinal, brain, and hematology. “The structure and organization allows us to collaborate with other groups and also allows us to get access to new drugs for trials.” A trial involving an oral agent for patients with myelodysplasia who could not tolerate or want aggressive chemotherapy demonstrated that the agent was somewhat effective. Plans are to follow this study with another combining the oral agent with low dose of standard chemotherapy. “A trial will be only way to access this new small molecule that is promising.”

There is lots of room for improvement with clinical trials in Canada and access to new drugs for trials, he concluded.

Effective National Collaboration Among Patients and Physicians in Hemophilia

Dr. Bruce Ritchie, Director, Dr. John Akabutu Centre for Bleeding Disorders

Very effective organizations have developed in Canada, including the Canadian Hemophilia Society (CHS), which is currently funded by Health Canada, Canadian Blood Services, industry and others. The Canadian Hemophilia Society and World Federation of Hemophilia were both founded more than 40 years ago. The Association of Hemophilia Clinic Directors of Canada (AHCDC) was established in 1993 and is funded by various sources. The Canadian Association of Nurses of Hemophilia Care (CANHC) has established its own policies, treatment guidelines and publications. Physiotherapy and social work groups also exist. The CHS lobbies on behalf of the other groups to help, guide and support; however, collaboration with these groups is key to the CHS’s success.

Treatment centres, blood product tracking systems, and a framework for providing expert advice to physicians on the use of blood products are critical.

Product use and cost is increasing on a steady basis, use of FVIII and FIX prophylaxis is up to 25 per cent annually per year. However, there is no system in place to show that products are being used rationally. One of the objectives of CHARMS is to feed information find back to provincial health ministries to justify the use.

Challenges include the rights of patients and associated responsibilities for medical professionals. Patient diaries and the CHARMS system are essential to ensure optimal treatment and care.

Other major issues in comprehensive care include clinic recognition, increased use of guidelines, inventory control and product tracking, and data collection and transfer. The network provides valuable vigilance of product safety and availability.

Gene therapy will eventually be an effective way to treat patients with genetic disorders, however, first more must be known about the diseases themselves, Dr. Ritchie said.

Patient organization advocacy is the most effective way to influence policy decision-makers; networking is key towards realizing common goals such as standards of care and research funding.

Effective National Collaboration Among Physicians: the U.K. Primary Immunodeficiency Network (UK-PIN)

Carrock Sewell, University of Lincoln, U.K.

Many of the U.K.'s immunology centres are run singlehandedly, making collaboration among centres essential, stated Dr. Carrock Sewell of the University of Lincoln in the U.K. All immunologists face the same problem: too many patients and not enough time, resources and expertise. "Collaboration is one of the solutions to that," he said.

Beyond the UK-PID network, networking also takes place regionally. The Trent Immunodeficiency Consortium comprises five counties, each with an immunologist. Three of the centres, however, are run by the immunologist singlehandedly; their colleagues cover for them in their absence through formal covering arrangements among the centres. The immunologists meet every two months at one of the sites to share clinical practices in immunology. The same principles would apply to other disorders, Dr. Sewell said. At these day and a half long seminars, the immunologists present cases, audit and make decisions about practice, and develop guidelines through formal consensus.

The UK-PIN website includes both active guidelines and a series of draft guidelines. While in theory guidelines must be evidence-based, when it comes to rare disorders, there is little evidence, Dr. Sewell noted. "We need to come to a compromise and recognize that guidelines comes in different forms and hierarchy," he suggested.

Consensus guidelines emphasize that guidelines may be adapted for local purposes, and that clinical judgment supercedes the guidelines. These guidelines may then evolve into evidence-based guidelines, as protocols and standard operating procedures are established. Guidelines are continually updated according to comments posted to the website.

A Model for Comprehensive Care for PID in British Columbia

Dr. Robert Schellenberg, Professor, Department of Medicine, University of British Columbia

The key to establishing proper comprehensive care centres for rare disorders lies with the support of local hospitals, stated Dr. Robert Schellenberg, Professor of Medicine at the University of British Columbia. There are many benefits to comprehensive care. Patients appreciate the convenience of home treatment, which comes with less exposure to infections from the hospital environment. This also alleviates demand on scarce resources and comes with cost savings to society. Standardized care across the province is essential, to ensure that patients in outlying areas are properly supervised and followed.

