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Anemia & transfusion targets

November 2, 2016 by Josh Farkas

(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/ironman.jpg?ssl=1)

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diagnostic approach to dropping hemoglobin

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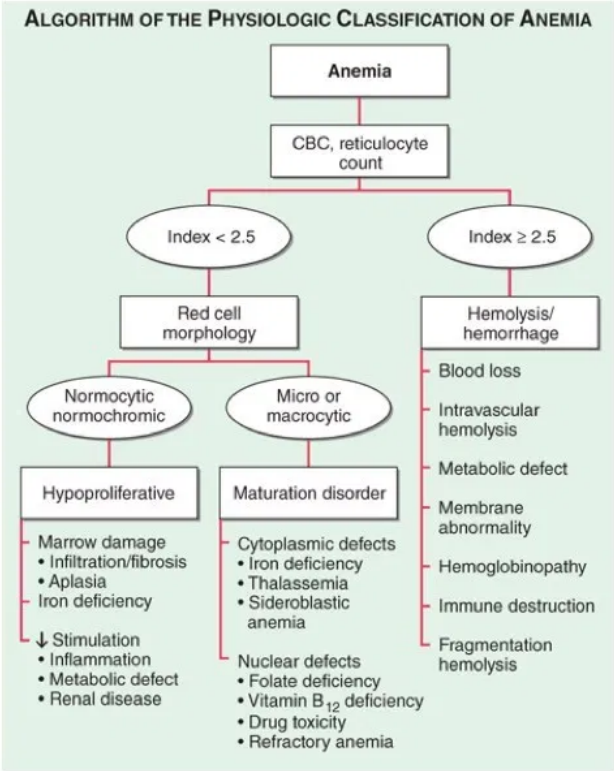


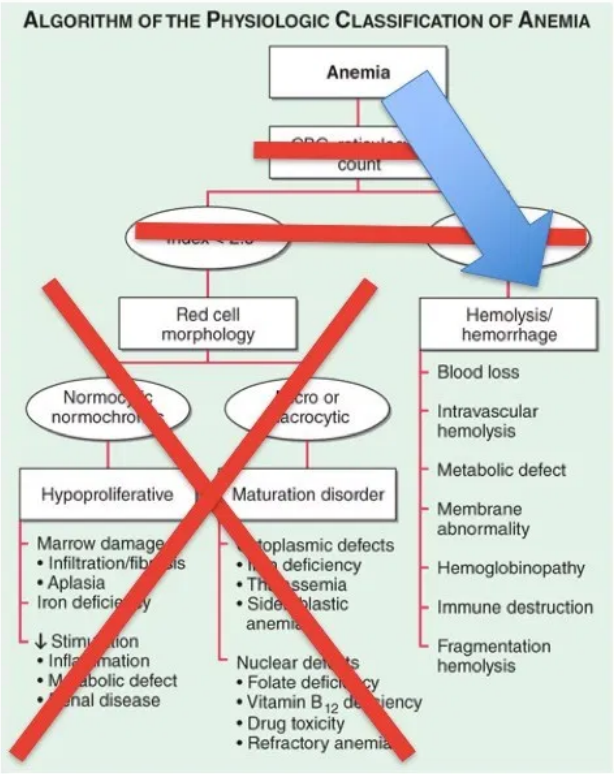
Harrison's Manual of Medicine, 18e, 2014

(https://i0.wp.com/emcrit.org/wp-content/uploads/2017/09/anemia1.jpg)

The standard internal medicine approach to anemia is shown above. This is a nice algorithm, but it is designed for the evaluation of *chronic anemia*. Evaluating a patient with *acutely dropping* hemoglobin is actually much simpler for the following reason: bone marrow failure cannot cause an acutely dropping hemoglobin.

- Erythrocytes have a half-life of 120 days.
- If the bone marrow shut down completely, the hemoglobin would fall by only about ~1% per day (e.g. from 7 mg/dL to 6.9 mg/dL the next day).
- Any drop in hemoglobin faster than this *must* be due to blood loss or hemolysis.

