Defining the clinical need for Rare Blood

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Issues Addressed

- Defining

  Rare Blood (ISBT WP on Rare Donors):

  Frequency is less than 1:1000 population

  - Antibody against a High Frequency (HF) antigen
  - Presence of multiple antibodies

  How do I recommend establishing the Clinical Need:

  - When & whom to transfuse
  - When blood is not available

- Not addressed

  - Perinatal & Neonatal Transfusion

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When and Whom to Transfuse

- Aim: Increase oxygen tissue delivery
  Lack of “gold standard” measurement
- Benefits, adverse effects and risks vs avoiding transfusion.
- Guidelines using Hemoglobin (Hb) levels referred as "Hb triggers" / "Hb thresholds“.
- Clinical factors:
  Symptoms related to anemia
  Hemodynamic stability
  Co morbidities
- Patients' beliefs and expectations
- Blood availability
- Other medico legal, social and cultural aspects
- CLINICAL DECISION

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RBC Indicated Immediately

- Unstable bleeding patient
  - Trauma, Obstetrics, GI bleeding, Surgery
- Symptomatic anemic patient
  - Various medical & surgical conditions
- Exchange Transfusion
  - Symptomatic patient (SCD)
- Intra uterine Transfusion
  - Fetal anemia, hydrops

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RBC Needed

- Stable patient
  - Bleeding
  - Anemia: variable levels & symptoms
    - underlying medical & surgical conditions
  - Adverse effects prevention protocols (SCD)
  - Elective surgery
  - Vaginal or Cesarean section delivery
  - Diagnostic procedure
  - Other

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Clinical Practice Guideline on RBC Transfusion

- Hg < 7 g/dL
  Adult & pediatric hemodynamically stable ICU
  Adult acute upper GI bleeding*
  excluding massive bleeding

- Hg < 8 g/dL
  Symptomatic (chest pain, orthostatic hypotension, fluid unresponsive tachycardia, CHF), post operative, preexisting cardiovascular disease (CVD)

- ? hemodynamically stable pt's acute coronary syndrome

Carson JL, Grossman BJ, Kleinman S, *et al: Ann Intern Med* 2012; 157:49-58
* Villanueva C, Colomo A, Bosch A, *et al*,: *N Engl J Med*. 2013 ;368 (1):11-21.

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Less is More ?

- Assumptions and transfusion practices challenged.
- Hemovigilance systems– adverse effects.
- Randomized controlled trials (RCT)
  Hgb triggers in different clinical scenarios.

- Is less blood more beneficial?

- HOT TOPIC – Blood management

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Less is More ?

- Anemia in acute myocardial infarction (MI) associated with worse prognosis.
- Meta analysis 10 studies (1 small RCT) 203,665 Patients (Pts), in anemic pt's with MI.
- Increased all-cause mortality associated with blood Tx vs no blood Tx during MI (18.2% vs 10.2%) (risk ratio, 2.91)
- Weighted absolute risk increase - 12%.
- Multivariate meta regression - blood Tx associated with higher risk for mortality independent:
  Hgb - Baseline, nadir, during the hospital stay.
- Blood Tx significantly associated with a higher risk for subsequent MI (risk ratio, 2.04).

Chatteriee A. et al: JAMA Intern Med. 2013;173(2):132-139.

Less is More ?

- **Clinical Question:** Is a lower (7-10 g/dL) vs higher hemoglobin threshold best for minimizing RBC use and adverse clinical outcomes in anemic patients in critical care and acute care settings?

- 19 RCT, including 6264 patients

- **Bottom Line:** Compared with higher hemoglobin thresholds, a hemoglobin threshold of 7 or 8 g/dL is associated with fewer RBC's transfused without adverse associations: mortality, cardiac morbidity, functional recovery, or length of hospital stay.
  No differences in all-cause mortality at 14 /60-day FU or in intensive care unit (ICU) mortality.

Carson JL , Carless PA,. He bert PC: JAMA, 2013 (309) 1; 83-84

FOCUS Trial

- 2016 pt's >50 years (mean 81), history of or risk factors for cardiovascular disease undergoing hip surgery
- Liberal Tx – Hgb < 10 g/dL
- Restrictive Tx - symptoms of anemia, or physician discretion Hgb < 8 g/dL).
- Primary outcome: No difference in death or an inability to walk at 60-day follow-up.
- Secondary outcomes: No difference in hospital MI, death rates at 60 days, other complications.
- Reasonable: withhold transfusion in pt's undergone surgery
  - Absence of symptoms of anemia,
  - Hgb <8 g/dL,
  - Elderly underlying cardiovascular disease or risk factors

Carson JL, Terrin ML, Noveck H et al: NEJM 2011; 365 (26):2453-62

Transfusion Support and Rare Blood

- Rare RBC's supplied by Rare Donor Programs (RDP): fresh or frozen units
- Family members - major resource
- Scarce publications on the transfusion support of patients with antibodies to high frequency (HF) RBC antigens

*

	2002	2003	2004 (8 months)
Requests completely filled by phone/fax	510 (88%)	574 (86%)	369 (84%)
Requests completely or partially unfilled	70 (12%)	96 (14%)	72 (16%)

* Flickinger C, Petrone T, Church A: Review: American Rare Donor Program *Immunohematology* 2004; **20** (4):239-244.

