Transfusion Camp 2023-2024

Day 2: Seminar 2A, November 24, 2023

"Labile Component Reactions", developed by Dr. Sumedha Arya & Dr. Christine Cserti-Gazdewich

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11:00 AM – 12:30 PM (1h:30min) ;

Suggested timetable:

11:00 – 11:22: Case 1 (TACO) → 22 minutes

11:22 – 11:33: Case 2 (FNHTR) → 11 minutes

11:33 – 12:06: Case 3 (TRALI) → 33 minutes

12:06 – 12:28: Case 4 (IgA deficiency Anaphylaxis/Allergics) → 22 minutes

Case 1

An 88 year-old group O+ man with chronic lymphocytic leukemia (CLL) presents to the ER with a 2d history of weakness, oliguria, and chills.

He has a history HTN, CAD, and CHF;

His outpatient medications are ASA, furosemide, ramipril, & metoprolol.

In the ER, BP is 92/60. He is given 1L NS, antibiotics, and antipyretics.

His diuretic and antihypertensives are held.

CBC shows Hb 79 g/L; one month prior his Hb was 100 g/L.

2 units RBC are ordered, each to be given over 1h. A 21 day old unit is hung.

Pre-transfusion vitals: HR 121, BP 100/60, T 37.3 O2 sat 100% R/A

After 1st unit: HR 140, BP 127/72, T 37.3 O2 sat 78% R/A →97% on 2L/min NP.

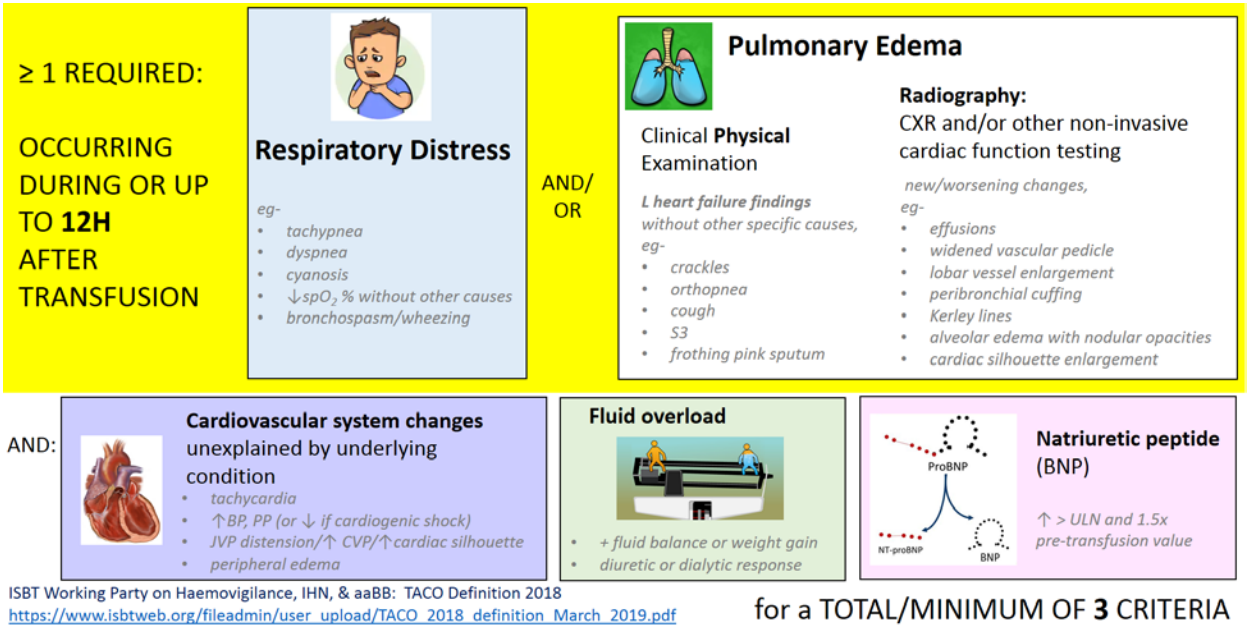
The 2nd unit is cancelled.

His JVP is at the angle of the jaw, his chest fields have crackles, and bipedal pitting edema is up to the knees.

CXR shows bilateral infiltrates with cardiomegaly, in keeping with pulmonary edema.

