Towards an Understanding of TRALI

CANADIAN BLOOD SERVICES
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QUESTION 2

HOW SHOULD TRALI BE DEFINED AND WHAT PROCESSES SHOULD BE IMPLEMENTED IN ORDER TO DEVELOP OBJECTIVE CRITERIA FOR USE IN THE CLASSIFIACTION OF TRALI REACTIONS?

Acute Lung Injury (ALI): 1994 consensus definition (slightly modified)

- Acute onset
- Hypoxemia
  - PaO_2/FIO_2 < 300 mm Hg or
  - Oxygen saturation is < 90% on room air or
  - Other clinical evidence
- Bilateral lung infiltrates on chest X-ray
- No evidence of circulatory overload (this may be difficult to exclude in suspected TRALI cases)

Newly proposed definition of TRALI*

- In patients with no ALI prior to transfusion, the diagnosis of TRALI is made if there is:
  - New ALI occurring during transfusion or within 6 hours of completion and
  - No other temporally associated ALI risk factor(s)

*adapted from the NHLBI working group on TRALI

Newly proposed definition of possible TRALI*

- In patients with no ALI prior to transfusion, the diagnosis of possible TRALI is made if there is:
  - New ALI occurring during transfusion or within 6 hours of completion and
  - One or more temporally associated ALI risk factor(s)

*adapted from the NHLBI working group on TRALI

ALI Risk Factors

Incidence of ALI varies considerably among these conditions (up to 40% for septic shock, as low as 2% for CP bypass)

- Aspiration
- Pneumonia
- Toxic inhalation
- Lung contusion
- Near drowning
- Severe sepsis
- Shock
- Multiple trauma
- Burn injury
- Acute pancreatitis
- CP bypass
- Drug overdose

TRALI in the setting of massive transfusion in critically ill patients

- In four studies, ARDS (ALI) occurred in 21-45% of massively transfused patients (defined as $\geq$ 8-15 units in 12-24 hours)
- Is this ALI due to an underlying condition or is it mediated by transfusion (i.e.: is it TRALI)?
- Proposed definitions would consider these cases as TRALI unless the transfusions were temporally associated with an ALI associated condition (e.g. multiple trauma, CP bypass)

Reasons for distinguishing TRALI and possible TRALI

- Uncertainty of diagnosis in possible TRALI
- Separate reporting in surveillance systems
- Targeted research programs
- Possibility of different approaches to donor investigation and management

Exclusions from the proposed TRALI definition

- Mild TRALI cases
  - Lookback studies suggest these exist
  - Criteria not well defined
- Cases that co-exist with circulatory overload
  - These can occur with ALI
- Worsening lung injury in a patient with pre-existing ALI
  - No diagnostic criteria

Achieving a standardized TRALI definition

- Definitions proposed by this Consensus Panel should be harmonized with those used by other groups (NHLBI, ISBT, BEST, AABB, EHN) so as to adopt a standard international definition
  - This process is underway
- These definitions are a starting point; should be expected to evolve

QUESTION 4

WHAT OPTIONS ARE AVAILABLE
FOR MANAGING DONORS
IMPLICATED IN TRALI REACTIONS?

Donor definitions

- Associated donor: unit transfused within 6 hours
- Implicated donor: Donor with anti-HLA (class I or II) or anti-HNA with specificity against an antigen on recipient cells (established via antigen typing or positive crossmatch)

Donor management options in TRALI

- Basis of donor management is to protect recipients of future (or co-component) donations
- Apply to possible TRALI as well as TRALI ?
- Uniform action on all donors vs. taking action based on result of lab investigations
    - Defer from future donation
    - Allow future donation but wash red cells and do not use plasma or apheresis platelets
    - Flag donor record for second hit
        - Raises issues of informed consent for recipient and notification of donors

Donor management options in TRALI

- Preferred option of panel is to perform lab investigation to find implicated donor

Considerations in performing a laboratory donor case investigation

- Requirement for good clinical case information before proceeding
  - Tests are costly and require access to specialized labs
  - Involves donor callback and may result in donor anxiety
- Requirement for recipient specimen or pre-existing antigen typing result
  - Influenced by policy on non-implicated antibody positive donors

Laboratory investigation of donors in a TRALI case

- Antigen-antibody pathway
  - Work-up of all donors simultaneously
  - Incremental strategy (female donors since ~17% shown to have HLA Abs, most recently transfused products, FFP before RBC donors)
  - Panel did not express preference for a given donor investigation strategy
- Recipient or component testing for neutrophil priming activity is not yet a routine test
  - Should be encouraged

Laboratory investigation of donors in a TRALI case

- Donor testing: HLA class I & II and HNA antibodies
  - Broad screening test and then antibody ID
- Recipient testing: HLA class I & II typing; neutrophil typing, if possible
- If antibody is found, perform cross-match (recipient cells and donor serum)

Recipient antigen testing or crossmatch is necessary to implicate a donor

Strategies for donor management based on laboratory results

- **If positive cross-match or cognate antigen:**
  - Take action and inform implicated donor
    - Reinstate donors with no antibody
    - Reinstate non-tested donors
    - ? for donors with non-matching antibody (deferral for anti-HNA, preference was reinstatement for anti-HLA)
- **If no donors with positive cross-match or cognate antigen:**
    - Reinstate donors with no antibody
    - ? for non-tested donors
    - ? for donors with non-matching antibody (see above)

QUESTION 5

IS THERE SUFFICIENT EVIDENCE, AT THIS TIME, TO RECOMMEND THAT ANY LABORATORY SCREENING TESTS AND/OR OTHER DEFERRAL MEASURES BE IMPLEMENTED TO EXCLUDE DONORS IN ORDER TO REDUCE THE RISK OF TRALI?

WHAT STRATEGIES COULD BE CONSIDERED TO REDUCE THE RISK OF TRALI?

- Adherence to current guidelines of blood component utilization, especially FFP utilization
- Defer donors “implicated” in a TRALI reaction
  - Based on positive lookback study
  - Will err on side of recipient safety and may defer some safe donors
- Divert plasma or defer selected groups of donors based on demographic or other characteristics

DIVERSION OF PLASMA FROM FFP PRODUCTION AND/OR DEFERRAL OF DONORS FROM APHERESIS PLATELET OR PLASMA DONATION

- All females and all transfused males
- All females
- All previously pregnant females
- Females with leukocyte antibodies

The panel suggests that each blood collection agency evaluate the benefit or the impact on the blood collection system (re: blood availability, impact on donors) of adopting any of these strategies. There was no recommendation by the panel to implement these.

ADDITIONAL PROPOSED STRATEGIES TO REDUCE THE RISK OF TRALI

- Consider age of components when transfusing at-risk patients
  - could be a factor based on two hit pathogenesis model but currently unproven
  - no clear way to identify at-risk patients
- Use of platelet storage solutions if licensed

QUESTION 6

WHAT FURTHER INFORMATION AND SYSTEMATIC RESEARCH IS NECESSARY TO BETTER EVALUATE THE ISSUES OF THE EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF TRALI IN ORDER TO REDUCE THE RISK TO TRANSFUSION RECIPIENTS?

Selected research issues: epidemiology/clinical

- Better characterize the epidemiology of TRALI
  - Determine incidence and severity with various components
  - Study possible TRALI cases in detail in research settings
- What clinical or genetic factors in the recipient predispose or protect against TRALI?
- Are there mild forms of TRALI?

Selected research issues: pathophysiology

- Continue work in animal model systems to explore pathogenesis
- Does TRALI occur in severe neutropenia and, if so, what is its mechanism?
- What are the mechanism(s) causing hypotension and fever in TRALI?