Objectives

At the conclusion of this activity participants will be able to:

• Describe the deliberative process involved in determining how ... and whether ... to transfuse an ultra-severely anemic patient (e.g., hemoglobin < 5 g/dL) who has a significant red cell incompatibility;
• Summarize the most important features involved in preventing, diagnosing, and managing the acute transfusion reactions associated with severe respiratory complications;
• Define the value of clinical-laboratory correlation when determining the cause of: (a) neonatal thrombocytopenia, and (b) unexplained and persistent/chronic anemia; AND ... • Review the most up-to-date indications for the transfusion of: (a) red blood cells, (b) platelets, (c) plasma, and (d) cryoprecipitate.

Outline

• Warm-up: “A-B-O is Crucial Ev’ry Morning”
• Some Case Studies
  1. Severe anemia meets vexing red cell incompatibility
  2. One very bad unit of plasma (+ acute respiratory reactions)
  3. It looks like FNAIT (but where’s the anti-HPA-1a?)
• Interlude: A few lessons I’ve learned over the years
• More Case Studies
  4. Heavy blood use/no excuse
  5. Appropriate indications for blood component therapy
• Wrap-up: “At Blood Banks”
There’s four A-B-O blood groups among us,
But that only scratches the surface cuz’,
Some of us have big-D,
With or without big-C,
And that doesn’t count M, N, Duffy, or P...
Case Study 1 – Continued

- **Additional information**
  - No history of stroke, acute chest syndrome
  - Had left previous hospital “AMA”
  - Known h/o:
    - Alleloanti-Fy(a), anti-Jk(a), and anti-E
    - Warm autoantibody
    - Possible previous hemolytic transfusion reaction
  - All RBC units were incompatible in presence of autoantibody plus potential new (not yet identified) alloantibody
- **Question**: Would you transfuse?

Transfuse: Main Pros
- ↑’d Hgb
- Potentially better outcome
- It “feels right.”

Transfuse: Main Cons
- Worsened alloimmunization
- Hemolytic reaction
- Hyperhemolysis syndrome

Case Study 1 – Continued

Discussion

- **What happened?**
  - Restarted hydroxyurea
  - Continued to provide robust supportive care, e.g.,
    - Hydration
    - Nutrition
    - Pain management
    - Social services support
  - Unfortunately, she again left hospital AMA
- **Question**: What to do next?

Outline

- **Warm-up**: “A-B-O is Crucial Ev’ry Morning”
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- **Wrap-up**: “At Blood Banks”

Case Study 2

- 54-year-old male being prepared for elective knee surgery
  - On warfarin (D/C’d 5 days prior) for h/o DVT
  - INR 1.3
- **Would you transfuse?**
- **If “yes,” what would you give?** [Continued …]
Indications for Plasma Transfusions

- **Diffuse bleeding (or imminent invasive procedure) associated with:**
  - INR > 2.0
  - PTT > 2.0 x mean normal
  - Coagulation factor assay < 25% normal activity
  - Suspected (but not yet confirmed) coagulopathy
  - Massive or potentially massive bleeding scenario
  - Warfarin overdose when other/better options not available/possible
  - Congenital or acquired hemophilia or other factor deficiency when other/better options unavailable

- **Plasma exchange for:**
  - TTP
  - Rare plasma protein deficiencies: e.g., C-1 esterase inhibitor, antithrombin III, protein C or S) when other/better options unavailable

Other Important Considerations for Plasma Transfusions

- **Dosage**
  - Loading Dose: Generally 15-20 mL/kg
  - Maintenance Dose: 10 mL/kg
  - Always attempt to transfuse as close in time as possible to when it is actually needed (because t_{1/2} of factor VII = 3 – 6 hours)

- **Post-transfusion assessment**
  - Clinical reassessment (look for evidence of reduced bleeding)
  - Look for sufficient correction of coagulation function test results

- **Contraindications**
  - Volume expander in the absence of clotting factor deficiency
  - Nutritional source or "wound healing factor"
  - Substitute for a readily available clotting factor concentrate, e.g. Kcentra for emergent reversal of warfarin
  - Counteragent to heparin (use protamine sulfate)