Rare Blood is not Always Available

Table 3. Completely or partially unfilled requests by phenotype

Requests	2002	2003	2004 (8 months)
Total requests completely or partially unfilled	70	96	72
U–*	14 (20%)	20 (21%)	12 (17%)
hr^S–*/hr^B–*	7 (10%)	13 (14%)	8 (11%)
Di(b–)*	3 (4%)	13 (14%)	5 (7%)
Vel–*	5 (7%)	3 (3%)	3 (4%)
Kp(b–)*	4 (6%)	2 (2%)	2 (3%)
Js(b–)*	0	3 (3%)	5 (7%)
Yt(a–)*	4 (6%)	1 (1%)	2 (3%)

*Antigen alone or in combination with other common antigens

Flickinger C, Petrone T, Church A: Review: American Rare Donor Program *Immunohematology* 2004; **20** (4):239-244.

Antibodies to HF Antigens may Decrease the Quality of Transfusion Support

- Retrospective analysis - 52 hospitalized pt's with antibodies to HF antigens.
- Admitted 5.2000 -12. 2001, Germany, Austria & Switzerland.
- 133 compatible RBCs supplied for 26 pt's.
- 104 antigen negative RBCs transfused to 22 pt's.
- Deviation from the standard transfusion policy occurred in 23/56 (41%).

Seltsam A, Wagner FF, Salama A, Flegel WA: *Transfusion* 2003;**43** (11):1563-1566

Antibodies to HF Antigens May Decrease the Quality of Transfusion Support

TABLE 1. Deviations from standard transfusion policy in patients with antibodies to high-frequency antigens

Type of deviation from protocol	Number of episodes				Antibodies involved*
	Germany	Switzerland	Austria	Total	
No compatible blood as backup†					
Surgery	5	1	0	6	anti-Kp^b (n = 2), anti-Yt^a (n = 2) anti-Lu^b, anti-AnWj
Diagnostic procedure	1	0	1	2	anti-LW^a, anti-Fy3
Vaginal delivery	2	0	0	2	anti-Kp^b, anti-Vel
Transfusion of antigen-positive units					
Emergency transfusion‡	3	0	0	3	anti-Vel (n = 2), anti-Lu^b
Elective transfusion	3	2	0	5	anti-Yt^a (n = 3), anti-Kp^b, anti-Lu^b
Transfusions cancelled or limited	4	0	0	4	anti-Vel (n = 2), anti-Co^a (n = 2)
Diagnostic procedure cancelled	0	0	1	1	anti-Lu8
Total	18	3	2	23	

* n = 1 unless otherwise indicated.
† No transfusions performed.
‡ Lack of time to obtain compatible units made deviation inevitable.

Seltsam A, Wagner FF, Salama A, Flegel WA: *Transfusion* 2003;**43** (11):1563-1566

Antibodies to HF antigens may decrease the quality of transfusion support

- 8 episodes of antigen-incompatible transfusion.
  5/8 delayed Hemolytic Transfusion Reaction (DHTR)
  all recovered with no negative effect 2nd hemolysis.

- Transfusion support unsatisfactory ~ 1/3 hospitalized pt's with antibodies to HF antigens.

- Maintaining a rapidly accessible stock of four types rare blood units would ensure adequate transfusion support for most of these patients.

Seltsam A, Wagner FF, Salama A, Flegel WA: *Transfusion* 2003;**43** (11):1563-1566

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Rare yet Different

- HF antibodies different clinical significance
  (anti-PP1Pk vs. anti-Lu^b)
  Test antibody subtype and titer.

- Previous transfusion history, pregnancies.

- Clinical significance is variable/unknown
  In vitro: Monocyte Monolayer Assay (MMA)
  (> 5% capable of shortening RBC survival)
  Chemiluminesence (CLT) opsonic index- (> 1.6)

  In vivo: Cr^{51} or In^{111} survival
  * Results may be discordant.

- "Biological cross match"

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Massive Postpartum Transfusion of Jr(a+) RBC's in the Presence of anti-Jr^a.

