Navigating Adverse Event Reporting

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Objectives

Case presentation

Brief Review of Transfusion Reactions

Transfusion Reaction Workups

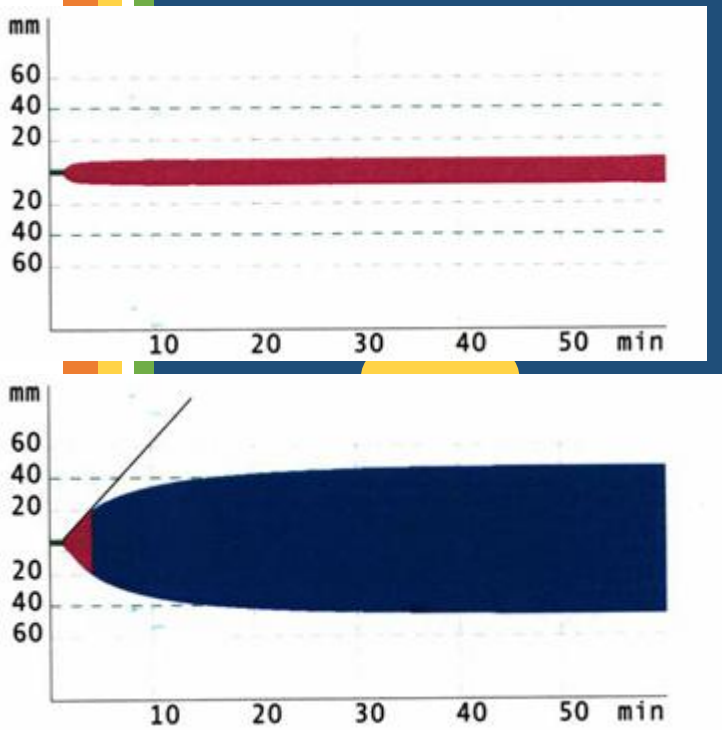
Adverse Event Reporting Overview

What did the FDA ask of us?

Unexpected emotional toll

Patient presentation

- 27 y/o M presented to the ED with abdominal pain, jaundice, and recent appearance of red blood in stool.
- Initial labs and radiology supported diagnosis of multiple alcohol-related disease states, including cirrhosis, coagulopathy, AKI, lactic acidosis
- Coagulopathy assessed by TEM and standard coagulation panel
  - Admit labs: PT 29, INR 2.59, aPTT 81.3
- 1 adult dose of Cryoprecipitate and 1 unit Fresh Frozen Plasma Ordered and prepared.



Patient presentation, continued

- All three bags of product were dispensed at 14:19
- Patient vitals and pre-transfusion assessment completed; patient tachycardic at 108 bpm
- Bag 1 of Cryo transfusion completed at 14:38
- Patient reported feeling anxious and heart rate had increased to 135. RN reports visible restlessness and called Med team at 14:40.
- By 14:42, patient was in asystole. RN began CPR and called the Code Blue.
  - Chart notes indicate rash may have been present about face and neck, but reports could not be confirmed

Patient presentation, continued

- Patient successfully resuscitated.
- Transfusion reaction investigation initiated.
  - Primary investigation is intended to discover potential clerical error, collection/typing error, other bench testing error, product mismatch, comparisons of pre and post transfusion samples (DAT, hemolysis, icterus, blood types, sometimes repeat antibody screen), who in the medical team was notified/responded, is it safe to continue transfusions, and finally, sign off by Transfusion Services Medical Director, or their Designee, upon review.
  - No technical or clinical error was found.
  - Preliminary Pathology Case consult added to patient EMR
  - Spent bag of cryo + un-transfused bag of cryo returned to blood supplier for further testing.

What is the relationship of this clinical event to the half-dose of Cryoprecipitate transfusion?

Patient presentation, continued

- What happened next??
  - Nothing, really, until 2 days after initial cardiac event.
  - The goal had changed to support through acute events until stabilized, then address chronic GI bleeding from varices.
  - After finding moderate amount of free abdominal fluid and patient stopped producing urine dialysis was required.
  - During the procedure to obtain dialysis access, patient desaturated to 30% with BP 40/20. Patient did not lose pulse, and was resuscitated again, though in clear organ failure.
- Call for Help
  - CBC Medical Director Consulted
    - Anaphylactic reaction is most likely, since it is the only one leading to arrest AND presents with rash.
    - Determined avoidance of transfusion is best, offer washed products if absolutely necessary, run pre-transfusion IgA level
    - Individual factor medication could be best, but may also be at risk for anaphylaxis.
  - Heme/Onc consulted for recommendations
    - Advised to hold off all transfusion as long as patient is not worsening.