This allows us to simplify the above algorithm as follows:



Harrison's Manual of Medicine, 18e, 2014

(https://i1.wp.com/emcrit.org/wp-content/uploads/2017/09/anemiaalgo2.jpg)

causes of acute hemoglobin drop

- **Hemorrhage** (usually)
  - External
    - GI bleed
    - Phlebotomy
    - Trauma/surgery
  - Internal
    - Hemoperitoneum
    - Hemothorax
    - Retroperitoneal hemorrhage, rectus sheath hematoma
    - Bleeding into thigh (common after hip fracture)
- **Hemolysis**
  - Malfunctioning intravascular prosthesis: Impella device, mechanical heart valve, vascular graft/shunt
  - Microangiopathic hemolytic anemia (e.g. DIC, TTP)
  - Infection (clostridia, babesia, malaria)
  - G6PD deficiency
  - Autoimmune hemolytic anemia (transfusion reaction, drugs)

lab evaluation of acute hemoglobin drop

- Repeat CBC to verify that hemoglobin is truly falling.
- Labs to evaluate for hemolysis
  - Hemolysis screen: Haptoglobin, lactate dehydrogenase (LDH), blood smear.
  - Sorting out cause of hemolysis: Direct antiglobulin (Coombs) test
- Labs to assist in *management* of hemorrhage
  - Type & screen (or type & cross-match if hemoglobin rapidly falling)
  - Check coagulation factors and fibrinogen

Pink urine due to massive intravascular hemolysis. Pink urine is *usually* meaningless (due to minor foley trauma), but it deserves more attention if the hemoglobin is acutely dropping, or if the patient has an Impella device.

Wehman B et al. 2014 PMID 25298699

(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/pinkurine.gif) **imaging evaluation of hemoglobin drop**

- Bedside ultrasonography (including FAST scan) should allow for exclusion of hemothorax or hemoperitoneum.
- CT abdomen/pelvis may be indicated to evaluate for retroperitoneal hematoma, particularly if there was a recent procedure that may have caused this.
    - If there is a high index of suspicion for retroperitoneal hematoma or hemoperitoneum, consider CT angiography as this may guide a subsequent procedure by interventional radiology.

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gradual anemia- the ICU hemoglobin drift

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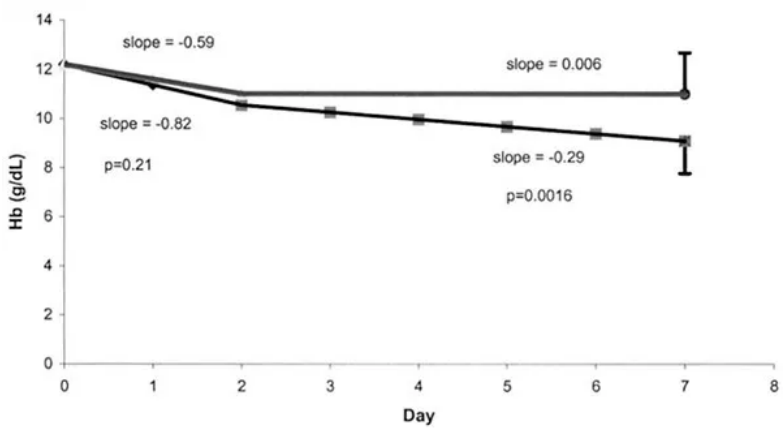

Hemoglobin trends among non-bleeding ICU patients. On average, patients lost ~1.5 mg/dL over the first three days. Subsequently, non-septic patients remained fairly stable (top curve) whereas septic patients continued to gradually lose hemoglobin (bottom curve).

- Ba VN et al. Crit Care Med 2003; 31: 406.