1. Which of the following might have been his *best defense* against TACO?
   A. Fresh (<14 day old) RBC
   B. Pre-transfusion furosemide
   C. Slower administration of the unit (over 3-4h instead of 1h)
   D. Treatment of his underlying CLL in order to open pulmonary lymphatics

This patient had tachypneic, hypoxic respiratory distress with features of pulmonary edema (crackles, radiographic CHF) and cardiovascular system changes (increased HR, BP, JVP with pedal edema) within 12h of blood product exposure. He meets diagnostic criteria for TACO by the minimum of 3 domains.



In the context of withheld diuretics, cardiac risk factors, and volume loading, he has significantly desaturated.

A. Fresher blood has not been shown to reduce the risk of TACO (be it across fresh-blood RCTs or in data beyond preclinical animal models)

B. A definitive study to establish the role or effect of furosemide as a premedication has not yet been done beyond pilot form; as this patient was oliguric and hypotensive, the strategy favoured volume restoration rather than reduction.

C. **CORRECT.** Though prospective studies on the efficacy of slower vs faster infusion rates in blood transfusion have not been performed, and though TACO can still occur with low volume loads (ie- the typical 1u RBC order), a **slowdown would have been the most feasible, intuitive, and affordable approach from among the choices listed.** It is also important to note that **one unit at a time** should be transfused in a non-bleeding, stable patient.

D. We can only speculate that the CLL contributed to his susceptibility to TACO by impairing fluid clearance by pulmonary lymphatic "impaction." The extent to which lymphatics play a role in TACO, or the extent to which lymphatics are impaired in lymphomas, is not known.

2. Which one of the following is true of TACO?
    - **A. A RBC unit is more "TACO-genic" than a platelet transfusion**
    - B. Fever with a suspected TACO argues for another diagnosis
    - C. It is the 2nd commonest cause of respiratory transfusion reactions
    - D. It is the 2nd commonest cause of transfusion-related death

A. **CORRECT. This is true for a variety of reasons.**

- Packed cell volumes (PCV) in cellular components are intravascularly retained (ie- RBC: >65% PCV, vs PLT: <1% PCV), exerting more effect per mL than cell-free, isotonic/iso-oncotic infusions;
- indeed, the typical volume that elicits TACO is 250-300cc in adults, and is "RBC-disproportionate" (ie- even when corrected for the number of RBC units issued in relation to other products); and
- RBC transfusions may follow fluid loading, wherein hemodilution reduces the Hb (truly ± artefactually), thereby triggering the order for a RBC unit that the circulatory system is even less able to accommodate.

B. In TACO, fever is NOT a rule out criterion (like "alternative explanations" in the HIT 4T score). In fact, a third of TACO presentations co-manifest with fever. As well, pre-transfusion fever increases the odds or apparent susceptibility to TACO. Which mediators are responsible (in which products, and in what amounts)… remain to be determined.

C. TACO occurs more often than originally appreciated. Though passive systems historically captured TACO at rates of 1 in 1000 or less, more active reporting systems recognize this as a top-tier-frequency risk (at 1-10% per encounter). TACO is more common than TRALI, TAD, and severe (cardiopulmonary-involving) allergic spectrum reactions.

D. This was once true but is now false, ie- TRALI (previously #1) and TACO (now #1 from 2) have traded positions. With TRALI mitigation, casemix changes (ie- more TACO-susceptible patients in modern times) and awareness/reporting, TACO leads as the cause of reported transfusion fatalities in the US (FDA), UK (SHOT), and Canada (TTISS).

Suggested References:

Parmar N, Pendergrast J, Lieberman L, Lin Y, Callum J, Cserti-Gazdewich C. The association of fever with transfusion-associated circulatory overload. Vox Sang. 2017 Jan;112(1):70-78.

Yuan, Yin, et al. "The impact of revised definitions for transfusion-associated circulatory overload and transfusion-related acute lung injury on haemovigilance reporting." *Vox Sanguinis* 118.3 (2023): 199-206.

Bulle et al.: *The recipe for TACO: A narrative review on the pathophysiology and potential mitigation strategies of transfusion-associated circulatory overload.* Blood Rev **2021**: 100891.

Case 2

You are called to the hematology ward to review an 87 year old woman admitted with febrile neutropenia after myeloma therapy. She has had 8 previous pregnancies, and also has hypertension.

She experiences fevers, rigors, and tachycardia following a 7-day-old platelet transfusion.