Dr. Schellenberg described the Providence Health Care Working Group, whose goals include establishing a provincial program for optimal management of primary immune deficiency (PID) patients; to develop a home therapy program with both intravenous and subcutaneous self-infusion of immunoglobulin products; and to involve patients and the patient database in ethical research initiatives. The group is currently developing a business plan for the B.C. Ministry of Health.

Other initiatives include establishing a clinic at a local hospital out-patient area; initiating a PID registry compatible with other PID databases; providing nursing support for teaching; and regular review of PID patients. A research study of subcutaneous immunoglobulin is evaluating efficacy, pharmacoeconomics and quality of life. The group is collaborating with the Canadian Immunodeficiency Patients Organization (CIPO) on advocacy with the ministry of health. However, he acknowledged that it will not be easy to push for subcutaneous therapy.

Scientific Collaboration and its Effect on Patient Care in Thalassemia

Dr. Alan Cohen, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine

Thalassemia is common in areas of the world from western Europe to Eastern Asia, but in many cases there are relatively few resources to provide clinical care, stated Dr. Alan Cohen, of the Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine.

The gradual disappearance of thalassemia in developed countries is having an impact on the ability to do clinical research on patients with thalassemia. Prenatal testing has been a major factor in preventing the disorder. In developed countries, the patient face has changed dramatically; in North America, life expectancy for patients with thalassemia has risen from 11.4 years in 1973 to 21 years in 2002. In the developed world, the demographics of the thalassemia population are shifting, with more patients reaching adulthood and fewer children being born with the disorder. "The opportunities to study thalassemia in North America are rapidly diminishing because of the change in

demographics.” But at the same time, Dr. Cohen noted, there has been the greater expression of the disease among populations in developing countries.

In 2000, the National Institute of Health (NIH) created the Thalassemia Clinical Research Network (TCRN), whose aim is to accelerate research, standardize treatment and evaluate new therapies. The network’s first project was to develop a registry of patients in North America with various forms of thalassemia; in a relatively short period of time, 900 patients with thalassemia had enrolled. The main purpose of the registry is to gain a sense of the prevalence of thalassemia and to provide a cross-sectional analysis of complications (e.g., osteoporosis, Hepatitis C infection, cell damage, etc.). The registry also provides an opportunity to make an impact on patient care by ensuring that patients periodically visit thalassemia treatment centres.

Education and outreach are key in order to reach patients who are under-served for various forms of therapy. It is critical to monitor blood safety to reduce the rate of complications in patients with thalassemia such as transfusion-transmitted infections, iron overload, poor adherence to chelation therapy, abnormal cardiac function and abnormal liver function.

Pharmaceutical trials underway include a study by Apotex on oral iron chelation for deferiprone involving more than 1,000 patients globally. Another study of oral iron chelation using ICL670 by Novartis involves 800 patients. Another study is examining the blood safety of pathogen-inactivated red cells for transfusion. “These trials are another way to bring patients into the system. Many patients get two benefits – they gain access to trials and early exposure to new drugs, and comprehensive care at the thalassemia centre where the trial is based.”

Collaboration with other rare disorder organizations on studies and approaches is key to advancing knowledge and improving care, and giving patients access to new therapies and major treatment centres. Collaboration is also extremely valuable among physicians not only on research but on treatment and care challenges as well.

Panel Discussion

The incidence of rare disorders in under-served populations is generally overlooked, with almost certainty that a large group of patients are waiting to be looked after, a participant said.

Another participant, noting accounts of late diagnoses of PID, asked whether neonatal screening would be recommended. However, D. Sewell noted that PID often does not present until the onset of adulthood; neonatal screening may lull patients into a false sense of security. Dr. Schellenberg noted that there is consensus on prenatal or newborn screening for SCID via a lymphocyte count.

Data is collected on blood products given to people with hemophilia, SCID, PID and thalassemia — is there a system for monitoring blood products for sickle cell disease or integrating its surveillance with other disorders? a participant asked. Sickle cell disease must be carefully monitored given that the nature of therapy may change over time; in recent years, indications for transfusions have increased dramatically, Dr. Cohen noted.

Diagnosis and prognosis for children with PID in Canada have greatly improved, however, adult screening guidelines are needed to familiarize health professionals (e.g., gastrointestinal or obstetric specialists) with PID. Dr. Sewell noted that an advantage of U.K. immunologists running labs is that test results are assessed quickly to determine if therapy is needed, whereas in less centralized systems, tests can be done but ignored because they are not understood.

Provincial ministries of health have a key role to play in setting standards across the province for blood products and their storage, administration and surveillance, including adverse events. Health ministries must also manage and optimize use of product. The CHARMS database reports all uses of blood products and presents a great opportunity for partnering to bring information forward together.

