TACO and the Indications for RBC Transfusion

Jim Perkins, MD
Director, Blood Banks
NorthShore University HealthSystem
Risks vs Benefits in Transfusion

- Rejection
  - Hemolytic reactions
  - Febrile reactions
  - GVHD, TRALI
- Allergic reactions
- Infection (HIV, HCV…)
- Volume overload (TACO)
- Toxic reactions

- Red Blood Cells
- Platelets
- Coagulation Factors
- Leukocytes
- Immunoprophylaxis
  - (RhIG)
Therapeutic vs. Prophylactic Indications for Transfusion

**Therapeutic Indications**
- risk of transfusion vs. benefit of transfusion
- benefit is generally observable
  - reversal of shock, stopping bleeding, symptoms of anemia....

**Prophylactic Indications**
- risk of transfusion vs. risk of no transfusion
- benefit not observable
- requires a controlled trial to demonstrate
Prophylactic Transfusion Equals Transfusion by the Numbers

BUT:

- Do the numbers truly predict a risk?
- Can the numbers be corrected?
- Does correction of the numbers reduce the risk?
TACO = Transfusion-Associated Circulatory Overload

Volume of transfusion

±

- Decreased functional capacity of the heart
- Increased intravascular volume
  - compensation for chronic anemia
  - other iatrogenic volume overload

↓

Pumping capacity of heart exceeded

↓

Pulmonary congestion and edema
  - shortness of breath
  - agitation
  - cough
  - headache
Note...

Concern typically for non-bleeding patients,

but... pulmonary problems frequently complicate resuscitation.
**TRALI**

Pathogenesis:
- Donor anti-WBC Ab (or other BRM)
  - WBCs lysed/activated
  - Capillary leak syndrome (ARDS)

Clinical features:
- Acute onset (6 hrs)
- Dyspnea, ↓pO₂
- Pulmonary edema
- Fever
- ↓BP (or ↑)
- +/- ↓WBC
- Any component but rate FFP>RBCs
70 y.o. woman, 5’4”, 110 # (TBV ~ 3370mL):
- Pancreatic cancer 2 yrs S/P Whipple
- Admitted for angioplasty for ischemic foot pain due to PVD
- Severe Aortic stenosis
- Hgb 7.6 → “Transfuse 2 units of RBCs”
- Anxious and dyspneic after ~240 mL (7% of TBV) over 1:45 → SO₂ = 36-40
- BNP → 1180 → 1879 (next day)

Baseline

10 minutes after transfusion: TACO

Transferred to ICU
76 y.o. man, 5’6”, 155 # (TBV = 4600):
• Weakness and iron deficiency anemia (hgb 7.7 @ PCP office)
• H/o CAD, S/P CABG 20 yrs ago, AMI 2 yrs ago
• VS: BP 126/61, HR 61 (paced)
• Hgb 7.4 → “Transfuse 2 units of RBCs” (785 mL = 17% of TBV)
• 4 hrs post-transfusion: SO₂ 88%, BNP 3570 the next day
Randomly assigned ICU pts.
- Restrictive (hgb < 7.0, target 7-9)
- Liberal (hgb < 10.0, target 10-11)
- 1° outcome; 30 day mortality

Younger & less-sick patients *did better with less blood*

Hebert, NEJM, 1999
Several outcomes were improved in the restrictive group

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Hebert, NEJM, 1999
85 y.o. man, 5’10”, 171 # (TBV = 5160):
- Lymphoma S/P stem cell transplant, now with myelodysplastic syndrome
- Admitted with anemia, hgb 6.8
- Troponin = 2.58 (nml < 0.06) → “NSTEMI”
- BNP = 444
- “Transfuse 2 units of RBCs” → (523 mL ~ 10% of TBV over 6 h, 20 min)
Immediately post-transfusion: **TACO!**

Moved to telemetry

Died 2 weeks later of multiple complications
86 y.o. woman, 5’, 108 #, (TBV 3050 ML):
• Rectal bleeding, hypotension (107/68), and anemia (hgb 7.5)
• H/o severe 3-vessel CAD, IDDM, and PUD
• “Transfuse 2 units RBCs”

Day prior to transfusion

Post-transfusion: TACO!

Died with pulmonary edema 1 ½ hrs post-tx; asked a cardiologist to review
86 y.o. woman, 5’, 108 # (TBV 3050 ML):
• Received 590 mL of RBCs (20% of her predicted blood volume)
• Developed CHF and probably an MI.