	Pre-transfusion	Post-transfusion
HR	75	110
BP	104/62	130/80
Temp	37.3°C	39.9 °C
RR	16	30
SpO_2	98% (room air)	95% (room air)

Labs:

Pre-transfusion: Hb 68, WBC 0.2, platelets 6

Patient blood group A+

Platelets transfused: Group O, day 7, single donor apheresis collection

3. Which one of the following is the best possible option for investigation and management of this patient?
   A. hemolysis biochemistry
   B. no investigation needed; already admitted with febrile condition
   C. review chart (temperature trends, antibiotics, cultures)
   D. serology and microbiology (patient & product)

A. Choice A only detects hemolysis but not its serologic driver (ie- would need repeat G&S, DAT and clerical check of platelet unit), nor does it consider sepsis from bacterial contamination.

B. Choice B would be under-investigation.

C. Choice C only looks at the underlying cause (e.g. febrile neutropenia). However, reviewing the chart is still often helpful in ascertaining whether there was a concomitant process, as well as the imputability of this reaction. While this should still be done, it is not the best possible option here.

D. CORRECT. This addresses serologic AND microbiologic causes of high-risk fever, given that acute hemolysis or bacterial contamination are high on the differential. If serology is positive, or if there is a high suspicion for hemolysis (as is the case here, with a group O platelet to a group A recipient), hemolytic markers (LDH, bilirubin, haptoglobin) should also be reflexed. **This is further discussed below.**

Clinical Pearls: Differential and approach to a high-risk febrile reaction:

This is a high-risk febrile reaction, marked by both rigors, and a Tmax >39°C (with >Δ1°C from baseline).

If she had no symptoms and no vital sign disturbances, with Tmax <39°C, she would have qualified as a "low-risk" fever, and would not require any further tests. This is due to the low yield of investigation. Acute

hemolytic transfusion reactions (ATHR) and transfusion-associated sepsis (TAS)/bacterial contamination (BaCon) must be ruled out for a high-risk febrile reaction.

AHTR may manifest with fever, chills, rigors, nausea/vomiting, pain (at infusion site or in flanks), dyspnea ± hypoxia, hypotension, tachycardia, visible hemoglobinuria and/or pigment nephropathy/acute tubular necrosis, and rarely disseminated intravascular coagulation (DIC).

TAS/ BaCon may likewise manifest with fever, chills, rigors, nausea, or vomiting, dyspnea ± hypoxia, hypotension/septic shock, tachycardia, oliguria, and DIC. This case may be at higher risk of BaCon since it involves a last-day shelf-life platelet and platelets have a higher risk of BaCon since they are stored at room temperature. Cultures (both patient and product) and serology, alongside hemolytic markers, would help distinguish between the two.

Diagnoses of exclusion are the underlying disease (eg. incipient/pre-existing febrile neutropenia) or a febrile non-hemolytic transfusion reaction (FNHTR). FNHTR would be the most common explanation for fevers not due to underlying illness.

The rise in HR and BP may be confounded by the fever and rigors, or may reflect an additional, independent cardiovascular insult (such as TACO). Fevers occur in 1/3rd of TACO cases (Parmar, Vox Sanguinis 2016).

The dyspnea with the reduced O_2 saturation may be an artefact of rigors (not being able to get an accurate pulse oximetry reading), or reflect a respiratory insult (such as a dyspneic febrile non-hemolytic transfusion reaction [FNHTR], and/or a change due to the underlying condition).

Based on the differential diagnosis above, the approach is:

- Rule out hemolytic reaction: A "transfusion reaction specimen" is assessed for the colour of the spun plasma (looking for hemolysis) and sent for DAT with a repeat G&S, while a clerical check of labels is also performed with a review of the typing of the patient and the product.
    - The product may contain anti-A
        - This could be an AHTR if there is a significant drop in Hb with associated hemolytic changes.
- Rule out microbiologic cause: The implicated product, and the patient (by infusion line, other catheters, and by peripheral blood venous stab) should be cultured. Suspected BaCon must be reported.
- Clinical case review should include: Pre-existing VS trends (fevers, daily Tmax), WBC/ANC trends (onset date for severe neutropenia), pre-existing microbiology culture results, symptoms/signs of a pre-existing focus of infection, antibiotic initiations, and radiologic investigations for a focus.

This was a transfusion-associated high-risk fever, probably due to a febrile non-hemolytic transfusion-reaction (FNHTR), with recently remitting/actively treated febrile neutropenia.

FNHTR has traditionally been defined as a rise in temperature of greater than or equal to 1°C that cannot be explained primarily by the patient's condition, and in some cases accompanied by chills, rigors, cold, discomfort, or some combination thereof. Occasionally, symptoms such as headache, nausea, vomiting, and dyspnea have also been described, & appear during or soon after transfusion.