Networks and collaborations with partners throughout North America are key to bringing together physicians and other healthcare professionals and creating improved treatment options for patients, particularly for rare disorders where there are scarce patients for clinical trials, stated Dr. Couban. In many cases, patients and families are willing to go to extraordinary lengths to gain access to new treatment. Industry and the healthcare community are working more collaboratively, such as through industry-sponsored trials.

Session 6 – Access to State-of-the-Art Therapies

Chair: Garry Cyr, President, Canadian Neuropathy Foundation

A Patient's Perspective on Access to Treatment for Fabry Disease

Adrian Koning, Chair, Canadian Fabry Association

Fabry's disease, while not a blood disorder, is nonetheless a rare disease, stated Adrian Koning, Chair of the Canadian Fabry Association and Vice-President at the Canadian Organization for Rare Disorders (CORD). Fabry disease is an x-linked genetic disorder and is considered an ultra orphan disease because the rate of occurrence is 1 in 117,000; there are about 300 patients in Canada and 5,000 to 10,000 worldwide. People with Fabry disease are missing a key enzyme, alpha-GAL, allowing GL-3 lipids and fatty acids to accumulate in the body. Life expectancy for males with the disorder is between 40 and 50 years of age.

Symptoms of Fabry disease include high risk of stroke, hearing loss and vertigo; high risk of heart failure; high risk of kidney failure; inability to tolerate temperature variations and

to sweat; stomach pain and digestive and intestinal problems; inability to gain weight; angiocharatomas (red spots on the body that first led to the discovery of Fabry disease in the late 1800s); and extreme pain in hands and feet.

The only effective treatment for Fabry is enzyme replacement therapy, with recombinant enzyme infusion. Enzyme replacement therapy is available in over 40 countries worldwide; it was approved by Health Canada in 2004.

The high cost of treatment, approximately \$250,000 per year, is a key obstacle to securing funding for enzyme replacement therapy. In addition, health ministries rely on the Common Drug Review (CDR) for guidance, and in November 2004 and May 2005 the CDR stated that there is insufficient clinical evidence for enzyme replacement therapy, and that it is not cost effective. “A key issue is that Canada is the only developed country in the world without an orphan drug policy,” Koning said. To resolve this issue, in October 2005 health ministers agreed to expedite the drug approval process and a research protocol is being developed.

Access to enzyme replacement therapy will require networking and unified lobbying. Patients must become experts on the disease, treatment and healthcare system. Education and public awareness is essential; media, federal, provincial and territorial governments, physicians, and patient groups all have a role to play in building momentum to overcome access to enzyme replacement therapy, Koning said. It is vital to learn what is going on in the international community. The U.K. model, for example, clearly indicates that orphan drugs need to be evaluated not only scientifically but also ethically, to decide which treatment products to pay for to help patients.

Who Will Adopt the Orphans? Drugs, Approval, the Common Drug Review and Provinces

Dr. Joel Lexchin, York University, University Health Network

Drug approval times in Canada are slow compared to other developed countries, even when it comes to priority drug approvals, stated Dr. Joel Lexchin, Associate Professor at the School of Health Policy and Management at York University and member of the Emergency Department of the University Health Network. The federal government has recognized the problems related to slow approval of new products in Canada and has been investing funds towards improving the regulatory process.

Industry is a key partner in improving the approval process; industry user fees support 50 per cent of the operating cost of the therapeutic products directorate of Health Canada, which is responsible for approving new drugs. Industry investment in the approval process has generally dramatically reduced the mean approval times and increased approval ratings — however, Dr. Lexchin noted that this also raises the issue as to whether faster approvals are always ideal. Stringent approval processes help prevent safety and risk issues down the line; studies show that for every month reduced in the

drug approval process, there is a one per cent increase in hospitalizations and two per cent increase in deaths due to adverse drug reactions.

Post-marketing surveillance is insufficient, with little resources made available to Health Canada to monitor the 5,000 products on the market. Dealing with limited resources is a delicate balance between getting drugs approved faster and monitoring product usage, Dr. Lexchin noted. A number of drugs have been around for many years without being approved and the conditions to getting them to market are not clear. At the same time, he cautioned that manufacturer-sponsored drug trials produce a bias in results, with four or five times the likelihood of positive results compared to trials by anyone else.