0649:
• L chest pain, 8/10

After 1st unit:
• “No reaction noted”

Start of 2nd:
• “Chest discomfort slightly better but slightly restless…”

Ekg, 0942:
• New LBBB

• “Approx 10:00 sat’s started decreasing, very restless and increasingly cool and clammy, rapid response called.…”

BNP: 274 → 415
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Hebert, NEJM, 1999
53 y.o. woman, 5’6”, 153 # (TBV = 4165):
- Bacterial meningitis 2° csf leak 16 days post lumbar fusion
- H/o ↑ BP & asthma; normal stress echo in ’07 (LVH)

- Debridement ➔ Hgb 7.3 ➔ "Transfuse 2 units of RBCs"

- 3 hours later: arrested
53 y.o. woman, 5’6”, 153 # (TBV = 4165):
• 756 mL RBCs (18% of TBV) over 4½ hrs (ordered over 3 hrs each)

Pre-transfusion: 10:00

Post-transfusion: 16:03

Patient arrested ➔ cath lab
• “Taku-tsubo cardiomyopathy”
• No significant coronary stenosis
• Intra-aortic balloon x 21 hrs
“Taku-tsubo” = traditional Japanese octopus trap

“Taku-tsubo cardiomyopathy” or “broken heart syndrome” = concentric hypokinesis (hypokinesis graded “1” to “3”)
79 y.o. man, 5’5”, 163# (TBV ~ 4740mL):
• BRBPR & hypotension (‘60/40’ in ambulance)
• H/o CAD s/p CABG, MR & TR, CHF & atrial flutter on coumadin, INR >9
• Resuscitated with 3L NS, 3 U RBCs & 2 U FFP ➔ Hgb 9.9, B.P. 120/70
• To IR for possible embolization ➔ SBP falling to “70’s” ➔
  4th U RBC’s (425 mL = 9% of TBV) given over 30’ ➔ respiratory failure

2 weeks before admission

Survived and went home
Randomly assigned pts. with UGI bleeding to:
- Restrictive (hgb < 7, 7-9) – 49% got RBCs
- Liberal (hgb < 9, 9-11) – 86% got RBCs

Primary outcome:
6 week survival was BETTER with less blood

From: Villanueva, NEJM, 2013
## Secondary outcomes

Villanueva, NEJM, 2013

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<td><strong>Rebleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10%</td>
<td>16%*</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>12%</td>
<td>22%*</td>
</tr>
<tr>
<td>Varices</td>
<td>11%</td>
<td>22%*</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>40%</td>
<td>48%*</td>
</tr>
<tr>
<td>TACO</td>
<td>&lt;1%</td>
<td>4%*</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>ACS</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1%</td>
<td>1%</td>
</tr>
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62 y.o. woman, 5’2”, 123# (TBV ~ 3400mL):
- Cervical cancer s/p chemo/radiation & ureteral stents
- Urosepsis & hematuria
- Hgb 8.7, BP 80/40 ➔ Resuscitated with 3L NS ➔ transient response ➔ Hgb 6.2 ➔ “Transfuse 2 units of RBCs”
- 1st unit given over 1 hour, 2nd over 1½ hr
- 583 mL, 17% of TBV

Morning of admission

Near end of 2nd unit

Did not require intubation
Risk Factors and Outcomes in TACO

- **Real time EHR surveillance**
  - Algorithm: ↓pO₂ + transfusion → Pulmonary edema on CXR?

- **Case control study; 83 cases/163 controls**
    - (i.e. pulmonary complications were hard to categorize)

- **Significant risk factors: odds ratios (cases vs. controls)**
  - Hemorrhagic shock, OR = 113 (14.1 – 903)
  - Chronic renal failure OR = 27 (5.2 – 14.3)
  - CHF OR = 6.6 (2.1 – 21)
  - + Fluid balance (per L) OR = 9.4 (3.1 – 28)
  - # Units (per unit) OR = 1.11 (1.01 – 1.22)

- **ICU-LOS increased from 2.6 D to 7 D**

  Murphy, Am J Med, 2013
97 y.o. man, 5’8”, 160# (TBV ~ 4835mL):
- CC: worsening dyspnea, peripheral edema, fall.
- PMHx: CAD, severe aortic stenosis, CHF
- Hgb 8.5, BP 94/52, PR 50

"Transfuse 1 unit of RBCs"

- Restlessness, cough, dyspnea, hypoxemia
- (SO2 93% ➔ 77% on RA)
97 y.o. man, 5’8”, 160# (TBV ~ 4835mL):

- Restlessness, cough, dyspnea, hypoxemia (SO₂ 93% → 77% on RA)
- Unit stopped after 2hrs, 15’
- 258 mL, 5% of TBV

Died of respiratory failure 18 hrs after transfusion
I hear you say, “But Jim, 258 mL is nothing! We give a 500 mL saline bolus at the drop of a hat.” And I say, “Blood is thicker than water.”