The frequency of FNHTR varies according to the type of product administered, its modifications (eg. prior leukoreduction), and the sensitization or exposure history of the recipient.

Platelet components have a roughly 2 to 20-fold higher reaction rate than do red cells (0.06 to 37.5 reactions per 100 transfusions ["1 in 20"], versus 0.04 to 6.8 per 100 units respectively ["1 in 300"]).

Two well-described mechanisms cause FNHTRs:

- recipient anti-leukocyte antibodies against residual product leukocytes
    - This grand multipara has a significant "exposure history"; and
- storage-generated pyrogenic mediators (e.g. cytokines).

Since 1999, Canada has had a policy to universally prestorage leukoreduce blood, which has cut the rate of FNHTR by roughly 50%.

Case 3

An athletic 17 year old male with ALL is undergoing induction chemotherapy (day 3 of the Dana Farber protocol, with no infusion reactions yet). He is hemodynamically stable, afebrile, and on room air.

His CBC today shows WBC 0.4, plt <10, Hb 69.
He is ordered 1 adult dose of platelets and 1u RBC.

The platelet transfusion is completed and the RBC unit is hung.
After 100mL of RBC have been transfused, the patient becomes febrile, dyspneic, tachypneic, and his spO2 drops to 78% on room air.

The transfusion is stopped and he transfers to the ICU.
He is given furosemide and salbutamol with no effect, and requires intubation.
CXR shows new bilateral infiltrates; admitting CXR is unremarkable.

4. Which one of the following is the most likely diagnosis?
    A. atypical pneumonia due to immune compromise
    B. chemotherapy-related ARDS
    C. type 1 ("definite") TRALI
    D. type 2 ("possible") TRALI

A. Atypical pneumonia is not impossible, but CXR shows new infiltrates (by contrast with a normal admitting CXR). This would be unlikely to present so rapidly and severely (and in such temporal correlation with the blood product). Further, he is noted to be hemodynamically stable and afebrile prior to transfusion.

B. ARDS in hematologic malignancy occurs more commonly in the neutrophil count recovery phase, so this is unlikely now. This would also not explain the temporal association with transfusion.

C. CORRECT. Definite (type 1) TRALI is the diagnosis if there is no alternative explanation. Though he has a new diagnosis of leukemia, there is no hyperleukocytosis (leukostasis), and his neutropenia has not (yet) presented with an apparent infection.

D. While type 2 TRALI acknowledges priming by background factors or an already compromised baseline, these are stable in the preceding 12h. Had he been hypoxic but on a stable level of supplemental oxygen, this may have been a consideration.

Clinical pearl: TRALI Incidence

TRALI accounts for ~1% of reported reactions, (and 4% of the serious ones), but it has not been eliminated, and it is still a leading cause of transfusion-related death (at 15%, second to TACO [36%]). After TRALI reduction measures, incidence has decreased by ~50% to less than 1 in 10,000. Plasma (antibody) – containing products have associated most strongly with TRALI.

5. The patient's parents are upset and want to know why this happened and what can be done to prevent it from happening again. What would you suggest?
    - **A.** antihistamine, acetaminophen, and furosemide reduce severity
    - **B.** irradiation of cellular products prevents TRALI
    - **C.** IVIG and steroid will mitigate recurrence risk
    - **D.** **supportive care is mainstay; most recover within 48-96 hours**

A. Incorrect for multiple reasons:
    i. Based on the most recent systematic review/meta-analysis of antipyretic and antihistamine premedications, there is insufficient evidence to prescribe acetaminophen to prevent FNHTR, or antihistamine to prevent allergic reactions, let alone other wishful bystander benefits in TRALI.
    ii. Furosemide as a pre-medication is of intuitive appeal for preventing **TACO**, but its role is yet to be definitively established. Furthermore, furosemide is not expected to help TRALI, as non-cardiogenic pulmonary edema is not a volume problem, and may in fact induce/worsen hypotension . While ARDS may benefit from diuretics, unconditional diuresis of suspected TRALI may be harmful, and is not recommended unless the patient's volume status suggests a need.

B. Irradiation is indicated to prevent TA-GVHD in those at risk of engraftment by potentially viable contaminating/residual lymphocytes in cellular components. Irradiation induces DNA damage, thereby stopping division/proliferation. Irradiation does not kill the bacteria that can cause BaCon, nor alter antibody molecules capable of causing hemolysis or TRALI.