While industry and government are generally favourable to the Common Drug Review (CDR), advocacy groups contend that the CDR lacks in clinical expertise, multiple reviewers and public input. The CDR is overly concerned with cost and lacks social perspective, and may give negative recommendations even if pharmacoeconomic reviews are positive. However, Dr. Lexchin noted that in the majority of cases, the CDR decisions correspond to those of independent sources on the products, such as the U.K. and France.

The time it takes to reach a decision on funding a drug varies from province to province, ranging from 267 days in Quebec to 437 days in B.C. By and large, the provinces agree with CDR decisions. However, he noted that provinces face definite pressures on resources and expenditures at different levels; indeed, since 1999, provincial drug spending has risen at least seven per cent each year, above the rate of inflation. At the same time, he noted that provincial drug spending is also closely related to per capita GDP; public spending for drugs is greater in the wealthier provinces than in the poor.

Dr. Lexchin outlined some recommendations for access to new therapies:

- Faster approval is needed for priority drugs, but the resources must come from the public purse to avoid industry bias.
- Faster approval should not come at the expense of post-market surveillance.
- To increase safety there should be mandatory post-market surveillance to ensure the safety of drugs.

The Canadian Notice of Compliance With Conditions facilitates the entry of new drugs into market, however, more transparency is needed on the conditions and timelines for meeting these conditions.

Transparency in critical all areas, including the release of manufacturer data on safety and effectiveness. The CDR should allow for public input into the approval process. In addition, resources need to be equalized across the provinces such as through a national approach to funding drugs. For drugs where effectiveness has not yet been fully proven, conditional funding for provincial clinical trials might be considered. Industry and government need to establish criteria to assess who is most likely to benefit from orphan products and the resources required to make them available. Ontario is a lead province in

orphan drug policy through restricted prescriptions for treatment that allow specialists and allied general practitioners to prescribe orphan drugs for particular disorders. Orphan drug policy needs to be addressed at the both the provincial and national levels, he concluded.

Panel Discussion

Dr. Lexchin noted that currently only nine cents of every dollar of the Canadian healthcare system is spent on purchased medication. Increased spending on medication would reduce hospitalizations, but funding for the treatment for rare disorders, which can cost as much as \$250,000 for a single patient yearly, remains a key issue for health ministries.

Lengthy approval processes are sometimes inexplicable and perhaps even dangerous for delaying licensing of safer products already approved and available in other countries, noted Dr. Irwin Walker. Do products for rare disorders present a greater challenge for licensing? A number of different factors come into play, replied Dr. Lexchin, for instance, companies sometimes submit their applications for approval in Canada some time after they have filed for approval in the U.S, or decide not to apply for approval on the basis that the Canadian market is too small. However, companies are reluctant to share information on how they prioritize products and decide whether or not to request priority review for a drug. There must be more information-sharing by manufacturers, he emphasized. “Transparency cannot be just supplied selectively — it must go all the way.”

At the same time, he noted that pharmaceutical companies are profit-making enterprises and cannot legitimately be asked to overlook their commercial interests for the sake of goodwill. He noted that the costs of getting products approved in Canada are not trivial, with applications expensive in themselves. A participant noted that there is an inherent bias in the way studies are funded and framed, based on outcomes predicted by the manufacturers, and there is an absence of public funding to conduct the larger studies on safety and efficacy that need to be done. At the same time, another participant noted the challenge in finding enough patients worldwide to participate in clinical trials for rare disorders.

Session 7 – Proposed Models for the Delivery of Comprehensive Care for Rare Blood Disorders

Chair: Dr. Bruce Ritchie, Director, Dr. John Akabutu Centre for Bleeding Disorders, Alberta

Proposal for the Comprehensive Care of Hemoglobinopathies in Ontario

Dr. Isaac Odame, Chair, Hemoglobinopathy Group of Ontario

There is clear evidence that early diagnosis of hemoglobinopathies through measures such as newborn screening programs greatly improve outcomes, said Dr. Isaac Odame, Chair of the Hemoglobinopathy Group of Ontario. Across Canada, the population risk for hemoglobinopathies is 18 per cent; in Ontario, risk is 25 per cent and higher still in Toronto, where ethnic diversity increases risk to 40 per cent. Although these disorders are considered rare, they are not uncommon and in fact are quite prevalent among ethnic communities. Proper prevention and care is needed. In Ontario, newborn screening was recently expanded from three to 26 disorders, including hemoglobinopathies. Newborn screening for hemoglobinopathies is important to early diagnosis, and must be followed with education, comprehensive care and treatment, and monitoring and evaluation.