- 31 year old woman, anti-Jr^a
- Life-threatening postpartum disseminated intravascular coagulopathy (DIC)
- Emergency Tx - 15 units Jr^a untested RBCs
- No clinical or laboratory evidence of acute hemolysis
- Pretransfusion anti-Jr^a : Titer 1:4
  MMA reactivity 68.5%
- Day 10 post Tx: anti-Jr^a : Titer 1:64
  MMA reactivity 72.5%
  Laboratory evidence Mild DHTR

Yuan S, Armour R, Reid A et al: Immunohematology 2005; 21(3):97-101

Management of Emergency Cardiac Surgery in a Patient with alloanti-Ge2.

- Untransfused 75-year-old man (blood group O) anti–Ge2 required emergency cardiac surgery.
- Cross-match compatible blood was not available.
- A 'biological cross-match' sequential transfusion of 20, 50 mL ,entire unit of incompatible RBCs before surgery.
- No clinical adverse effects observed.

- Two incompatible RBCs transfused during surgery.
- No clinical & laboratory evidence of major intra - or extravascular haemolysis.

- Particular anti-Ge2 was not clinically significant.

Selleng S, Selleng K, Zawadzinski C: Transfus Med. 2009 Feb;19(1):50-2

Anti- Yt^a

- Variable clinical significance.

- Most frequent HF antibody seen in Israel.
- Liquid units often available & frozen inventory.

- Yt(a-) units supplied if antibody subtype IgG1/3, high titer, increase in titer, physician demand.

- Patients transfused with Yt(a+) RBC's acute bleeding, surgical procedures.

Antibody Characteristics Change

- Patient with anti-Kp^b (1)

  CLT opsonic index 0.8 (normal up to 1.6)
  Elective procedure, 1 incompatible RBC's
  14 days post transfusion – CLT opsonic index 1.1
  ^{51}Cr survival 24.3% 60 minutes, 2% 24 hours.

- Patients with anti-Yt^a (2) & our unpublished data

  Antibody characteristics may change
  Not necessarily in parallel with Ab Titer.

- No predictors for change in clinical significance.

1. Mazzara R et al: Transfusion 2001 41 (5): 611-4
2. AuBuchon JP et al: Vox Sang 1988;55:171–5.

Liver Transplantation & "Regular" Alloantibodies

- 13.7% of adults, 6.3% of children had significant RBC alloantibodies.
- 17 pt's had 28 significant RBC antibodies:
  15 Rh, 8 Kell, 3 Kidd (Jk), 2 Duffy (Fy).

- Received ≥8 units of antigen-negative RBCs before untyped incompatible blood given for massive bleeding.

- Of 7 patients received >2 incompatible units – Hemolysis occurred in 2 (1 with underlying PNH).

- Switch to compatible blood performed once bleeding has stopped. ? WHEN TO SWITCH

Ramsey G, Cornell FW, Hahn LF, et al. Transplant Proc 1989; 21:3531.

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When Blood is (not) Available

- **Pharmacological:**

  Crystalloid infusions
  Iron supplementation
  Erythropoiesis stimulating agents
  Antifibrinolytics (Tranexamic acid, Aminocaproic acid).
  ra Factor VII.

- **Surgical**:

  Minimize iatrogenic blood loss
  Normovolemic hemodilution
  Intraoperative blood salvage
  Careful surgical hemostasis
  Fibrin glues & hemostatic bandages.

- **Investigational – not routinely available**:

  Perfluorocarbon
  Polymerized hemoglobin solutions

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Personalized Blood Management: Patients with Antibodies to HF Antigens

- Balance the risks of withholding transfusion with the anticipated chance of significant hemolysis after transfusion of incompatible RBCs.
- Need for close communication & cooperation transfusion services, clinicians and patients.

- Different medico legal, public & cultural aspects.

- Hgb < 8 g/Dl
  Unstable, symptomatic.
- Hgb < 6 - 7 g/dL
  Hemodynamically stable, asymptomic, no comorbidities.

- **Integrative clinical decision**

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Hope for the Future

- Ex vivo expansion of RBC's
  - Peripheral blood
  - Cord blood
  - Induced pluripotent stem cells
  - Human embryonic stem cell lines

- Alternative transfusion products could become a significant source for maintaining and supporting individuals with rare blood & alloimmunized patients.

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Summary

- Scarce documented data on transfusion support of pt's with antibodies to HF antigens.
- Less (blood) is often more.
- Same antibodies – Different outcome
- No easily accessible & reliable diagnostic aid for clinical significance of antibodies to RBC .
- ESSENTIAL: Communication & Clinical judgment
  Personalized blood management
- Need for data: Outcome of transfusion of incompatible RBC's in Pt's with rare blood types and antibodies.
  * ISBT W/P Rare Donors centralized web database

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