Hemophilia Treatment（血友病治療）

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1. Definitions of hemophilia
   - A genetically inherited bleeding disorder
   - Two types of hemophilia: hemophilia A and hemophilia B
2. Incidence
   - The global incidence of hemophilia A is one in 10,000 males, severe form, one in 16,000
   - Worldwide, there are approximately 350,000 with severe or moderate hemophilia A
   - In Taiwan, there are about 900 hemophiliacs
   - Hemophilia B is five times less common than hemophilia A
3. Severity
   - Severely affected, bleed spontaneously into major joints and muscles
   - Moderately affected, bleed only after trauma, sometimes will bleed spontaneously
   - Mildly affected usually bleed only as a result of surgery or major injury
4. Manifestations
   - Severe hemophilia usually manifests in the first year of life with raised unsightly bruises, at circumcision, or when prolonged bleeding suggests something unusual, often from minor lesions in the mouth
   - Moderate or mild hemophilia often first appears following surgery or dental extraction as prolonged or secondary hemorrhage
   - Bleeding can occur at any time of the day or night
   - Without treatment bleeding is prolonged
   - Hemophilic bleeding into confined spaces (skull, joints, major muscle masses) stops only when the pressure of the surrounding tissues equals or exceeds the pressure of escaping blood
   - Bleeding into joints or muscles is recurrent
   - Severe hemophilia bleeds about 35 times a year, hemophilia B bleeds less frequently.
   - Bleeding frequency is higher in tissues or joints already damaged by uncontrolled hemorrhage
   - Acute pain is one of the immediate results of untreated internal bleeding, the best pain control is treatment of the bleeding episode
   - Repeated bleeding into the same joint eventually results in a breakdown of normal tissues and the development of a chronic, painful and incapacitating arthritis, may be relieved by major reconstructive surgery

- Untreated hemophilia is a lethal disorder. At the beginning of the 20th century the life expectancy of hemophiliacs was 15 years. Today, with good treatment, the life expectancy would be 10 years less than that of males without hemophilia

5. Joint disease
   - Most joint bleeds are referred to as spontaneous
   - Once bleeding has occurred, the joint will be predisposed to future episodes
   - In severe hemophilia, joint bleeds begin before the age of three. However joint bleeds many occur throughout life
   - Knees, elbows and ankles are most frequently affected
6. The ecomonic impact of hemophilia
   - Hemophilia is eminently treatable
   - Untreated, it results in early chronic disability, and too often in premature death
   - While proper treatment is expensive inadequate treatment is even more so
   - The lack of prompt, appropriate treatment may lead to the following situations
     - Joint damage and the need for orthopedic treatment
     - Multiple joint damage and loss of normal muscle structure, leading to severely restricted mobility
     - Permanent use of calipers, crutches, or a wheelchair
     - Prolonged hospitalization
     - Frequent absences from school, which in turn limit the educational and employment opportunities
     - Disruption of family life
7. Treatment

   I. Basic treatment, involves the simple injection of the deficient factor, can either prevent bleeds or minimize their effects

      1) On demand
         Treatment at first sign of bleeding episode
      2) Prophylaxis
         Bigin after a child has established a pattern of repeated bleeding but before frequent joint bleeds occur
         - Primary prophylaxis
           Initiation of regular factor replacement therapy soon after diagnosis of severe hemophilia (1-2years of age). Intention is to prevent joint bleeding
         - Secondary prophylaxis
           Initiation of regular factor replacement therapy to prevent further bleeding or progression of joint disease in a patient with recurrent joint bleeds or a target joint

- Prophylactic doses
  - Factor VIII
    - 3x week at 25-30 IU1kg on Monday and Wednesday, i.u/kg on Fridays or
    - 20-40 i.u/kg qod
  - Factor IX
    - 45-50 i.u/kg twice per week
  - The goal is to keep trough levels of VIII or IX above 1%
  - Morning infusions are recommended as peak level occur during waking, active time of the day.

3) In many cases of mild hemophilia A, and most cases of VWD, the synthetic hormone Desmopressin can be given to release sufficient factor VIII, intravenously, by subcutaneous injection or in a highly concentrated preparation by intranasal spray
4) Severe bleeding or surgery require either continuous or intermittent replacement therapy to maintain adequate levels of the clotting factor

II. Comprehensive care
   1) Address in a coordinated matter the many issues faced by an individual with a bleeding disorder
   2) Addresses everything from diagnosis to musculoskeltal problems, from homecare, mobility and physiotherapy to emotional and psychological effects of living with a bleeding disorder for both the individual and his or her family
   3) It involves a variety of treatments and careful monitoring (bleeding incidents, treatment, inhibitor, assays, musculoskeletal and immunological assessments, physiotherapy and exercise assessments, and psychological adjustment among other things).

III. Inhibitors to factor VIII or factor IX
   1) Inhibitors are antibodies to factor VIII or factor IX which prevent therapy from being effective
   2) An inhibitor is usually detected in one of two ways; by routine screening in a comprehensive evaluation or suspected when, suddenly and unexpectedly, bleeding does not stop as quickly as it should in response to treatment with factor
   3) High responder (Bethesda titer of at least 5 B.U), low responder (usually under 5 Bethesda units)

4) Incidence

   Hemophilia A 15-20% generally
   30-50% include those with transient inhibitors
   Hemophilia B 1- 4%

5) Not increased frequency of bleedings, but induce difficulty in treatment and decrease the quality of life
6) Improvements in the treatment
   - Low responder

     High dose of factor VIII or factor IX to overcome the inhibitor and to stop bleeding
   - High responder
     - High dose of factor VIII or IX after plasmapheresis
     - Prothrombin complex concentrate (proplex Tetc)
     - aPCC (Autoplex, Feiba)
     - r VIIa

       Effective in both minor and life-threatening bleeding as well as in the prevention of surgical bleeding
     - Porcine factor VIII (Hyate-C)

       Effective in patients whose inhibitor does not destroy porcine factor VIII
     - Immune tolerance therapy, high cost

8. Gene therapy
   - Four clinical trials of gene transfer in hemophilia, two in hemophilia A and two in hemophilia B, are current underway or have been completed
   - Two other trials have been approved
   - The current approaches and doses are safe and that low levels of expression are detected
   - These studies support the continued development of gene transfer as a potential treatment option for hemophilia