A model for comprehensive care of hemoglobinopathies in Ontario would involve interlinked screening centres, diagnostic labs and follow-up centres, with the primary healthcare provider responsible for patient education. Screening can also identify carriers of globin disorders, while rare hemoglobins and new mutations can be identified in diagnostic labs using DNA technology. Given its demographic diversity, Canada may be well-positioned to study and describe mutations that have not yet been identified.

Comprehensive care clinics should be linked to newborn screening programs and based in the province's academic centres of medicine and pediatric and adult centres. Standards of care in transitions from pediatric to adult settings remain an issue. Comprehensive care clinics should be staffed by a physician, nurse, social worker, genetic counselor and other specialists. Education, psychosocial support and community-based programs are all important components of comprehensive care. It is essential for patient groups to come together to advocate for accessibility and availability of state-of-the-art therapy and become the expert advisors in their fields. There must be designated funding for comprehensive care, otherwise funds will inevitably be redirected to other areas, and measurement of the health outcomes.

Comprehensive care is the only effective strategy for the management of patients with hemoglobinopathies. Strong collaboration among healthcare providers, patients and families and advocacy groups is key to success. Provinces and territories must get on board to help craft a Canadian strategy for hemoglobinopathies, he concluded.

Proposal for Comprehensive Care of Myelodysplasia in Toronto

Dr. Richard Wells, Toronto Sunnybrook Regional Cancer Centre

Myelodysplasia is an acquired bone marrow disorder characterized by low blood cell counts that typically affects older adults and requires transfusion therapy. There are an estimated 1,500 new cases in Canada each year. There is a long journey ahead towards establishing comprehensive care for myelodysplasia, stated Dr. Richard Wells, Co-Director of the Myelodysplastic Syndromes Programme at the Toronto Sunnybrook Regional Cancer Centre.

The prevalence of myelodysplasia is not known but can be estimated based on population rates for unexplained anemia and blood abnormalities. In Canada, it is estimated that there are 25,000 people with myelodysplasia, indicating that it is not all that rare a condition.

Myelodysplasia is a complex, chronic disease that would benefit from comprehensive care. Patients may require fairly constant contact with the medical system due to complications arising from the disorder and treatment. The field is rapidly evolving with the introduction of new therapeutic agents. It is known that 50 per cent of myelodysplasia patients require chronic red blood cell transfusion, which leads to iron overload and requires treatment with desferal.

The Myelodysplastic Syndromes Programme at Toronto Sunnybrook Regional Cancer Centre was established in 2005 with the objective of providing an integrated program of basic care and the translation of clinical research into practice. The program is staffed by clinical scientists, clinical trial experts, hematologists and nurses. The program is working to develop practice guidelines, a patient database and tissue bank, and undertake research on new agents and issues affecting quality of life outcomes. Clinical trials underway include a study on the advantages of transfusion with products with shorter storage periods. New agents such as decitabine and lonafarnib are being studied, along with new combination therapies including Immunomodulatory drugs (ImiDs). The program is also involved in a multi-centre collaboration on iron chelation and quality of life.

National treatment guidelines are essential to ensuring that standards of care across the country do not fall short. Registries must also span the country in order to be useful, and better linkages need to be established among myelodysplasia physicians across Canada, he concluded.

Proposal for a Comprehensive Care Program for Rare Blood Disorders in Alberta
Bruce Ritchie, Director, Dr. John Akabutu Centre for Bleeding Disorders

Dedicated funding for comprehensive care of rare blood disorders is critical to avert the diversion of funds to other areas and ensure minimum standards of care, said Dr. Bruce Ritchie, Director of the Dr. John Akabutu Centre for Bleeding Disorders in Alberta. Hemophilia treatment centres present a successful model for comprehensive care clinics and the supervision of home therapy. A dedicated staff of physicians, nurses, social workers, physiotherapists, and clerical support is essential. An insight board comprised of patients, clinic staff and administrators may be a good forum to regularly discuss cases and issues at the clinic.

Panel Discussion

Collaboration among patient groups, physicians and healthcare practitioners is key to advocacy for the development of a national healthcare program for the treatment of rare disorders, a participant said.

For patients with thalassemia, a major challenge is how to increase physician interest in the field of thalassemia given the decreasing prevalence due to screening interventions, a participant noted. Dr. Odame stated that a national network of comprehensive care clinics, with collaborative research and fellowship programs would help attract young physicians to the field.

