TRANSFUSION SUPPORT FOR PATIENTS WITH SICKLE CELL ANEMIA

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I. Review of Pathophysiology in Sickle Cell Anemia
   a. Genetic mutation leads to single amino acid change in the beta chain of Hgb -> results in HgbS, which has altered surface charge
   b. HgbS polymerizes and crystallizes when deoxygenated/under hypoxic conditions -> increased rigidity of RBCs, which become sickle cells, which are prematurely removed from the circulation (hemolytic anemia)
   c. Increased viscosity of the blood exacerbates the hypoxia as sickled RBCs transit through microcirculation more slowly, which allows increased oxygen extraction, perpetuating further sickling
   d. Occlusion in microvasculature by sickle cells-> inflammation, ischemia and end organ damages. (e.g. splenic and brain infarcts, pain, acute chest)

II. Overall Transfusion Goal
   a. Improve oxygen carrying capacity
   b. Decrease the percentage of HgbS both by dilution and suppression of endogenous erythropoiesis over time
   c. Prevents sickling and attendant complications, both short and long term.

III. Transfusion Methods
   a. Simple transfusion (1-2 units)
      i. Pro: readily available, less donor exposure
      ii. Con: risk of iron overload, increased viscosity
   b. Exchange transfusion through apheresis( 1-2 blood volumes, at least 6 units in adults)
      i. Pro: Reduces HgbS % more efficiently, low risk of Fe overload , no increased viscosity
      ii. Con: Resource (apheresis instrument, nursing etc) dependent, more donor exposure, often requires central line placement

IV. Various Clinical Scenarios and Transfusion Indications
   a. Aplastic Crisis
      i. Often associated with infectious disease (especially parvovirus B 19), usually resolves spontaneously in 1-2 wks
      ii. Dramatic decrease in Hgb level (as low as 2-3 g/dL)
      iii. Simple or exchanged transfusion indicated
   b. Acute Pain Crisis (APC)
      i. Occlusion of microcirculation by sickled cells =>affect musculoskeletal and soft tissues =>pain, fever, bone pain
      ii. Precipitated by hypoxia, infection, acidosis, or unexplained
iii. Rarely occurs when Hgb S < 50%
iv. Conservative management: hydration and analgesic should be tried first. Transfusion typically not necessary unless Hgb has fallen more than 2g/dL, or Hb level is below 5g/dL
v. Transfusion goal: raise hct to ~30%, reduce Hgb S% to < 35%
vi. Some patients experiencing frequent APCs may require prophylactic transfusion to keep Hgb S < 50%

c. Acute Splenic Sequestration
i. Splenomegaly often seen in childhood due to sequestration of RBCs. This usually leads to fibrosis of the spleen and “auto-splenectomy”.
ii. Prior to auto-splenectomy, acute splenic sequestration of RBCs can occur.
iii. Usually in the first 2 years of life, associated with precipitous drop in Hgb.
iv. Hypovolmic shock and death may occur. Splenic sequestration is the cause of a large proportion of death in early childhood among sickle cell patients.
v. Splenectomy for patients at risk for recurrence.
vi. Transfusion to keep HgbS% < 30% may also prevent recurrence.

d. Acute Chest Syndrome
i. Present as acute illness, cough, chest pain, hypoxia, fever, CXR shows pulmonary infiltrate.
ii. Mechanism: Possibly due to sickling in the pulmonary microvasculature -> V/Q mismatch + pulmonary infarction? Infection? Fat emboli from bone marrow? All of the above?
iii. Can be self-limited or result in respiratory failure and death.
iv. Precipitates a neurological event in 22% patients in one study. Recent pulmonary event considered as the non-neurological risk factor that is most predictive of stroke in SCD.
v. Supportive therapy with oxygen, IV fluids, antibiotics may suffice in mild cases.
vi. Transfusion improves oxygenation (both simple and exchange).
vii. Exchanged transfusion needed in bad cases.

e. Stroke
i. Children between 2-5 year of age at highest risk.
ii. Often unrecognized and under-diagnosed.
iii. High mortality (20%) and morbidity, high recurrence rate.
iv. Acute episode managed with exchange transfusion, get HgbS below 30% ASAP, below 20% if severe hemorrhage present or if angiography is planned.
v. Exchange transfusion also effective prophylaxis against recurrence.
vi. Children at high risk should be put on chronic exchange/simple transfusion program. Maintain HbgS below 30% for 3-5 years, then below 50% thereafter.

vi. Recent studies suggest that if chronic transfusion stopped, even after 5-12 years, strokes recur at very high rates. Optimal duration of chronic prophylactic RBC exchange unclear at the moment.

vii. For patients who have never had a stroke, the risk for CVA is assessed with transcranial Doppler (TCD) ultrasound-> high flow rate=high risk (a reflection of the decreased diameter of the vessel).

viii. Prophylactic exchange transfusion is effective at preventing first stroke, although this is associated with the risks of alloimmunization to RBC antigens.

ix. MRA may be of value in further assessing risk in patients with abnormal TCD results.