Types of Reactions

Febrile non-hemolytic

Acute Hemolytic

Bacterial Contamination

Fever

Anaphylaxis (potential for IgA deficiency + anti-IgA)

Urticaria

Allergic

TACO and TRALI

Hypoxemia/Dyspnea

TA-GvHD

Post-transfusion purpura

Transfusion-related alloimmune neutropenia

Cytopenias

Acute Hemolytic Reaction

Delayed Hemolytic Reaction

Non- RBC Antibody-mediated hemolysis

Hemolysis

UNCOMMON

Can result in fever, tachycardia, and/or hypotension

Infection

Types of Reactions

Usually bradykinin mediated; systolic drop ≥30mmHg or systolic <80mmHg

Hypotensive

Usually only found in chronically-transfused or with underlying disease.

Iron Overload

Antibody formation without positive DAT or evidence of hemolysis

Delayed Serologic

Anaphylaxis

This HAS to be the cause, right?

- Maybe?
  - Mechanism of action is related to IgE/mast cell activation, haptoglobin deficiency, or IgA deficiency with anti-IgA.
- Patient never experienced severe allergies or asthma in early life. Histamine is known to be a vasoDILATOR, and arrest is due to vasoconstriction.
- Post-transfusion IgA level result was on the high side of normal range. Haptoglobin was low-normal.
  - But wait, the patient received a unit of FFP, so this could be donor IgA detected, and not patient IgA.
  - **EXCEPT** by this point, Medical Staff members present during the code had been interviewed individually, and we learned the MD leading the initial code instructed a RN to 'just throw it out'. This was not in the EMR.

- This must mean either Cryo contains a ridiculously high level of IgA since half an adult dose could create a high/normal reading in an assumed deficient patient.

Or, IgA is not implicated, and cardiac arrest was due to…..????

Cardiac Arrest and Acidosis

This was determined to be the ultimate cause of death.

- Unfortunately, the patient did not regain consciousness, experienced worsening organ function, and was moved from full code to comfort measures after losing basic reflexes.
- Lactic acidosis is common with liver failure
  - Lactate is cleared from circulation by healthy liver tissue
  - Low blood pH is known to contribute to vasoconstriction

Adverse Reaction Governance

- AABB
  - Standards, Chapter 7 (entirely)
  - Addresses issues in manufacturing, nonconformance to SOP (if affecting safety, purity, or potency of product), classifying events, actions specific for suspected hemolytic reactions
  - 7.2 Fatality Reporting
    - Fatalities confirmed to be caused by... transfusion shall be reported to outside agencies as required.
- TJC
  - Standards addressing adverse event reporting include Process Improvement, Leadership, Quality Systems Assessment
  - PI.01.01.01 EP7, LD.03.07.01 EP2, LD.03.09.01, QSA.05.18.01, QSA.05.19.01. QSA.05.19.03
  - Standards direct facilities to utilize specialty-specific governing resources (basically, TJC directs Transfusion Services to AABB Guidelines and does not have extensive oversight)
  - *Anecdote:* Survey review included reporting clerical check, DAT, specimen collection info, review vitals, transfusion details (start-stop, volume transfused, and "reaction observed?"), was it fully reviewed by the Medical Director of Transfusion Services, prove the results were viewable by medical team.
- CAP
  - TRM.41650, 41750, 41770, 41800, **41850,** 42000, 42050, 42060
  - Match AABB guidelines closely

Transfusion Reaction Workups

- Combining requirements of all standards reviewed, reaction workups must address:
  - Inspecting blood container, including accompanying tubing/infusion sets and IV solutions; Labeling should be inspected for accuracy and appropriateness (correct patient, correct product)
  - Clerical checks of all pre-transfusion testing and activities
  - Evaluation of pre and post-transfusion samples for hemolysis
    - Bench tests on post-transfusion sample:
      - DAT for C3 and IgG, repeat ABO
      - May compare to pre-transfusion, if positive or unexpected result obtained
      - Potential cultures?
  - Documented date/time of Physician review (Pathologist)/ interpretation of Medical Director