Final Thoughts About Plasma

- **Thawed plasma**
  - Can be stored for up to 5 days (compared to 24 hours for thawed FFP)
  - Most transfusion services now apply it to their practices

- **Liquid plasma**
  - Typically stored for up to 26 days
  - Used as a "bridging product" for massively bleeding trauma patients

- **Group A "pseudo-universal" plasma**
  - Indicated for initial transfusion of adult trauma patients
  - Reduces strain on limited group AB plasma supply

Case Study 2 – Conclusion

(Middle-aged elective knee surgery patient with warfarinized INR = 1.3)

- Patient was given 1 unit of FFP
- Developed respiratory arrest ~ 45 minutes post-transfusion
- Died 6 hours later
- Eventual diagnosis: TRALI associated with 5b granulocyte antibody

Acute Transfusion Reactions: Allergic (Ranges from Mild to Anaphylaxis)

- **Manifestations:** Within 4 hours of transfusion's end, ≥ 2 of following:
  - Edema in various locations, hypotension, pruritis, urticaria, respiratory distress with bronchospsm
- **Causes:** Plasma-soluble allergen in blood product
- **Pathophysiology:** Usual IgE-driven pathway (though for anaphylactic form, IgG antibodies have been implicated)
- **Incidence:** 1 in 30-100 (for mild); 1 in 20,000-50,000 (anaphylactic)
- **Treatment:** Antihistamine … sometimes with corticosteroid (for mild); epinephrine and other support (for anaphylactic)
- **Prevention:** Same as above (rarely, washing of blood product or other special actions are required)

Acute Transfusion Reactions: TACO*

- **Manifestations:** Within 6 hours of transfusion’s end, ≥ 3 of following:
  - ARDs, ↑‘d BNP, ↑‘d CVP, left heart failure, pulmonary edema, and/or + fluid balance
- **Causes:** Too much blood given too rapidly
- **Pathophysiology:** Rapid, uncompensated ↑ in intravascular volume
- **Incidence:** Can be as high as < 1 in 100
- **Treatment:** Stop transfusion, sit in upright position, O₂, diuresis
- **Prevention:** Slow transfusion (in rare cases as slow as 1 mL/kg/min)

*(Transfusion-Associated Circulatory Overload)
Acute Transfusion Reactions: TRALI*

- Manifestations: Within 6 hours of end of transfusion, acute lung injury plus the following:
  - Hypoxemia and radiographic evidence of pulmonary edema
- Causes:
  - Immune (usually donor antibodies to WBC antigens)
  - Non-immune ("biological response mediators")
- Pathophysiology: Damaged WBCs release cytokines that ↑ lung permeability
- Incidence: 1 in 5,000 (fatal in 5-10% of cases)
- Treatment: Aggressive supportive therapy (and no diuretics)
- Prevention: Many steps (mostly related directly to blood products)

(*Transfusion-Related Acute Lung Injury)

Case Study 3

The Value of Clinical-Laboratory Correlation: I

- 27 year-old, G3P1 Caucasian woman
- First child (born 5 years earlier) had numerous petechiae at birth and a platelet count of 20K/μL
- No "obvious" causes for thrombocytopenia, e.g., no:
  - Fetal infection
  - Birth trauma
  - Absent radii
- No incompatibility between mom’s plasma and dad’s platelets by solid phase immune adherence assay (Capture-P)
- Baby’s platelet count responded well to single dose of HPA-1a-neg. platelets

Case Study 3 – Continued

- Mother was now approaching 3rd trimester
- Repeat serologic testing was performed
  - She appeared to be HPA-1a-negative (based upon testing with unlicensed anti-serum) but …
  - No evidence was seen (once more) of incompatibility between mother’s plasma and father’s platelets by same test used previously

Case Study 3 – Continued

- Specimens were sent to Blood Centers of Southeastern Wisconsin (now Versiti) for genotyping
  - Mom was confirmed HPA-1a-neg. and Dad confirmed as homozygous HPA-1a-pos.
- Antibody vs. HPA-1a was identified in mother’s serum via:
  - Indirect immunofluorescence and …
  - Antigen capture ELISA
  - (but not Capture-P)
- Percutaneous umbilical blood sampling (PUBS) was scheduled for approximately 28 weeks gestational age
Under normal circumstances, only maternal IgG (and not IgM, IgA, or IgE) is capable of crossing the placenta.