Another challenge is attracting patients to newborn screening programs and tracking patients. The success of any screening program relies critically on how successful follow-up and retrieval are, Dr. Odame noted. "Testing is the easier part; what is more challenging is to have a follow-up centre mandated to track every patient and maintain contact with patients, their families and primary healthcare providers. Follow-up centres would also be well-placed to monitor the effectiveness of screening and treatment programs.

Genetic counselors should be readily available at follow-up centres to inform families of the care options available and risks involved. Once enrolled in a comprehensive care clinic, education and counseling of patients should be a continuous process. Formal structures for collaboration would amplify recruitment for hematological specialists in rare disorders such as thalassemia and myelodysplasia, a participant said.

Dr. Odame noted that another issue relates to the increasing numbers of families without family physicians; tracking down patients becomes more challenging. In addition, given the ambiguity that can be involved with ethnic identification, he advocated universal screening programs as an effective and cost-efficient method of preventing mortality and managing treatment for rare disorders. "It's clear that early diagnosis saves lives and given the efficacy and affordability of testing, universal screening simply makes sense."

Conference Wrap Up

Silvia Marchesin, Conference President

Conference President Silvia Marchesin reviewed the Network for Rare Blood Disorder Organizations vision for comprehensive care. The NRBDO and its member organizations will advocate with provincial governments for comprehensive care for rare blood disorders. The essential characteristics of comprehensive care include:

- Provincial designation
- National patient registries
- Self/family administration of therapeutics
- Patients, family and association involvement
- Standards of care and portability
- Decentralization through outreach
- Multidisciplinary care
- Defined core services delivered by a comprehensive care team
- Program evaluation and accreditation
- National collaboration among healthcare professionals and patient organizations
- Blood borne pathogen surveillance
- Collaborative research
- Flexibility

Dr. Bruce Ritchie recommended that the characteristic “Blood borne pathogen surveillance” be augmented with post-market surveillance. Another participant concurred, saying post-market surveillance should be a separate characteristic on its own.

Another participant said that territories must also be involved in program design.

Dr. Irwin Walker recommended that education, awareness, advocacy and lobbying are also important characteristics. Advocacy is key, a participant said, particularly for drugs not licensed in Canada. Marchesin suggested that these characteristics are embedded characteristics such as “patient, family and association involvement.” Education and training of healthcare professionals is critical; sometimes patients know more about disorders and their treatment than medical professionals. Effort must be made to ensure that these disorders are part of the basic curriculum in medical school, a participant said.

Participants voted, without any objections, to support the following essential characteristics to comprehensive care:

- Provincial **and territorial** designation
- National patient registries
- Self/family administration of therapeutics
- Patients, family and association involvement

- Standards of care and portability
- Decentralization through outreach
- Multidisciplinary care
- Defined core services delivered by a comprehensive care team
- Program evaluation and accreditation
- National collaboration among healthcare professionals and patient organizations
- **Post-market surveillance**, including blood borne pathogen surveillance
- Collaborative research
- Flexibility in organization
- **Education**

Participants also voted unanimously that:

- Health Canada/PHAC, CIHR, Provincial and Territorial Health Ministries continue to support the work of the Network of Rare Blood Disorder Organizations.
- The Public Health Agency of Canada establish a national working group to coordinate and support the development of national data base registries, including quality of life measures, for the rare blood disorder disease groups including, but not limited to: primary immune deficiency, hereditary angioedema, rare blood disorders, hemoglobinopathies, bone marrow disorders, porphyria, hemophilia/bleeding disorders; and that Dr. Tom Bowen be mandated to represent the Network of Rare Blood Disorder Organizations for this initiative.

The working group's tasks will be to develop a model for database registries and strategy for comprehensive care, and the continuation of the network.

Conference President Silvia Marchesin thanked the speakers, sponsors and participants for taking part in the conference, and David Page in particular for organizing the conference with the committee.

Comprehensive Care for Rare Blood Disorders Conference Organizing Committee

Tom Alloway, Ph.D., Past President, Canadian Hemophilia Society
Tom Bowen, M.D., University of Calgary
Lucia Celeste, President, Canadian Hereditary Angioedema Society
Garry Cyr, Chairman, Canadian Neuropathy Association
Riyad Elbard, Vice-President, Thalassemia Foundation of Canada
Jacques Hébert, M.D., Centre de recherche appliquée en allergie de Québec
Silvia Marchesin, Past President, Aplastic Anemia and Myelodysplasia Association of Canada
Tina Morgan, President, Canadian Immunodeficiencies Patient Organization
Dotty Nicholas, Sickle Cell Association of Ontario
David Page, Canadian Hemophilia Society
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