I hear you say, “But Jim, these patients all had lots of reasons for pulmonary edema.” And I say, “Yeah, but why is it so often happening right after a transfusion?”
Recognition & reporting of TACO fatalities is poor

Transfusion-related fatalities reported to the FDA
Transfusion Associated Circulatory Overload (TACO): Definition

- Volume infusion that cannot be effectively processed by the recipient either
  - due to high rates and volumes of infusion or
  - underlying cardiac or pulmonary pathology.
TACO Case Definition: Signs and Symptoms

- **Definitive:** Characterized by the onset or exacerbation of ≥3 of the following within 6 hours of transfusion:
  - Acute respiratory distress (dyspnea, orthopnea, cough)
  - Evidence of positive fluid balance
  - Elevated BNP (Brain Natriuretic Peptide)
  - Radiographic evidence of pulmonary edema
  - Evidence of left heart failure
  - Elevated CVP (Central venous pressure)

- **Probable:** N/A

- **Possible:** N/A
TACO: Relationship to Transfusion - **Imputability**

- **Definite:** Meets definitive protocol criterion and no other cause of volume overload.
- **Probable:** Judgment call by attending physician. Patients received other fluids, and transfusion is likely contributory to volume overload.
- **Possible:** For patients with pre-existing cardiac insufficiency, imputability should not be classified higher than “possible.”
Randomly assigned ICU pts.
- Restrictive (hgb <7.0, target 7-9)
- Liberal (hgb <10.0, target 10-11)
- 1º outcome; 30 day mortality

*But what about patients with an acute ischemic syndrome? (MI, accel. angina)*

Hebert, NEJM, 1999
RBC Transfusion in CAD

Re-analyzed outcomes of 357 pts with CVD:

*Restrictive was equivalent to liberal*

- 30-day mortality same
- Multi-organ dysfunction same
- Complications (shock, MI, arrest) same
  - Exception: acute pulmonary edema worse with liberal (9 vs 18%)

Re-analyzed 257 pts with coronary ischemia:

*Trend to better survival in liberal group*

- 5% increased 30 day mortality ($p=.38$) in restrictive group
- MI rate same

Authors concerned for restrictive strategy in patients with acute MI and unstable ischemia

Hebert, Crit Care Med, 2001
So what is the appropriate trigger in Acute Ischemic Syndromes?

- 24112 subjects in 3 studies of intervention in AIS
- 10% transfused
  - Transfused pts were older with more co-morbid disease.

- Transfusion → higher unadjusted rate of death/MI
  - (29% vs 10%)

- Effect remained with adjustment for other predictors

- Below hct = 25, transf. NOT assoc. with death/MI
- Above hct = 25, transfusion WAS assoc. with death/MI

Rao, JAMA, 2004
Is the survival improvement with restrictive transfusion plausible?

Villanueva, NEJM, 2013

Hebert, NEJM, 1999
Do other studies show a deleterious effect of transfusion?

- Review of 45 studies using multivariate analysis to study the relation of transfusion to mortality, infection, ARDS, and MODS in various patient populations.

- In 42/45 studies the RBC transfusion risks > benefit.
  - Only 1 study showed benefits > risks: elderly patients with an acute MI and an ICU admission hematocrit <30% (Wu, 2001)
  - 17/18 studies: RBC transfusion independently predicted death
  - 22/22 studies: RBC transfusion independently correlated with infection
  - 6/6 studies: RBC transfusion was independently correlated with ARDS

Transfusion and nosocomial infection

Prospective, observational, cohort study:
- ICU admissions at a single institution
- Correlated development of nosocomial infections (NI) with RBC transfusion.
- 2,085 patients
  » 21.5% received RBC transfusion
  » Average of 3.7 units

Results:
- Post-transfusion NI = 14.3% vs. non-transfused NI rate = 5.8%
- Dose dependent: Each unit of RBCs increased NI risk by 9.7%

Conclusion:
- RBC transfusion is an independent risk factor for nosocomial infection
Do other randomized trials of a restrictive vs. liberal transfusion trigger agree?