Maternal transport of IgG occurs via active transport, and begins around gestational week 14.

Platelet destruction occurs due to interaction between: (1) Antigen, (2) IgG, and (3) Reticuloendothelial Fc receptor.

In preparation for PUBS, we collected ½ plateletpheresis unit from mother – unit passed all required screening tests.

We irradiated, albumin-resuspended, and volume-reduced unit prior to issuing it.

Following transfusion, fetal platelet count increased from 22K/μL to 106K/μL.

IVIG therapy was started at this time – 1 g/kg/week given to mother.

Next PUBS was performed at approx. 34 weeks gestational age.

An HPA-1a-negative apheresis platelet unit was collected from another (CMV-negative) donor.

Unit was handled similarly to previous unit (e.g., irradiated, albumin-resuspended, volume-reduced, …).

Fetal platelet ct ↑’d from 45K/μL to 152K/μL.

Fetus required no additional transfusions and was delivered by C-section:

- At 39 weeks gestational age
- With platelet count = 154K/μL

Gresens C. The Diagnosis and management of an especially challenging case of fetal/neonatal alloimmune thrombocytopenia. CBBS Today 1999 (Fall); 17: 42-44.
Case Study 3 – Conclusion

- Unusual case of F/NAIT* that was “un-diagnosable” by system we initially used for detection of IgG antibodies to platelets
- Illustrates importance of looking at other clues to determine whether fetus is at risk, e.g.,
  - Clinical history
  - Absence of other probable causes for ↓d platelets
  - Mother’s and father’s phenotypes/genotypes
- Also demonstrates an effective means (albeit one that since that time has been refined) for managing special platelet requirements of F/NAIT cases

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Listen and Collaborate …

From Pearls before Swine, by Stephan Pastis (05/01/17)

Plan … (But Also “Do” and “Adjust”)

From Pearls before Swine, by Stephan Pastis (04/21/15)

… And Learn

One Way to Approach Life

New York Times columnist Thomas Friedman suggests thinking like:
- A (“hungry”) immigrant
- An (inspired) artisan
- A (great) waitress
And Remember …

“A Man [or woman] may do an immense deal of good if he [she] does not care who gets the credit”

(Quote attributed to multiple people)

When planning for the future, consider …

Mission

Margin

Expertise

So that we may (per “Curly’s Law”) …

... “[f]ind one [or a few] thing[s]” that is [are] most meaningful

Jack Palance in City Slickers, MGM (1991)

Some of you may remember “Curly’s Law” …

• Curly: “Do you know what the secret of life is? [pause] ... This [raises his right index finger]?”
• Mitch: “Your finger?”
• Curly: “One thing ... just one thing. You stick to that and the rest don’t mean s*t.”
• Mitch: “But what is the ‘one thing’?”
• Curly: [smiles] “That’s what you have to find out.”

Jack Palance in City Slickers, MGM (1991)

All of us must determine what is

Mission

Margin

Expertise

Our “one [or a few] thing[s]”

And, as we do this, we must remember to …

... Focus on

Mission

Patients

Margin

ExPerTISE
Cuz’ if we don’t, the rest (per Curley) …

... “don’t mean [excised].”

Jack Palance in City Slickers, MGM (1991)

Our light at the end of the tunnel …

... It’s coming …

And we don’t want it to look like this …

... but (rather) like …

Like this

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Case Study 4

The Value of Clinical-Laboratory Correlation: II

Heavy Blood Use/No Excuse
33-year-old white ♀ with chronic hepatitis C virus
Alleged “unspecified platelet function abnormality”
H/o multiple RBC/platelet transfusions 2° to periodic, vaguely documented bleeding disorders
Heavily alloimmunized
- 100% PRA
- Anti-Jk<sup>a</sup>, -Fy<sup>a</sup>, -M, -S, and -f
Recent unexplained/heavy transfusion requirement
- 12 rare RBC units x 21 days
- 36 HLA-matched apheresis platelets x 5 months