- Suggest further investigation, if
  - Fatality occurs, clerical error found, discrepancy in blood types, unexpected lab results obtained during workup
  - Repeat pre-transfusion testing, antibody testing on post-transfusion sample, AHG crossmatch, antigen typing, urinalysis and free hgb, liver studies, LDH, haptoglobin, unit examination, cultures

FDA Center for Biologics Evaluation and Research

- Pre-event SOP
  - If fatality occurs and is related to transfusion, notify CBER within 24 hours of the death.
  - Complete a written report within 7 days.
  - That was it.
  - Lab called the lawyers.
- Enter "Notifying the FDA…" Guidance for Industry.
  - If fatality occurs as a result of transfusion reaction, report must be made by the facility that performed compatibility testing (note – the responsibility could be shared, depending on facility and product manufacturer relationship).
  - Initial notification from Recipient Facility to include…
    - Date/Time of the notification
    - Reporter's info (facility, title, contact info, FDA number if you have one)
    - Patient demographics and brief details of the event
    - Patient medical history/current disease states necessitating transfusion
    - Product details, including unit number and manufacturer demographics.
  - FDA suggests email reporting, as the response is custom and easy to track.

What did they ask of us?

Quite a lot, actually.

Complete transfusion reaction report

Recalls associated with ALL products used

Physician consults

Transfusion records

Death Certificate

Details of the blood collection system

Infectious disease test results (this stay or ever)

Radiology reports

Minutes from Transfusion Committee review

Corrective Action Plans

All relevant labs, differentiating admission and post-transfusion values

Discharge Summaries

All investigation steps and conclusions

Admission notes

…and no suggestion on the format or approach to compile and report

Did you know you have SEVEN DAYS?

- At my facility, the transfusion reaction workup was designed to identify a Hemolytic reaction.
  - Transfusion Reaction Pathology Consult further defines classification of the reaction to allergic, febrile, etc., in a formal manner.
  - LIS build was not intended to translate to a written report, so emergency IT ticket to address building a report.

Reported To	[redacted]
Date & Time Reported to Dr.	1440
Reported By:	[redacted]
Unit Number	[redacted]
Date & Time Return	08/23/2024 17:00
Amount Return	< 1.0 ml
Date & Time Issued	08/23/2024 14:19
Recepient	Agreement
Unit(s)	Agreement
XM label(s)	Agreement
Clerical Error	N
Pre-Hemolysis	N
Post-Hemolysis	N
Pre-Icterus	Y
Post-Icterus	Y
Anti-A	0
Anti-B	0

zReported To	[redacted]
Date & Time Reported to Dr.	1440
Reported by:	See Below T8
Post-I ABORH	O POS
Trxn Interp	See Below T9
Post-DAT Interp	Negative

Textual Results

T6: 8/23/2024 18:25 CDT (Current Medication)
see MAR

T7: 8/23/2024 18:25 CDT (Symptoms)
restless, AMS, asystole

T8: 8/23/2024 18:25 CDT (Reported by:)
[redacted]

T9: 8/23/2024 18:25 CDT (Trxn Interp)
No Evidence of Hemolytic Transfusion Reaction

Did you know you have four DAYS?

- Call for an Urgent Case Review
  - Invited entire Transfusion Committee (reps all specialties)
  - Included Hematology/Oncology, due to extensive consult
  - Legal Team
  - Found there was no formal process for conducting or documenting a case review

- We chose Morbidity and Mortality Conference format.
  - Peer-review that seeks to identify systemic improvement over placing blame.
  - Conducted case review, lab and radiology records review, differential diagnosis of transfusion reaction(s), product analysis
  - Minutes recorded on general word processing template.