(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/hgbdrift.jpg)

defining ICU hemoglobin drift

- Most ICU patients experience gradual decrease in hemoglobin over time. This is probably multifactorial, with the following contributory factors:
- 1) Suppression of hematopoiesis due to inflammation (similar to anemia of chronic disease).
- 2) Phlebotomy for laboratory studies.
- 3) Minor, subclinical stress ulceration in the GI tract.

interventions to avoid

- Checking an extensive anemia panel (iron, folate, B12, reticulocyte count) isn't helpful, as discussed above.
- Iron supplementation is generally unhelpful. Oral iron is poorly absorbed and may irritate the stomach. Intravenous iron doesn't seem to affect blood transfusion requirements in the ICU.[1] Patients with systemic inflammation may have suppressed hematopoiesis regardless of their iron stores.
- Erythryopoietin has been trialed several times for this, with disappointing results.[2] For most patients, this isn't worth the expense and work involved. Erythropoietin should be considered, however, for the Jehovah's Witness patient (see below).

management of hemoglobin drift

- Minimize phlebotomy
  - Avoid unnecessary labs.
  - For patients at increased risk from anemia (e.g. ARDS patients with limited oxygen delivery), draw labs in pediatric tubes.
- Conservative transfusion strategy (more on this below)
- Discontinue unnecessary anticoagulants. For example, some patients are on chronic aspirin for primary prevention – this should be discontinued.
- Prevention/treatment of stress ulceration
  - Prevention of stress ulceration: enteral nutrition if possible, possibly proton pump inhibitor (more on this to come).
  - For patients who are consistently losing more hemoglobin than is usual, initiation of a proton pump inhibitor may be considered for empiric treatment of gastrointestinal erosions.

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transfusion targets for patients not exsanguinating