- 17 trials: 8 surgery, 5 blood loss/trauma, 3 ICU, 1 leuk.
- “Restrictive” group variably defined: [hgb] ≤ 7 to 9 g/dL
- 8 trials with > 100 pts.
- 5 trials didn’t show ↓ blood use (trial goal not met)
- Risk ratios show equivalence or favor restrictive
  - 30-day mortality: RR = 0.83 (0.66 -- 1.05)
  - Cardiac events: RR = 0.76 (0.57 -- 1.00)
    » MI, arrythmia, pulmonary edema, angina
  - Transfusion: RR = 0.63 (0.52 -- 0.74)

Carson, AABB, 2010
FOCUS trial

• Pts >50 years old having hip fracture repair
  – History or risk factors for cardio-vascular disease
  – [hgb] < 10 g/dL

• Post-op randomized to:
  – Liberal: [hgb] < 10 g/dL
  – Restrictive: [hgb] < 8 g/dL or “anemia symptoms”

• 1° outcomes;
  – Death
  – Inability to walk across the room 60 D post-op.

• 2016 pts randomized:
  – Average age 81.3, 3F:1M, 40% had CAD
  – Pre-tx hgb 9.2 vs. 7.9
  – Median # RBCs 2 vs. 0; % transfused = 97% vs 41%

• Groups identical for 1° outcome (35%)

  Carson, NEJM 2011
Effect of a restrictive transfusion strategy on transfusion-attributable severe acute complications and costs in the US ICUs: a model simulation
Marya D Zilberberg*1 and Andrew F Shorr2

Address: 1University of Massachusetts, 715 North Pleasant Street, Amherst, MA, 01003, USA and 2Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010, USA
Email: Marya D Zilberberg* - MZilberb@schoolph.umass.edu; Andrew F Shorr - AFShorr@DNAMail.com
* Corresponding author

Could avoid 40,000 “severe acute complications” and save $1 billion per year!
1. Transfusion with RBCs should be avoided if possible.

2. Critical care pts <60yo without AIS have better outcomes when transfusion is restricted to those with Hb <7 g/dL. (Level I)

3. Elderly postoperative patients with a history of heart disease can avoid transfusion if their Hb is >8 g/dL. (Level I)

4. Patients with upper GI bleeding have better outcomes when transfusion is restricted to those with Hb <7 g/dL. (Level I)
   - The survival advantage is particularly marked in patients with Child-Pugh Level A and B cirrhosis.
   - There is a trend to improved survival among patients with peptic ulcer disease.

5. Anemia with Hb >7 may be tolerated by hemodynamically stable patients without CAD. In particular candidates for avoiding transfusion include patients whose anemia is treatable with iron or other hematinics. (Level I)
6. Patients with AIS (MI, unstable angina) may benefit from transfusion if their HB < 9 g/dL and are likely to benefit if Hb < 8 g/dL. (Level II)

7. Transfusion to [hgb] > 11 g/dL does not augment oxygen availability and is contraindicated in virtually all patients. (Level II)

8. In stable patients back-to-back RBC transfusion should be avoided. (Level IV)
   - Reevaluation before a 2nd unit is encouraged (includes clinical and laboratory evaluation).
   - Patients at high risk for TACO include those with renal failure, CHF, and severe valvular stenoses.
   - For patients at risk for TACO consideration should be given to transfusion of RBCs as half-unit aliquots (each given over 3½ hours).
So what should WE do?

- Split up “2 unit transfusions” in non-bleeding patients
  - “Single unit transfusion” is not a bad thing
  - Many 2nd units would be cancelled if we looked at a CBC after the first
  - Multiple guidelines endorse ‘1-at-a-time’ RBCs
Why give 2, when 1 will do?

Complications associated with transfusions are dose-dependent.

Impact of Blood Transfusion on Surgical Outcomes: NSQIP Database

1. Bernaud et al, JAmCollSurg 2006;203
2. Ferrare et al, Arch Surg. 2012;147(1)

March 4-10, 2012
Patient Safety Awareness Week
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- **Transfuse split units in patients with severe CHF**
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- **Transfuse split units in patients with severe CHF**

- **Don’t transfuse patients who don’t need it!**
Blood is not a ‘life force’

Intervene based on evidence!
Would you eat hamburger that had been in your refrigerator for 42 days?

Only to save your life!