Jehovah’s Witnesses and Transfusion: A Hematologist’s Perspective

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Jehovah’s Witness Patients: General Suggestions for Health Care Providers

- Work in partnership with the patient & JW community; act as patient’s advocate.
- Know & explore the acceptability of the full range of non-blood therapeutic options with the patient--and use them!!
- Act pre-emptively if possible
- Realize physiological tolerance of anemia is generally greater than you may think

Jehovah’s Witness Patients:

- What’s Acceptable?
- How Low Can You Go?
- Cases Illustrating a Range of Options That Can (Sometimes) Save the Day

Jehovah’s Witnesses: What’s Acceptable?

- Religious objection to the use of many blood products

  - Acceptability of blood products:
    - Unacceptable: Whole blood and its primary components: RBCs, platelets, plasma, WBCs
    - Possibly acceptable (individual conscience): Plasma derivatives: cryoprecipitate, albumin, fibrin glue, factor concentrates, IVIG, (Hb-based O2 carriers)

  - Acceptability of transfusion -sparing interventions:
    - Unacceptable: Autologous predonation
    - Conditionally acceptable (with certain devices/techniques only--blood must remain in unbroken circuit with body): Isovolemic hemodilution, some peri-operative salvage devices
    - Almost always acceptable: Epo
    - Always acceptable (no issues): darbe (albumin free), ddAVP, antifibrinolytics, recombinant factors, rVIIa
Whole Blood 450 ml

Primary Components

- Plasma (~250 ml)
- Platelets
- WBCs
- RBCs (~200 ml)

MAY be acceptable: “MATTERS OF CONSCIENCE”

- Plasma derivatives
- Cryoprecipitate (~10 ml)
- Fibrin glue
- Clotting Proteins (FVIII, FIX)
- Albumin
- IVIG; RhIg
- Many others

Plasma pools

Physical and/or chemical separation (s)

“Tips” on explaining “fractions” and transfusion alternatives:

- Ask if the patient has an “Advance Directive”—there is a special section of this dealing with “fractions”
- Use a special “Refusal Form” to help guide discussion between you and the patient (OHSU = possible prototype)
- Usually if one “fraction” is acceptable, all are
- Erythropoietin = “matter of conscience” (stabilized with traces of albumin); darbepoietin = no issues (albumin free)

Additional Management “Tips”:

- The “fractions”/transfusion alternatives discussion is useful and should be done:
  - I have seen all named fractions contribute to saving lives
  - The therapeutic relationship is served
- Don’t be shy about asking for advice elsewhere—call me, call Dr David Rozencrantz at Legacy
- Ask if the patient has a specially trained Hospital Liaison Elder working with them—these individuals are often knowledgeable and compassionate and can help both the patient and the treating MD

OHSU BLOOD REFUSAL FORM
Transfusion of Minors poses medical legal issues
BUT... Court Orders are NOT often necessary at OHSU:

Refusal of Blood transfusion for a minor: As the parent/guardian of a minor child I understand that the decision to treat my child will make every effort to request my consent regarding the transfusion of blood products as indicated above. I understand that if my child's physician believes that transfusion is necessary to keep my child alive or to prevent serious irreversible harm, my child may be transfused, although every effort will be made to avoid this. If consent is granted, the decision for transfusion will rest with the attending physician.

<table>
<thead>
<tr>
<th>Patient's Name</th>
<th>Parent's Name</th>
<th>Signature</th>
<th>Date and Time</th>
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Signature of Witness to this Refusal Date and Time

Hb/ Hct: How Low Can You Go?

- Normal Hb: ~12-16 g/dl; Hct ~36-56
- Response to anemia:
  - Cardiac: ↑HR, coronary vasodilatation, as decompensate: shift to anaerobic metab; blood from subendo → epicardium
  - Peripheral tissues: ↑ blood flow thru vascular beds; ↑ O2 extraction (if possible); recruit more capillaries
  - ↑ RBC, 2,3 DPG: facilitates offloading O2 to tissues

⇒ Tolerance to anemia is determined by multiple factors including:
  - Chronicity of development
  - Underlying cardiovascular status
  - Age
  - O2 demands

⇒ One size does not necessarily fit all...