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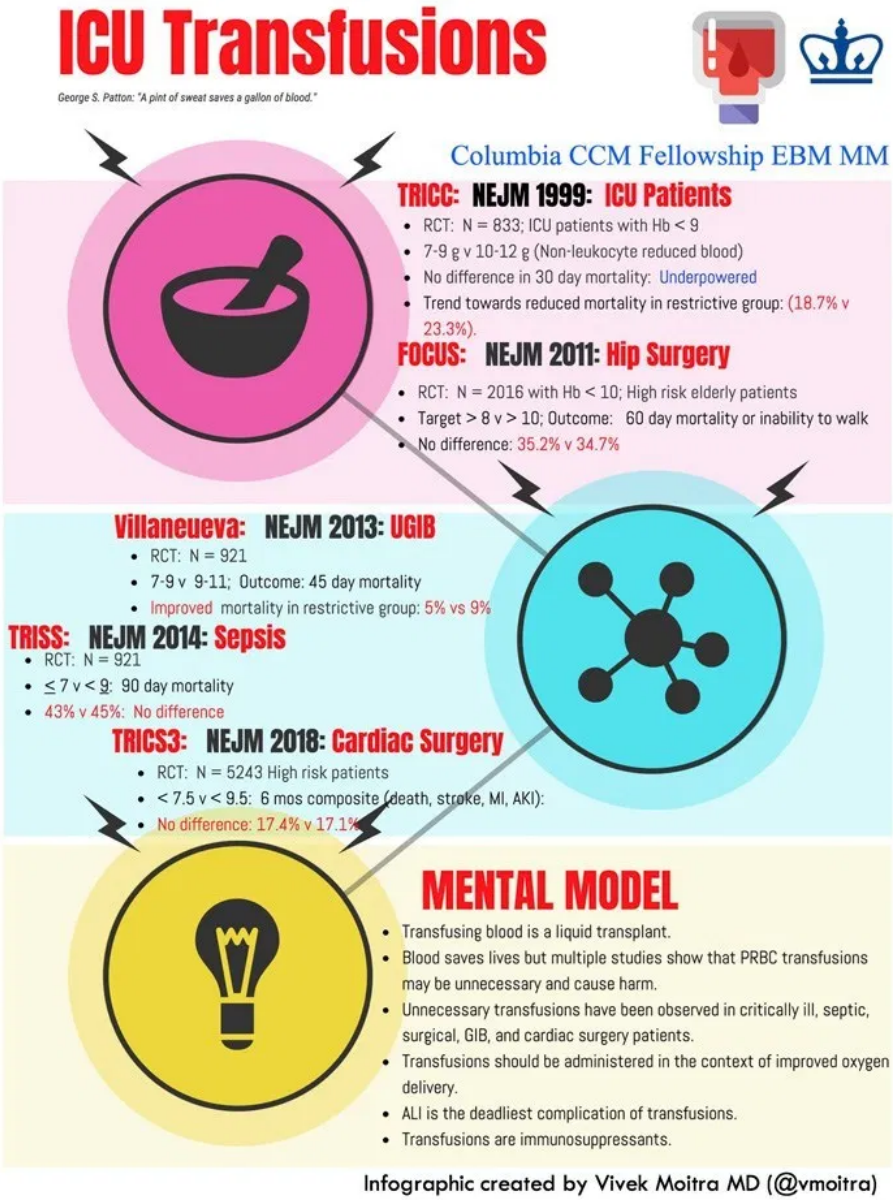
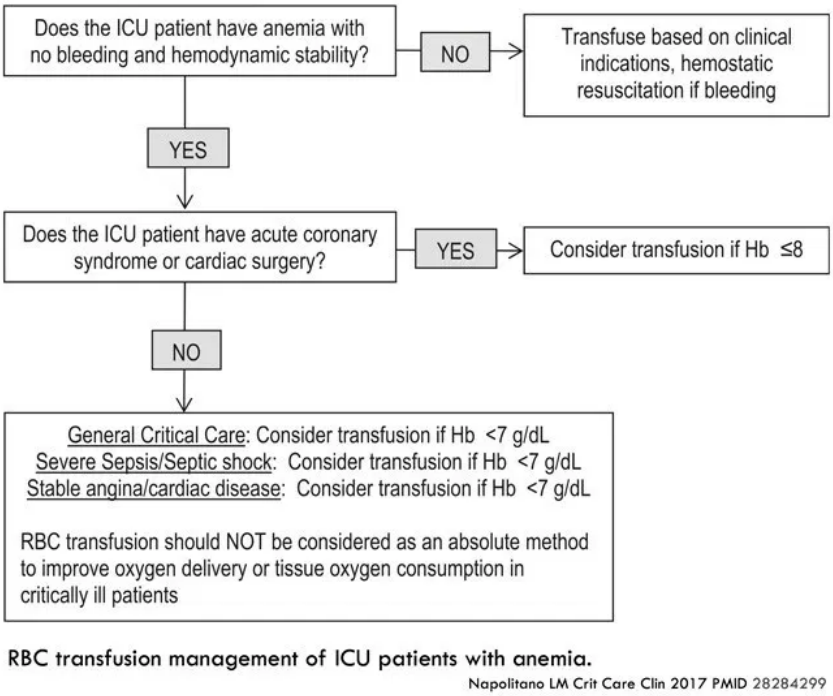
transfusion should be used carefully and judiciously

- Transfusion may cause numerous problems:
  - Transfusion associated circulatory overload (TACO) – fancy name for volume overload.
  - Transfusion reactions including transfusion-related acute lung injury (TRALI) and anaphylaxis.
  - Immunosuppression.
  - Hyperkalemia, hypocalcemia.
- More liberal administration of blood products has been shown to be non-beneficial or *harmful* in most studies of critically ill patients.