Patient was said to have "derived great satisfaction from her transfusions" due to combination of:
- Attention/sympathy
- Pre-medications (meperidine, promethazine, diphenhydramine)
- Perception transfusions helped her wound healing/overall health
- H/o aggressively pushing her healthcare providers to “get her way”
- “Very adept at doctor-shopping”
  - **New CVC had been placed one week before acceleration of RBC/platelet usage**

Upon discharge, hematologist recommended removal of CVC; patient balked
Hematologist “laid down the law,” stating:
- No further RBC transfusions while CVC was in place
- No further platelet transfusions until comprehensive platelet function study performed
- Use/abuse of RBC/platelet transfusions ended

Case Study 4 – Conclusion

**Munchausen Syndrome**
- Persons present with factitious symptoms and signs that initially may seem plausible
- Named for Baron von Munchausen, 18<sup>th</sup> C. cavalry officer/braggart
- Patients often have Thespian’s flair plus:
  - Vagueness/consistency when questioned
  - Drug-seeking behavior
  - “Woe-is-me” attitude

From The Adventures of Baron Munchausen (1988)
Outline

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- Wrap-up: “At Blood Banks”

Case Study 5

- 66-year-old female patient requiring hip replacement for recent fall and fracture
  - Hemoglobin levels
    - Preoperative – 10.7 g/dL
    - Postoperative – 8.7 g/dL
  - Feeling a little “light-headed” several hours after her transfer to floor
- Would you transfuse?
- If “yes,” what would you give? [Continued …]

Transfusing Blood Appropriately

Starting Point: Abbreviated discussion of 5 well designed and implemented randomized clinical trials

PC Hebert et al. A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care
NEJM 1999; 340: 409-17

- Background: To determine if restrictive vs. liberal transfusion strategies in critically ill patients yield equivalent results (non-inferiority study)
- Methods: 838 euvolemic, critically ill patients were randomly assigned to receive transfusions only if:
  - Hgb < 7 (afterwards, maintained at 7-9 g/dL) or
  - Hgb < 10 (afterwards, maintained at 10-12 g/dL)

The Evidence for RBC Transfusions

<table>
<thead>
<tr>
<th>Citation</th>
<th>Patients</th>
<th>Hgb Transfusion Thresholds (g/dL)</th>
<th>Outcome-Based Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC Hebert et al, NEJM 1999; 340: 409-17</td>
<td>Adult ICU</td>
<td>7.0 versus 10.0</td>
<td>Restrictive strategy was non-inferior</td>
</tr>
<tr>
<td>J. Lacroix et al, NEJM 2007; 396: 1609-1</td>
<td>Pediatric ICU</td>
<td>7.0 versus 9.5</td>
<td>*</td>
</tr>
<tr>
<td>LA Hajjar et al, JAMA 2010; 304:1559-67</td>
<td>Post-cardiac surgery</td>
<td>8.0 versus 10.0</td>
<td>*</td>
</tr>
<tr>
<td>J.L. Carson et al, NEJM 2011; 365:2453-62</td>
<td>Elderly, post-hip surgery</td>
<td>8.0 versus 10.0</td>
<td>*</td>
</tr>
<tr>
<td>C. Villanueva et al, NEJM 2013; 368:11-21</td>
<td>Severe acute upper GIb</td>
<td>7.0 versus 9.0</td>
<td>Restrictive strategy was superior</td>
</tr>
</tbody>
</table>

Results

- 30-day death rates were similar for both groups (~18.7% for restrictive vs. 23.3% for liberal group (p = 0.11), but …
- Mortality rates in restrictive group were significantly lower in two specific subgroups – e.g., among:
  ✓ “Patients who were less acutely ill” (8.7% vs.16.1%)
  ✓ Patients < 55 years old (5.8% vs. 13.1%)

Conclusion: Most patients respond at least equally well to restrictive (Hgb < 7.0 g/dL) RBC transfusion triggers … as compared to more liberal (Hgb < 10.0 g/dL) triggers – i.e., non-inferiority of restrictive strategy demonstrated
Methods

- Enrolled 921 patients with severe acute upper GIB
  - Liberal strategy (transfused if Hgb < 9.0 g/dL; n = 460)
  - Restrictive strategy (transfused if Hgb < 7.0 g/dL; n = 461)

- Outcome measures:
  - Survival at 6 weeks
  - Incidence of continued bleeding

Conclusion: “A restrictive strategy significantly improved outcomes in patients with acute upper [GI] bleeding.”