Case #1: 1991, Univ of Alberta: High dose EPO saves the day...

- 52 yo man, JW, admitted with 15% burns to hands and face and inhalational injury
- Hb 15.4 → 8.0 after grafting hands; intubated; confusion and need for O2 to maintain acceptable gases.
- Needed to graft face but probable 4 ‘U’ blood loss
- Reticulocytopenic; on Fe++; no correctable nutritional deficiency.
⇒ Begun on Epo 300 U/kg/d x 7 d, then 150 U/kg/3x wk x 3 wks
⇒ Epo administration accompanied by 10x ↑ in retics and ↑ in Hb 7.4 → 10.4 in 12 d
Aside: This case taught me:

- That pure “dilutional coagulopathy” (here 1½ blood volumes worth!) can be surprisingly well-tolerated IF:
  - the patient has a good liver
  - is not allowed to become hypotensive and acidotic and
  - does not have major crush or head injury or other procoagulant drive

Nonetheless, this patient was clearly in trouble…

Aside: This case (and my next few) taught me:

- That epo levels are generally “low normal” for the degree of anemia post-op—but the patients are reticulocytopenic—implying resistance to epo’s action
- That pharmacological doses can partially overcome this block (but what dose is optimal?—I use 300-500 U kg/d of epo)
- That serum iron measurements are near useless in critically ill patients — I basically give almost everybody IV Fe++ (also folate +/- a dose of B12)
Case # 3: 2002, OSHU:

- 61 yo JW woman with strong vasculopathic history
- Tachycardic post-op (~110) with O2 sat’s low
- Need higher doses of epo than in renal failure
- epo gene transcription, ↓ Fe++ availability,
- ↓ erythroid precursor response to epo, direct bone marrow suppression
- Need higher doses of epo than in renal failure
  (renal failure dose: 150 U/kg or 10,000 U/wk)
- Epo is expensive and optimization of dosing andcost/benefit has been uncertain
- Concern re: potential thrombogenicity if rapid rise
  in Hct esp in patients with underlying cardiovascular
disease (epo not licensed in U.S. for correction of pre-op
anemia in CV patients); max ↑ tumor growth / mortality

Caveats re: issues with Epo in the critical care setting:

- Epo response blunted in critically ill patients by
  inflammatory cytokines (TNF, IL-1, IFN, TGFβ)
  → ↓ epon gene transcription, ↓ Fe++ availability,
  ↓ erythroid precursor response to epo, direct bone marrow suppression
  → Need higher doses of epo than in renal failure
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Some bottom lines with Epo in critically ill patients:

- It’s unsuitable for rapid amelioration of anemia
- Max response rate attainable with epo ~ 4x normal basal
  bone marrow RBC production
- It can attenuate ICU anemia in a diverse group of
critically ill patients at a dose of 40,000 U SQ wk
- It’s expensive—already coming up on “top 10” drug
  expenses esp at hospitals with significant dialysis populations
- Optimization of dosing remains unclear
- Patient must be iron replete to respond
  → Need IV Fe++ if ongoing blood loss
  → How best to assess Fe++ status in critically ill patients?
  → How best to administer Fe++
  → Potential of Fe++ to worsen sepsis

Criteria for Compassionate Release of Hb based O2 carrier (HBOC)*:

- Hb < 6.0
- Reversible disease/ “bridging” therapy
- No other alternative to transfusion/ on
  maximal Epo, Fe++ etc
  (Note: court order in kids = an alternative)

* Compassionate Release Programs are made
  available by companies, but overseen by FDA—
  unfortunately NO such programs are open in
  US currently

Case # 3: 2002, OSHU: A Hb-based O2 carrier
(maybe) saves the day… or at least helps a bit…..