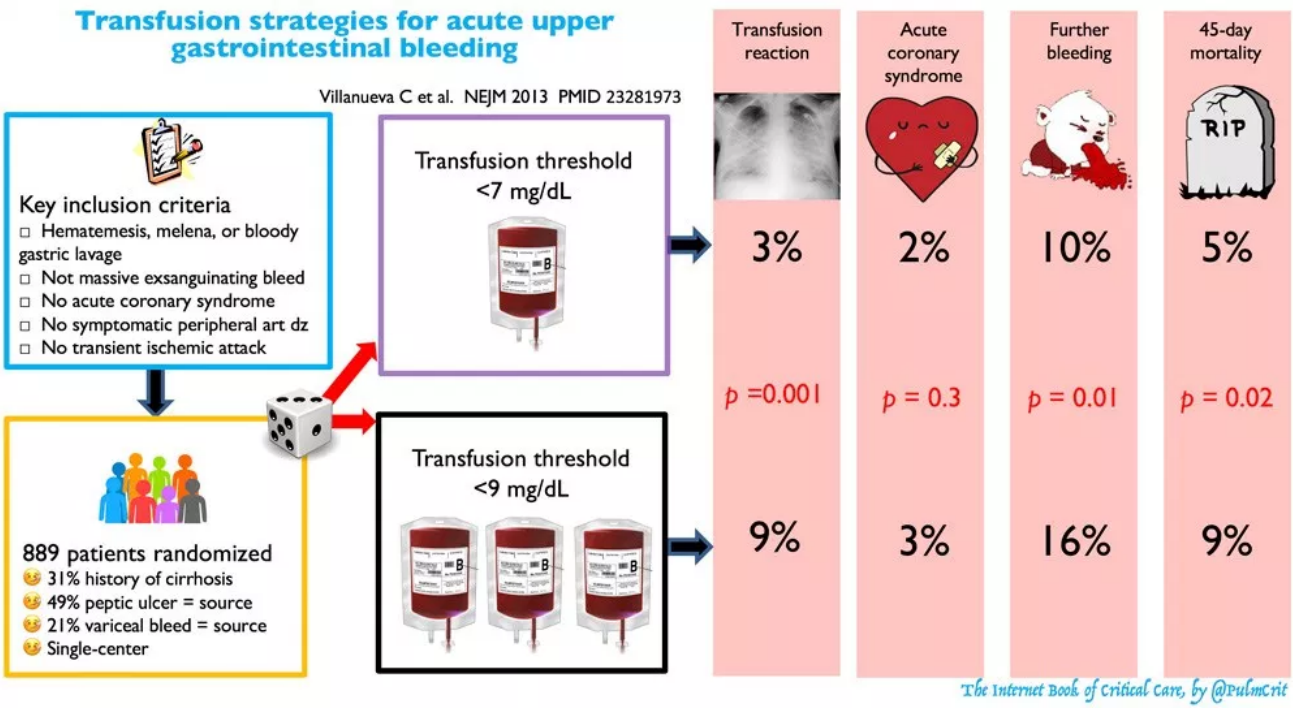
(https://i2.wp.com/emcrit.org/wp-content/uploads/2016/11/icutransf.jpg?ssl=1) **transfusion target for the patient who is not acutely hemorrhaging**



RBC transfusion management of ICU patients with anemia.
Napolitano LM Crit Care Clin 2017 PMID 28284299

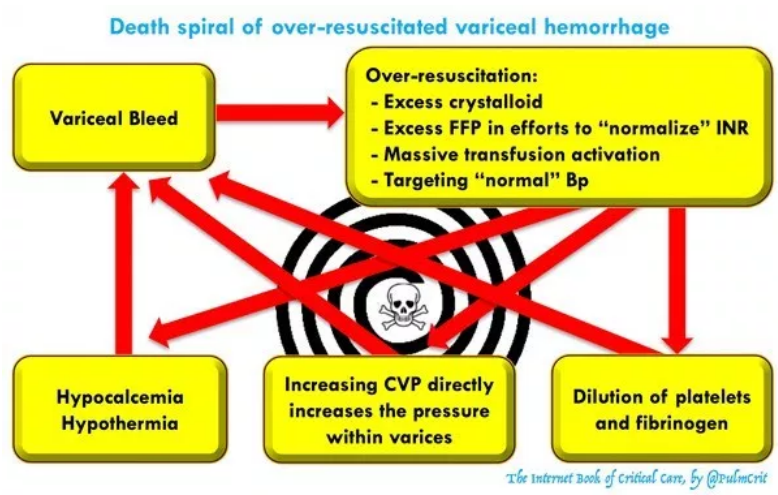
(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/nap.jpg?ssl=1)