f. Priapism

i. Males with SCD are prone to nonthrombotic obstruction of penile venous outflow -> priapism. Can result in impotence if recurrent and prolonged.

ii. Affect ~90% of males with SCD by age 20.

iii. Conservative management: IV hydration, analgesia

iv. IF persists for more than 2-3 hours, urologic intervention (aspiration followed by local instillation of epinephrine) may be required.

v. Exchange transfusion can be done, with a target of bringing HgbS below 30%. Transfusion can relieve pain in a day, complete detumescence may take days.

vi. Surgery is less preferred due to impotence risk.

vii. Watch out for ASPEN!! (Association of Sickle Cell Disease, priapism, exchange transfusion, neurological events)

1. Neurological symptoms (HA, seizures, hemiparesis, obtundation etc) shortly (1-11 days) following red cell exchange for priapism

2. Mechanism: higher post-exchange hct and coagulation abnormalities??

3. Treatment: Simple transfusion, keep HgbS <30%

viii. Recurrent priapism should be treated with chronic transfusion to keep HgbS <30% for 6-12 months.

g. Pregnancy

i. Mother at risk during pregnancy for anemia, acute chest, aplastic crisis

ii. Fetus at risk for IUGR, prematurity, death

iii. Utility of prophylactic transfusion in pregnancy remains controversial

iv. The only fully prospective randomized trial in 1988, and two more recent studies (1995) showed that prophylactic RBC transfusions do not change perinatal outcomes.
v. Actual clinic practice is variable, depending on patient and the provider.

h. Surgery/Anesthesia
   i. Surgery and anesthesia are associated with acidosis, hypoxia, venous stasis, hypothermia -> all can precipitate sickling
   ii. Historically, many SCD patients are transfused pre-op to keep HgbS < 30-50%. But there is no general consensus
   iii. Vitreoretinal surgery: one situation where there is general agreement that transfusion is helpful
   iv. 1995 multicenter study: concludes that in the perioperative period, as long as the patient is hydrated, conservative transfusion (keep total Hgb >10g/dL, without respect to percent HgbS is good enough. More aggressive transfusion goals result in increased donor exposure, alloimmunization risks, and other transfusion complications.

V. Alloimmunization and Prevention
   a. Alloimmunization rate very high (35% in some studies) among SCD patients because patients are 1) multitransfused 2) predominantly African American, have important antigenic differences compared with the predominantly Caucasian donor population
   b. Prophylactically providing SCD patients with phenotypically matched blood shown to be effective at preventing alloimmunization. However, cost-effectiveness is controversial.
   c. Still does not prevent formation of antibodies against high frequency antigens (U, Js\(^b\)), and many African Americans are negative for these antigens
   d. Practices vary widely:
      i. Do no matching at all- wait until alloantibody develops and provide antigen negative units
      ii. Match Rh Kell only (UCLA practice): These antigens are most immunogenic, and alloantibodies against them are most capable of mediating hemolytic transfusion reactions
      iii. Extensive phenotype match: Rh, Kell, Kidd, Duffy, Ss: limited by resources and available inventory
   e. If providing phenotype match units, then need to determine phenotype of the patient accurately. This may be complicated because patients are often multi-transfused. Potential approaches:
      i. Hypotonic saline treatment:
         RBCs containing HgbS or HgbC are resistant to lysis in hypotonic saline, normal RBC are not. Treated blood samples should only have patient’s own HgbS positive RBCs left.
      ii. Molecular genotyping
      iii. Call the previous facility, and ask if they have a reliable phenotype on the patient

VI. Delayed Hemolytic Transfusion Reactions (DHTR) and hyperhemolysis
a. DHTR can mimic sickle crisis: present with pain, hemoglobinuria, labs consistent with hemolysis
b. High clinical suspicion is required to make the diagnosis.
c. Consider DHTR if 1) new alloantibody identified, 2) DAT is positive, with mixed field reactivity 3) more than “baseline” amount of hemolysis / hgb drop is present (which might be tricky to establish)
d. DAT may also be negative if all transfused cells have already been cleared
e. “Sickle hyperhemolysis syndrome”
   i. Patients presents more severe anemia following transfusion than before (e.g., Hgb falls below pre-transfusion level)
   ii. Two mechanisms proposed to explain hyperhemolysis:
       1. antigen-negative RBCs are removed due to “bystander hemolysis”
       2. transfusion suppresses endogenous erythropoiesis
   iii. Stop transfusion. If must transfuse due to critically low Hgb level, give IVIg and steroids concurrently may mitigate hemolysis

VII. Iron Overload
a. Each unit contains 200-250 mg of Fg,
b. Transfusion -> Fe overload over time, deposition in heart, liver, endocrine glands etc. leading to organ dysfunction
c. Patients should have serum ferritin monitored and be put on iron chelating agents
   i. Intravenous: poor patient compliance, cumbersome and time consuming to administer
   ii. Oral agent (Exjade): New, greater ease of use and better compliance, leading to improved efficacy