Results

- Survival at 6 weeks:
  - 91% (liberal)
  - 95% (restrictive); p = 0.02

- Further bleeding:
  - 16% (liberal)
  - 10% (restrictive); p = 0.01

- Portal pressure gradient significantly higher in liberal versus restrictive groups during first 5 days (p = 0.05)

Indications for RBC Transfusions

- Asymptomatic anemia in hemodynamically stable inpatients – In most cases wait until:
  - For non-surgical: Hgb < 7 g/dL before considering transfusion
  - For post-surgical: Hgb < 8 g/dL before considering transfusion

- Symptoms believed to be related to anemia:
  - Indications are less clear
  - If normovolemic with chest pain, orthostatic hypotension, tachycardia, and/or CHF, consider ↑’d Hgb “trigger cut-off” (e.g., < 8 g/dL … possibly even somewhat higher)

Indications for RBC Transfusions

- Hospitalized, hemodynamically stable patients with acute coronary syndrome – Unclear whether to apply liberal or restrictive threshold (studies pending; maintaining Hgb ≥ 10 g/dL is not unreasonable)

- Significant (including massive) bleeding – Transfuse as required

- Red cell exchange – Transfuse as required for patients with sickle cell disease or overwhelming malaria

- Occasional exceptions exist – e.g., maintaining Hgb of 10-12 g/dL in bleeding patients who are refractory to platelets

Other Important Considerations for RBC Transfusions

- Dosage:
  - For adults: One unit increases Hgb/Hct in “typical” 70 kg patient by 1 g/dL/3% (when non-bleeding/hemolyzing)
  - For infants/toddlers: Equivalent dose = 5-8 mL/kg weight

- Post-transfusion assessment:
  - Clinical reassessment
  - Look for above dose response ≥ 15 minutes post-transfusion

- Contraindications:
  - When other (e.g., pharmacologic) means are more appropriate
  - When significant, transfusion-associated risk exists
Case Study 5 - Conclusion
(Elderly female s/p hip surgery with Hgb 8.7 g/dL and light headedness)

- She was not transfused
- Found to be iron deficient with no other cause for anemia (other than recent surgical bleeding)
- Given 1,000 mg iron intravenously prior to discharge
- 6 weeks later her hemoglobin was 11.8 g/dL and she was continuing to recover nicely

Transfusing Blood Appropriately

Case Study 6

- 10-year-old boy with AML and platelet count of 35,000/uL
- Experiencing persistent epistaxis refractory to packing, etc.

Would you transfuse?
If “yes,” what would you give?  [Continued …]
Indications for Platelet Transfusions

Slide 1 of 2

- **For prophylactic purposes**
  - If no clinical factors – Maintain plt ct ≥ 10,000/μL
  - If significant clinical factors (e.g., sepsis, DIC) – Consider maintaining plt ct ≥ 20,000/μL.

- **If patient is bleeding or pre-surgery/other procedure**
  - Maintain plt ct ≥ 20,000/μL for elective CVC placement
  - Maintain plt ct ≥ 50,000/μL for most other situations (includes elective lumbar puncture)
  - If microvascular bleeding is present, and suspected to be due to qualitative platelet defects, transfuse as needed (though judiciously)
  - When appropriate, be prepared to invoke massive transfusion protocol and also transfuse with RBCs and other “yellow components” according to pre-defined ratios.


Indications for Platelet Transfusions

Slide 2 of 2

**Exceptions** – Sometimes/rarely it may be better to keep platelet count closer to 100,000/μL, e.g., for:
- ECMO.
- Neuraxial surgery.
- Intra-aortic balloon pump support, and
- Bleeding due to acquired factor V inhibitor.