- The transfusion target for nearly all ICU patients is 7 mg/dL (70 g/L). However, a target of >8 mg/dL (80 g/L) is preferable for patients recovering from CABG surgery or patients with *active* myocardial ischemia (NSTEMI or unstable angina).[3]
- Blood should generally be transfused one unit at a time.[4] Avoid transfusion of more than one unit blood unless the patient is actively hemorrhaging or the hemoglobin is extremely low. This is done for two reasons:
  - 1) Hemoglobin bounces around a bit from day to day. Over-reacting to a "low" hemoglobin with two units blood transfusion will often over-correct the anemia.
  - 2) Blood transfusion tends to cause pulmonary edema (more so than crystalloid). Two units of blood is a significant volume bolus for a patient who may have euvolemic or hypervolemic anemia.



(https://i1.wp.com/emcrit.org/wp-content/uploads/2018/09/infographicv.jpg?ssl=1) **transfusion target for the patient with a gastrointestinal hemorrhage**

- For patients who don't have a massively exsanguinating bleed, a conservative transfusion target (>**7 mg/dL**) was shown to *improve mortality* compared to a liberal transfusion target (>9 mg/dL).[5]
- If you're worried that the patient might suddenly open up, the safest approach is to order blood to be typed & crossed and placed *on hold in the blood bank*. Make sure the patient has good intravenous access. Then, if the patient starts exsanguinating, you're all set – just request that the blood be infused. The vast majority of the time the patients *won't* bleed, allowing you to avoid exposing them to the risk of excessive transfusion.
- The harms from over-transfusion are probably greatest for patients with ***variceal hemorrhage,*** (https://emcrit.org/ibcc/gi-bleeding/#variceal_bleed) where over-transfusion can push patients into a death spiral:



(https://i0.wp.com/emcrit.org/wp-content/uploads/2018/09/deathspiralcvp.jpg?ssl=1) **contraindications to transfusion**

- Transfusion may be especially problematic in:
  - Patients with increased blood viscosity (e.g. due to hyperleukostasis in uncontrolled AML).
  - Patients with thrombotic thrombocytic purpura (TTP) – may increase hemolysis.
  - Uncontrolled hypervolemia (especially dialysis patients).
  - Hyperkalemia (potassium leaks out of RBCs in storage, potentially increasing serum potassium levels).
- In these contexts, it may be reasonable to hold transfusion in patients with a hemoglobin <7 mg/dL in the absence of signs of organ hypoperfusion.
  - It is often wise to transfuse dialysis patients *during* hemodialysis, to avoid volume overload or hyperkalemia.

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managing Jehovah's Witness patients

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getting started: clarify goals

- Discuss with patient and/or family whether they would accept blood transfusion if necessary.
- Clarify whether some blood products may be acceptable (for example, some patients may accept coagulation factor concentrates).
- If at all possible, these discussions should occur early, when the patient is stable. When in doubt, ethics consultation may be helpful.