- 61 yo JW woman with strong vasculopathic history
  (mesenteric bypass, carotid stenosis, CVA, chronic ST ↑)bled post angiography for ischemic R leg
- Hb 10.1 → 6.5
- Put on high dose Epo, IV Fe++, and taken to
  repair pseudoaneurysm
- Hb 6.5 → 5.7
- Tachycardic post-op (~110) with O2 sat’s low
  90’s on 2L nasal cannula

⇒ Compassionate Release PolyHeme
  requested from Northfield and approved by FDA

So… this aside how did the patient do on the HBOC?

<table>
<thead>
<tr>
<th>HB</th>
<th>HCT</th>
<th>MCV</th>
<th>RDW</th>
<th>RETIC</th>
<th>REL. ARS</th>
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* = OR  ** = Post-op pneumonia (POD3)  *** = R prox DVT (POD6)
**Case # 4: 2004, OSHU: rVIIa, Fibrin Glue, Thrombin, etc and a Good Surgeon Save the Day….

- 60 yo woman, JW, admitted bleeding to ICU with abdomen packed following failed attempted resection of pelvic schwannoma elsewhere (huge feeding vessels and diffuse ooze elsewhere noted)
- Hct 32.9→28.4 overnight; taken to OR early AM

  **Treated with:**
  - rVIIa immediately pre-op (90 mcgm/kg)
  - Intra-op: lots of fibrin glue + thrombin-soaked gelfoam, albumin (cell saver ready but not used re: tumor)
  - Pre/post-op: High dose Epo, IV Fe++, folate, B12

- EBL: 900 cc, episodes of hypotension
- Hct 20.0 (Hb 6.6) immed post-op
  ⇒ Hct 15.1 (Hb 5.2) POD 1
  ⇒ Hct 14.4 (Hb 4.9) POD 2

- Developed major problems with atrial fibrillation (had previous history of this) but never had frank ischemic event
- Hct 14.4 (Hb 4.9) ⇒ Hct 22.1 (Hb 7.5) POD 7
- Discharged and did well

<table>
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<th>Steroids, IVIG, and darbe begun</th>
<th>DISCHARGED</th>
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<tr>
<td>Day 1</td>
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<tr>
<td>Hct</td>
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<td>Retics Relative Absolute</td>
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**Case # 5: 2005, OSHU: IVIG + Darbe + Steroids Save the Day….

- 79 yo man, JW, admitted through Hematology Clinic—walked in c/o fatigue!
- Hb 2.7 with Hct 7.7; HR 89-102; O2 satns RA: ~98% (desaturation to low 90’s on exercise)
- Previously healthy; had become progressively more anemic over 8 month period
- Reticulocytopenic; on Fe++, epo, vits
- Bone marrow: pure red cell aplasia

  **Treated with:**
  - high dose corticosteroids
  - high dose IVIG (400mg/kg/d x 5d)
  - darbepoetin 200 mcgm SQ MWF

<table>
<thead>
<tr>
<th>Post-Op Hb</th>
<th>30d in hospital mortality</th>
<th>30d morbidity/mortality</th>
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<tr>
<td>Normal</td>
<td>Normal CV disease</td>
<td>Normal CV disease</td>
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<tr>
<td>1.1-2.0</td>
<td>100 %</td>
<td>100 %</td>
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<td>&lt;2.1-3.0</td>
<td>52.6 %</td>
<td>60 %</td>
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</table>

- Abnormal        | 88.9 %                    | 100 %                   |

- Steroids, IVIG, and darbe begun       | DISCHARGED |
| Day 1  | Day 4  | Day 8  |
| Hb     | 2.7    | 3.1   | 4.0   |
| Hct    | 7.7    | 9.2   | 12.8  |
| Retics Relative Absolute | 0.4 | 2.69  | 35.0 |
|        | 3.3    | 24.4  | 264.2 |

**Case # 6: 2005, OSHU: The Courts Get Involved….

- 17 yr + 8 mos “mature minor”, devout JW, admitted to DCH with newly diagnosed Acute Lymphoblastic Leukemia (ALL)—estimated complete remission/ultimate cure rate ~ 75%
  ⇒ needed leukemic induction therapy
- Hb 5.2 (Hct 14.7) on admission
- Reticulocytes: Relative 1.9% (0.5-1.5)
  Absolute 28.0 (10.0-90.0)