Other Important Considerations for Platelet Transfusions

- **Dosage**
  - For adults: One apheresis platelet unit (rarely two) ideally leads to: (1) 30-50,000/μL increase in count with (2) improved platelet function
  - For infants/toddlers: Equivalent dose = 5-10 ml/kg weight

- **Post-transfusion assessment**
  - Clinical reassessment (look for evidence of reduced bleeding)
  - Look for sufficient dose response at 10-60 minutes post-transfusion

- **Contraindications**
  - TTP/atypical HUS*
  - Heparin-induced thrombocytopenia*
  - ITP*
  - Coagulation defects unrelated to platelets

*Unless patient is bleeding and is affected by profound thrombocytopenia and/or platelet dysfunction

Case Study 6 - Conclusion

(10-year-old boy with AML, severe thrombocytopenia, and persistent epistaxis)

- Transfused with ½ unit of apheresis platelets (patient weight was 36 kg)
- Platelet count increased from 35,000 to 82,000/μL
- Nosebleeds resolved

Transfusing Blood Appropriately

Fresh Frozen Plasma (FFP) and Other Plasma Components

Discussed earlier in this presentation.
Indications for Cryoprecipitate

- Bleeding or imminent invasive procedure associated with fibrinogen < 100-150 mg/dL (e.g., in DIC, fibrinolysis, and/or dilutional coagulopathy due to bleeding)
- Congenital dysfibrinogenemia
- Correction of factor VIII deficiency or von Willebrand’s disease (when a specific factor concentrate is not available)
- Factor XIII deficiency (better options exist)
- Source of fibrin glue (last choice)
- Congenital hypo- or afibrinogenemia (last choice)

Other Important Considerations for Cryoprecipitate Transfusions

- Dosage (to achieve ∆ of 50-100 mg/dL)
  - A single (i.e., un-pooled) unit for an infant
  - 1 - 2 units/10 kg body weight – which works out to:
    - One “S-pack” for initial transfusion of patients < 40 kg
    - Two “S-packs” (i.e., for a total of 10 units) for larger patients
- Post-transfusion assessment
  - Clinical reassessment (look for evidence of reduced bleeding)
  - Look for correction of fibrinogen and other coag function test results
- Contraindications: Always first consider safer, more effective therapies, e.g., …
  - DDAVP or Humate-P for vWD
  - Factor VIII/IX concentrate for hemophilia A/B
  - Tisseel or Evicel for fibrin sealant purposes
  - RiaSTAP for congenital hypo- or afibrinogenemia

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Objectives

At the conclusion of this activity participants will be able to:

- Describe the deliberative process involved in determining how … and whether … to transfuse an ultra-severely anemic patient (e.g., hemoglobin ≤ 5 g/dL) who has a significant red cell incompatibility;
- Summarize the most important features involved in preventing, diagnosing, and managing the acute transfusion reactions associated with severe respiratory complications;
- Define the value of clinical-laboratory correlation when determining the cause of: (a) neonatal thrombocytopenia, and (b) unexplained and persistent/chronic anemia; AND
- Review the most up-to-date indications for the transfusion of: (a) red blood cells, (b) platelets, (c) plasma, and (d) cryoprecipitate.
"At Blood Banks" (Sung to the tune of "On Broadway")

Solo
- One-Two-Three-Four!!!
- Bump! Bump! Buh-duh-duh! Give blood!
- Bump! Bump! Buh-duh-duh! Give blood!

All – 1st Stanza
- The blood is always sitting there at blood banks,
- Just waiting to help you save patients' lives,
- 'Cause how you gonna' shake their blues,
- When you ain't got blood to transfuse?
- And saline just ain't getting you nowhere.

All – 2nd Stanza
- The techs and docs are there for you at blood banks,
- They're ready to help you save patients' lives,
- If you have questions, take the phone,
- They'll take you to the "knowledge zone,"
- I promise that they won't give you no jive.

All – 3rd Stanza [One key higher]
- We’re glad to share our knowledge here at blood banks,
- For that’s just one of many things we do,
- If we can help, please let us know,
- ‘Cause that is what colleagues are for,
- That is a guarantee we give to you.

So now we may come to …

All
- Bump! Bump! Buh-duh-duh! Give blood!
- (softer) Bump! Bump! Buh-duh-duh! Give blood!
- (even softer) Bump! Bump! Buh-duh-duh! Give blood!
- (super-soft) Bump! Bump! Buh-duh-duh! (very loud) Give blood!

Last "song lyrics slide" coming up ...!
"You’re still here?"

"It’s over ... go home."

Thank you
Q & A + Other Discussion
Chris.Gresens@BloodSource.org
(916) 453-3728