Erythropoeisis in Burn Patients

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Blood Transfusions Carry Risk

- Old blood has lysed cells and all kinds of bad ju ju.

- Academic Centers get the older blood.

- Many cardiac and ICU studies show worse outcomes with increased number of blood transfusions.

- All ICU patients are at risk for anemia.
There is no transfusion standard in the burn field.

- Arbitrary transfusion criteria between burn units.
- Kwan et. al reported a transfusion trigger of Hgb of 7.0 vs. 9.8 resulted in less organ dysfunction.
- Sv$_{02}$ saturation in large burn dictate higher transfusion criteria.
- Giving less blood is good, but how can we maintain adequate hemoglobin in patients that require higher levels of hemoglobin while minimizing transfusions?
Decrease Need for Transfusions

- Bloodless surgery
  - Tourniquets for extremity surgeries
  - Tumescent technique for donor sites
  - Tumescent technique for burn excision

- Iron therapy

- Erythropoietin therapy, but only after iron stores are replete.
Iron Metabolism

- Our body contains 3000-4000 mgs iron.
- 20 mgs are needed/day for erythropoiesis.
- We lose 1-2 mg/day in stool.
  - There is no iron exportation pathway.
- Serum iron levels and body stores of iron are tightly regulated through absorption.
- Proteins involved are transferrin, transferrin receptor, ferritin, ferroportin and hepcidin.
Ferroportin Provides Iron

- Ferroportin is major iron exporter protein from cells into the blood stream.

- Null mutations in ferroportin gene are lethal in mice.

- Strongly expressed in duodenal enterocytes and macrophages.

- Some human ferroportin mutations cause iron overload.
Ferroportin provides serum iron.
Early Serum Iron Levels in Burn Patients

Hospital Day
Hepcidin is Hormonal Regulator of Iron Metabolism

- Hepcidin: 25 amino acid peptide synthesized by hepatocytes.
- Hepcidin negatively regulates ferroportin.
- Hepcidin null mutations are lethal and over-expression of hepcidin causes anemia.
- Hepcidin production is stimulated by iron, IL-6 and inhibited by anemia or hypoxia.
- Hepcidin blocks ferroportin activity by forcing internalization of ferroportin protein on both enterocytes and macrophages.
Hepcidin Blocks Ferroportin.

What happens in a burn patient?

- IL-6 rises and increases hepcidin concentration, which forces internalization of ferroportin.

- Iron accumulates inside macrophages and enterocytes and is not released into bloodstream.

- The bone marrow quickly depletes serum iron as it synthesizes new red blood cells.

- Burn patients become anemic and cannot absorb oral iron or release iron from transfused blood.
Burn patients need IV iron to replace any losses.

- Oral iron and blood transfusions will not replace iron losses.

- IV iron in moderation is safe:
  - Hemodialysis pt’s no correlation between free serum iron and serum peroxide levels.
  - No good data showing increased risk of infection with IV iron in critically ill patients, including premature infants.
  - Clinical studies in cardiology patients are equivocal.
How We Titrate Iron

- Provide IV iron sucrose (Venofer) 100mg/day-200mg/day.

- Every week, measure serum iron, serum transferrin levels (TIBC) and calculate iron saturation, 48 hours after last Venofer dose.

- Aim for iron saturation between 25-80%.

- Then and only then do we start erythropoietin therapy.
29 y/o Female with Bilateral Severe Lower Extremity Burns

- Type I diabetic who fell onto her bed during a hypoglycemic event.
- A lit candle also fell onto the bed.
- She was rescued by neighbors.
- Pt’s burns were so severe she needed bilateral BKA’s.
Burn Pt’s Require IV Iron to Restore Iron Stores

Serial Iron Studies

- Serum Iron Level (ugm Fe/dl)
- Iron Saturation (%)

Chart showing the relationship between Serum Iron Level and Iron Saturation over time.
Iron Therapy is Not Enough

Reticulocytosis after Iron Therapy

- Serum Iron gm/dl
- Iron Saturation %
- Absolute Reticulocyte Count

Hospital Day

0 20 40 60 80 100 120

Serum Iron gm/dl
Iron Saturation %
Absolute Reticulocyte Count
Erythropoietin is protein hormone produced in kidney. Made in response to hypoxia/anemia. Erythropoietin binds to a protein receptor on surface of immature erythroid cells. Erythropoietin stimulates red cell production, by decreasing apoptosis of erythroid progenitor cells.
Inflammation Inhibits epo serum levels and epo action

- Anemia of chronic disease is associated with depressed serum levels of erythropoietin.

- Cancer related anemia requires higher doses of erythropoietin than chronic renal failure patients.

- Chronic kidney dialysis patients have increased erythropoietin needs when infected/inflamed.

- Burn patients are resistant to action erythropoietin.
Young male 35% TBSA With Inhalation Injury

- Intubated with severe ARDS and unsafe for surgery during first three weeks of hospitalization.
- With increasing doses of epo able to get hematocrit up to 45%.
- Able to perform surgeries with no transfusions.
- During pt’s hospital stay, he received no blood.
Erythropoietin Increases Reticulocytosis.

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<th>Retic%</th>
<th>Corr%</th>
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35% TBSA with Inhalation

Graph showing trends over Post Burn Day:
- **Hct.**
- **Retic.**
- **Epo dose.**
- **Iron sat.**

Legend:
- sat
- retic
- hct*10
- epo dose
Young Male 25% Full Thickness Skin Defects From Bacterial Infection

- Pt. also severely malnourished.
- Once iron stores replete, remained anemic.
- Titrated epo-alpha dose weekly to get a robust reticulocyte count and performed a debridement without transfusing patient.
- Once epo-alpha therapy stopped, pt. started needing blood transfusions.
Severely Malnourished Young Male

Graph showing the changes in hematocrit (Hct), reticulocyte count (Retic), and erythropoietin (Epo) over post-burn days. The graph illustrates the patient's response to epo dose (epo dose) with a peak on post-burn day 25 and subsequent decline.
Complications from Iron Therapy

- No evidence of increased infections
- No evidence of hypotension
  - Venofer has lower side effect profile.
- No evidence of increased inflammation
Complications of Erythropoietin Therapy

- Increased risk of thrombotic events with increased hematocrits.
  - No thrombotic events in our patients.

- In future will titrate erythropoietin to maintain hct below 36%.

- One pt. developed red cell aplasia that resolved with discontinuation of epo-alpha therapy.
Summary

- We do need to give our patients less blood.
- We help by decreasing blood loss during surgeries and increasing pt’s synthesis of blood.
- Supplemental iron needs to be given IV because burn patients produce hepcidin.
- Standard doses of erythropoietin are inadequate to increase patients hemoglobin levels and need to be given only after iron levels are replete.
- Burn patients are not the only critically ill patients to overproduce hepcidin.
Questions

- How do we best treat the anemia associated with burn patients? Epo is expensive!!!
- How much is hepcidin overproduced in burn patients and how is it regulated?
- Why are erythropoietin levels depressed in burn patients?
- Why are burn patients resistant to erythropoietin?
- How much erythropoietin needs to be supplemented?
- What will be the benefits of using erythropoietin instead of blood transfusion?
- What is the best SvO₂ value for resuscitation?