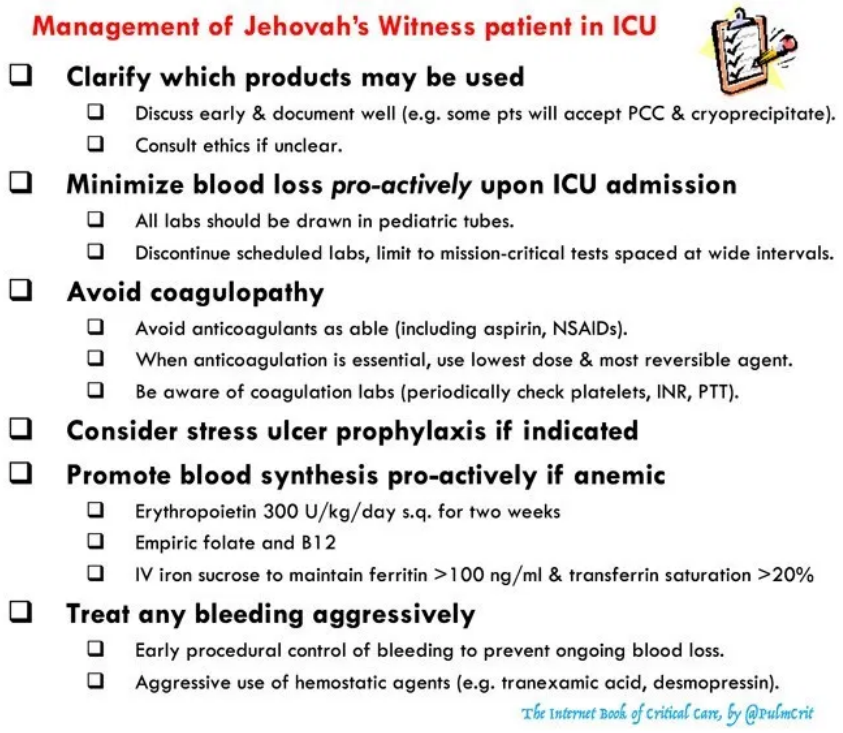
avoid blood loss

- **Avoid hemoglobin drift:** The major threat to these patients isn't necessarily an acute hemorrhage, but rather gradual blood loss which is commonly seen in ICU patients (see above: "hemoglobin drift"). Gradual blood loss can easily become a major problem over a 1-2 week ICU stay. The following measures may be used to avoid this:
  - Begin aggressive efforts to conserve blood *immediately* upon arrival to the ICU (don't wait until the patient's hemoglobin has dropped to 5 mg/dL).
  - Draw labs in pediatric tubes.
  - Discontinue all scheduled blood draws (no "cycling" of labs). Every blood draw should represent a deliberate decision by the treatment team. Consider giving patients "lab holidays" (e.g. checking basic labs q48hr or q72hr).
  - Lab draws should be strictly limited to mission-critical tests which are absolutely required for patient care.

- **Adequate stress ulcer prophylaxis.**
  - NSAIDs should be avoided to reduce the risk of peptic ulceration (as is the case for most critically ill patients).
  - Stress ulcer prophylaxis should be considered.
- **Avoid coagulopathy**
  - Whenever possible, avoid or minimize anticoagulation.
  - When anticoagulation is necessary, use the lowest dose possible of a *reversible* agent. Avoid direct-acting oral anticoagulants.
  - Be aware of coagulation labs and act accordingly – especially for patients with active bleeding or when prescribing an anticoagulant.
- **Avoid unnecessary procedures** which pose a risk of bleeding.
- **Aggressive management of any acute hemorrhage**
  - Early operative intervention (e.g. prompt endoscopy for GI hemorrhage)
  - Use of pro-coagulants (e.g. tranexamic acid) may be rational.

promote blood synthesis

- The use of erythropoietin hasn't been shown to be beneficial in most patients, but it may improve hemoglobin levels. Among Jehovah's Witness patients, this is a rational therapy. This may be achieved as follows:
- 1) sq erythropoietin 300 U/kg/day for two weeks if necessary, then three times per week.[6 7]
- 2) IV iron sucrose as needed to maintain ferritin >> 100 ng/mL and transferin saturation >20%.[2] Erythropoietin won't work without adequate iron stores.
- 3) Give empiric folate and vitamin B12 to support hematopoiesis.



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podcast

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questions & discussion

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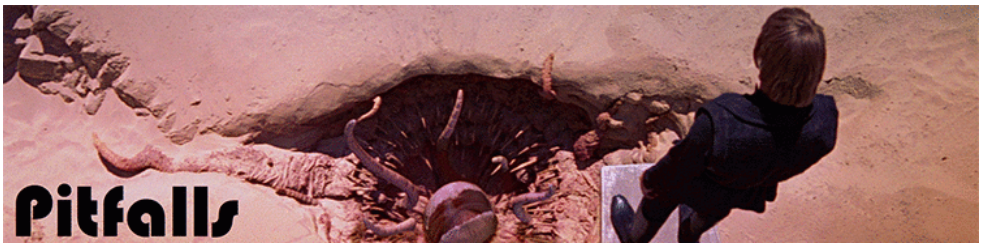
To keep this page small and fast, questions & discussion about this post can be found on another page ***here*** (https://emcrit.org/pulmcrit/transfusion/) .