Did you know *you have three days?*

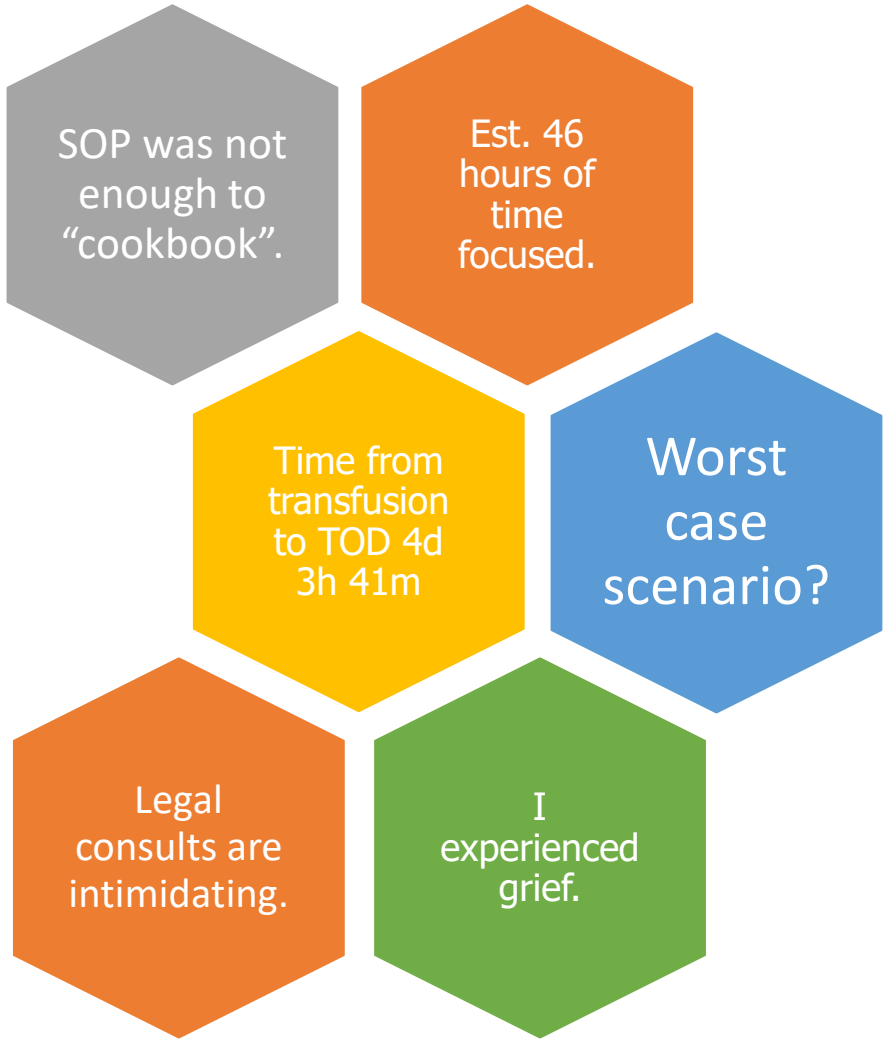
- Final report composed by Legal Department.
  - Format chosen was legal memo
  - Memo began with statement of the fatality
    - "The fatality occurred (at this address on this date). The patient involved is (de-identified description). The cause of death was determined to be…"
  - Very brief overview of the event
    - "Patient was ordered to receive (blood products) prior to (procedure) and experienced (this reaction)"

- Details were given in a bulleted list, to include
  - Underlying medical conditions necessitating hospitalization, Reason for transfusion, product(s) involved, Products administered AFTER transfusion reaction, Patient response to treatments and medical interventions,
  - Minutes recorded on general word processing template.

FDA Center for Biologics Evaluation and Research

- Over 6 MB of data was emailed to the FDA as requested.
- The refused to access encrypted email.
- Over 6 MB worth of printed materials was faxed to the FDA as requested.
- We received confirmation of information received, but have not received additional feedback to date.

Final thoughts



Advice for workplace grief

- Our work is in saving lives.
  - Grief and loss can hit secondary caregivers in the “shouldn’ts”
- What can I do?
  - Validation of confusing emotions is crucial to building trust
  - Debrief with those involved. Review policies and the investigation to prove there was no human error. Do your best to communicate personal autonomy.
  - Add a layer of thorough peer review to rebuild team trust, if affected.
  - Allow involved staff to review/revise policies.
    - It is normal to desire a sense of control and purpose.
  - Support access to EAP or HR trainings
  - Cultivate resiliency by focusing on small wins and praising skills
  - Provide a means for individuals to support each other

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College of American Pathologists Transfusion Medicine Checklist. CAP Accreditation Program. August 2023.

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U.S. Department of Health and Human Services, Food and Drug Administration Center for Biologics Evaluation and Research. Notifying FDA of Fatalities Related to Blood Collection or Transfusion; Guidance for Industry. August 2021.

Thank you!

Presentation Resources