  **Induction therapy begun**
  **Treated with:**
  - High dose EPO (300 U/kg/d), Fe++, folate
  - All “matters of conscience” acceptable
⇒ Parents refused to sign portion of OHSU Refusal form recognizing MDs obligation to transfuse to prevent “loss of life or serious irreversible harm”—patient concurred

- Counts ↓↓ ↓↓: Induction ~day 7 ~day 14
  - WBC 2.4 → 0.9 → 0.3
  - Hct 14.7 → 10.7 → 7.9
  - Hb 5.2 → 3.7 → 2.8
  - Plates 49 → 31 → 75

⇒ At Hb 2.8: HR ~120, good O2 sat’s, afebrile BUT...
  - Clinicians very concerned re: potential septic morbidity given WBC < 0.5 for days
  - Patient and family continued to refuse transfusion

⇒ Court Order obtained mandating transfusion; Patient and family unhappy but accepting and 2 ‘U’ RBCs given:

<table>
<thead>
<tr>
<th>Counts:</th>
<th>Pre-txn</th>
<th>Post-txn</th>
<th>Post-txn</th>
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<tbody>
<tr>
<td>Hct</td>
<td>7.9</td>
<td>19.2</td>
<td>23.6</td>
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<tr>
<td>Hb</td>
<td>2.8</td>
<td>6.9</td>
<td>7.6</td>
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⇒ He turned 18 2 months later and has since completed the remainder of his leukemic therapy

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<tr>
<th>Post-Op Hb</th>
<th>1std in hospital mortality</th>
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<td>3.1-4.0</td>
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<td>62.5 %</td>
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<td>4.4-5.0</td>
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<td>7.1-8.0</td>
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<td>9.8 %</td>
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Case # 7: 2005, OSHU: rVIIa, huge doses of EPO and a good surgeon save the day....

- 44 yo JW man in bad T-bone MV A and brought to OHSU:
  - Shock (bp 50)
  - R tibial plateau/fibular fractures, open
  - R posterior leg superficial burn
  - R femur fracture, open
  - R superior/inferior pubic rami fractures
  - Hb 12.2, Hct 35.5→blood spurting from leg

⇒ Treated immediately with:
  - OR and external fixation
  - rVIIa 90 mcgm/kg

⇒ Ultra high dose EPO (800 U/kg/d) begun; IV Fe++, folate, B-12, vit K....

⇒ Serial Hcts:
  - 35.5 → 17.9 → 13 → 11 → 10
  - Hct 8.0 (Hb 2.8)

- CK peak 11,002 (POD 2)
- Persistently tachycardic, 120-140
- FIO2: 0.35; O2 sat’ns > 95%
- Dressings removed POD 5

⇒ Conversion of R posterior leg burn to full-thickness
⇒ Major septic risk
⇒ Needed debridement / amputation
Post-Op Hb 30d in hospital mortality

<table>
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<tr>
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⇒ We desperately tried to get PolyHeme for him ASAP on 3 different occasions, but the Compassionate Release Program had been “suspended” for ~ 2 years (ironically) due to the Trauma Trial…

Well, the future wasn’t accessible to us at this point so in Desperation we did a tourniquet amputation using dry ice….

Survived, improved, had 3 minor debridements of stump since….

He had a long, long way still to go to get him home and functioning again……

Postscript: I last saw him for L hip surgery Oct 2007—additional revision planned but doing OK!