(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif)

- Ordering iron studies on ICU patients to evaluate the etiology of *acute-onset* anemia. As discussed above, *acute* anemia can never be due to iron deficiency.
- Over-transfusion of blood remains a considerable problem in the ICU, despite repeated studies showing that this is dangerous. When in doubt, it's generally better to err on the side of *not* transfusing blood.
- A transfusion target of 7 mg/dL means that you don't transfuse unless the hemoglobin is *actually below seven.*
- Trying to transfuse blood to improve a patient's dyspnea is generally ineffective or harmful, unless the patient is severely anemic.

Going further:

- Transfusion Literature Summaries (https://lifeinthefastlane.com/ccc/transfusion-literature-summaries/) (Chris Nickson, LITFL)
- Blood transfusion in ICU (https://lifeinthefastlane.com/ccc/blood-transfusion-in-icu/) (Chris Nickson, LITFL)
- Blood Transfusion Strategies in the Modern Era (http://maryland.ccproject.com/2014/06/05/giora-netzer-blood-transfusion-strategies-modern-era/) (Giora Netzer, Maryland CC project)
- Anemia in the ICU (https://pulmccm.org/review-articles/anemia-in-the-icu-2012-update-review-ajrccm/) (PulmCCM)
- The TRICC trial (https://intensiveblog.com/tricc-trial/) (Kent Lavery, INTENSIVE blog)
- Iron?
  - IRONMAN trial (http://www.thebottomline.org.uk/summaries/icm/ironman/) – TheBottomLine
  - IV iron in emergency medicine (https://emergencymedicinecases.com/iv-iron-for-anemia-in-emergency-medicine/) (Anton Helman, Emergency Medicine Cases)
- Severe anemia in Jehovah's Witness patients (https://wikem.org/wiki/Severe_anemia_in_Jehovah%27s_Witness_patients) (Kevin Claire et al, WikEM)

References:

1. IRONMAN I, Litton E, Baker S, et al. Intravenous iron or placebo for anaemia in intensive care: the IRONMAN multicentre randomized blinded trial : A randomized trial of IV iron in critical illness. *Intensive Care Med.* 2016;42(11):1715-1722. [PubMed (https://www.ncbi.nlm.nih.gov/pubmed/27686346)]
2. Corwin H, Gettinger A, Fabian T, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med.* 2007;357(10):965-976. [PubMed (https://www.ncbi.nlm.nih.gov/pubmed/17804841)]
3. Napolitano L. Anemia and Red Blood Cell Transfusion: Advances in Critical Care. *Crit Care Clin.* 2017;33(2):345-364. [PubMed (https://www.ncbi.nlm.nih.gov/pubmed/28284299)]
4. Napolitano L, Kurek S, Luchette F, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Crit Care Med.* 2009;37(12):3124-3157. [PubMed (https://www.ncbi.nlm.nih.gov/pubmed/19773646)]
5. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med.* 2013;368(1):11-21. [PubMed (https://www.ncbi.nlm.nih.gov/pubmed/23281973)]
6. Berend K, Levi M. Management of adult Jehovah's Witness patients with acute bleeding. *Am J Med.* 2009;122(12):1071-1076. [PubMed (https://www.ncbi.nlm.nih.gov/pubmed/19958881)]
7. Zeybek B, Childress A, Kilic G, et al. Management of the Jehovah's Witness in Obstetrics and Gynecology: A Comprehensive Medical, Ethical,

and Legal Approach. *Obstet Gynecol Surv*. 2016;71(8):488-500. [PubMed (https://www.ncbi.nlm.nih.gov/pubmed/27526872)]

The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.