Supporting Erythropoiesis and Avoiding Bleeding in Thrombocytopenia in Jehovah’s Witnesses Undergoing Aggressive Chemotherapy: OHSU approach

2009: 2 leukemias and 1 medulloblastoma undergoing intensive chemo (+/- RT):

- 26 yo woman pre-T ALL on CALGB 10403-00 from June – Oct 09
- 66 yo woman M3 AML on ACTRA and chemo from Dec 09 – present
- 14 yo boy with aggressive medulloblastoma on RT and ACN0332 high dose chemo from June 09 - present
Basic approach: Hemoglobin, Platelets, Coagulation:
• High dose erthropoietin 40,000 units (400-600 U/kg) SQ MWF (or darbepoietin 200mcgm SQ twice weekly (q M, Th))
• Baseline course of Venofex at full marrow repletion doses: 200 mg IV/d x 5d (or 500 mg IV/d x 2 d)
• Folate 1 mg PO/IV q d
• Cyanocobalamin (Vit B12): one spray (500 mcgm) one nostril Q wk
• Pediatric tubes for all blood draws
• Vit K 1 mg PO/IV q Mon, Thurs
• For platelets < 30K: prophylactic infusion tranexamic acid 2000 mg in 500 ml of D5W q 8 h (Avvisati et al 1989—double-blind trial 12 patients with APL—significantly decreased bleeding; no thromboembolic complications)
• For platelets < 10K: prophylactic administration of 1 x 5 pool cryoprecipitate daily
• For ALL on asparaginase: Monitor antithrombin—AT concentrates to keep AT > 0.8

Results: Hemoglobin, Platelets, Coagulation:
26 yo woman pre-T ALL on CALGB 10403-00 from June-Oct 09
• Initial Hb 9.4 g/dl at start of chemo—was in 8.8 – 12.8 range from early June to early Sept when came in with major bleed and platelet count of 5K—day 21 marrow had showed erythroid hyperplasia; with bleed Hb fell to 4 then to a low of 2.1 with ongoing chemo-induced pancytopenia
• Hemostatic despite platelets < 5-10 x one month—blood blisters in mouth disappeared as did petechiae on legs and elsewhere; no excess bleeding from marrow biopsy
• INR 1.73 was corrected to 1.06 with Vit K prior to Ommaya reservoir placement
• Fibrinogen nadired at 60 and AT at 0.69—received cryoppt and AT concentrates with good effect
• Minimum Hb 2.1—supported with HBOC from S Africa
• Died of sepsis on Oct 2—at Hb 3.5 on HBOC PaO2 was in 300’s on O2 by mask
  unfortunately HCO3 was 12 with lactate 24 and pH 6.9

Results: Hemoglobin, Platelets, Coagulation:
66 yo woman M3 AML on ACTRA and chemo from Dec 09 – present
• Initial Hb 8.3 g/dl at start of chemo—nadired at 6.8 in mid-Dec 09 and was 11.8 on Jan 14th
• Platelets initially 18 and nadired at 13. No significant petechiae or bruising.
• In probable mild initial DIC: INR 1.29, PTT 25.7, fibrinogen 248 with mod elevated d-dimer (~2) on presentation; fibrinogen nadired at 147 with other coags well maintained.

Results: Hemoglobin, Platelets, Coagulation:
14 yo boy with aggressive medulloblastoma on RT and ACNS0332 high dose chemo from June 09 – present
• Initial Hb 14.7 g/dl and fell to 10.4 post neurosurgery; received RT then high intensity chemo—Hb nadired at 5.5 in early Dec and was 5.7 on Jan 20th
• On 4 of 6 cycles of high dose chemo. Platelets initially 174 at start of chemo and have nadired:
  • at 3-6K x 3 days in early Oct;
  • at 1-7K x 5 days in early Nov;
  • at 9 K x 2d in early Dec, then
  • at 1-5 x 4d in mid-Jan. Platelet count of 1 was accompanied by nose-bleed and oral petechiae—patient received 1 unit apheresis platelets Jan 15 as counts were still falling (WBC 0.1).
  Family accepting we had truly intervened only to prevent “serious or irreversible harm or disability.”

Summary: Jehovah’s Witness Patients:
• Transfusion alternatives and “fractions” can be life-saving in Witness patients
• An integrated approach is best
• Don’t be afraid to get treatment advice elsewhere and ask for help
• Treatment of Witnesses poses many challenges BUT can provide unique opportunities both for learning and for the exercise of compassion