C. Though murine models show some attenuation of lung injury with IVIG given before leukoagglutinin infusion, it is impractical to administer IVIG before all transfusions for such a rare reaction type, and IVIG is not without its own adverse effects. (Note that case reports of TRALI are also described with IVIG.) Steroids are neither a prevention nor definitive treatment of TRALI.

D. **CORRECT.** As TRALI is donor- or product-attributable, improvement is expected as long as the patient has adequate reserves; the harmful mediator was passive and finite. If ALI/ARDS continues beyond 4-7 days, one should consider pathologies other than TRALI.

6. Based on what is known about TRALI, which of the following is the strongest measure by which to protect other recipients?

   A. informing the Transfusion Transmitted Injuries Surveillance System (TTISS)

   B. launching an incident report

   C. placing an alert in the patient's allergy profile

   D. **reporting the suspected TRALI to blood bank**

A. Though reporting to TTISS enables the country to have data to inform risk discussions and observe trends over time, it does not link to donors or producers and products for testing and isolating problematic materials.

B. TRALI is not a medical error but an intrinsic biologic hazard in the product. Ad hoc corrective action meetings on hospital processes will not change the fate of this reaction having occurred in the patient or in others, unless there was indeed a process of concern (ie- infusing too quickly without supervision, or ordering a product that was unnecessary in retrospect).

C. TRALI is not an allergic reaction, and labelling the patient as having a blood allergy may cause the harm of undertransfusion or delay to transfusion with the next instance that blood products are indicated.

D. **CORRECT**. By reporting to the blood bank, a series of actions follows. Every effort is made to quarantine co-components (wherever they may be) so that any humors responsible for the observed severe reaction are not administered to others by in-date products from the implicated donor/donation. A TRALI Review Working Group assesses for whether the donor ought to be investigated, and if so, is contacted for tests of the anti-leukocyte antibody (HLA PRA) repertoire, and for whether or not it is cognate with the recipient's (HLA) profile. Alignment would support the provisional diagnosis of immune complex TRALI. If the case is suspicious enough, then the donor is deferred. If moderate doubt and concern co-exist, then the donor may be flagged ("on surveillance") so that a future adverse occurrence triggers deferral by proof of reproducibility.

Clinical Pearl: Preventative Strategies

Blood supply systems world-wide have reacted with donor selection and component production adjustments. In Canada, non-nulliparous donors are deferred from apheresis (plasma or platelet) donations. Whole blood from ever-potentially-pregnant donors is manufactured in such a way that the plasma is "recovered", ie-diverted to the fractionation industry for pooling, while whole blood buffy coat-derived platelets are pooled in a pack suspended with a male donor's plasma ("buffy coat platelets"). These changes were implemented in Canada in 2008.

Suggested Reference:

https://professionaleducation.blood.ca/en/transfusion/publications/transfusion-related-acute-lung-injury-trali

Case 4

A 52 year old male was in the OR for a 4-vessel CABG.
He received a 400mg dose of protamine at 17:15,
then 1 dose of platelets, 2u FP, and 1u RBC.
As he was coming off bypass pump, he developed an extensive urticarial rash (75% TBSA) with shock (BP 70-80/40) and bradycardia (20-80).

He had no known history of allergies and no prior exposures to blood products.

He was bolused phenylephrine 40 mcg IV with dopamine at 3 mcg/kg/min IV & norepinephrine at 0.1 mcg/kg/min IV.
He was also given diphenhydramine 50 mg IV + hydrocortisone 100 mg IV.
There were no respiratory/oxygenation changes, with P/F ratio remaining >300 with FiO2 30 – 50% during mechanical ventilation, which was continued, as he had significant airway and peri-orbital angioedema.
On transfer to the CVICU at 19:15, he was hypothermic (33.1°C), and required ongoing boluses, pressors, and inotropes for a period of 12h.

7. Which one of the following investigations yields a result most likely to guide future transfusion advice to the patient?
   - **A. baseline IgA level and presence of anti-IgA IgG**
   - **B.** CBC, PT, aPTT, fibrinogen
   - **C.** culture patient and blood products
   - **D.** repeat blood group, IAT, and DAT

A. CORRECT. It is important to determine if the patient has severe IgA deficiency because:

- IgA deficiency-related anaphylaxis was thought to be a major cause of anaphylaxis [--although >80% of anaphylaxis cases remain unexplained in hemovigilance systems despite this testing!], and
- Knowing the cause allows for specific treatment/products to be secured e.g. IgA deficient products or washed products.

B. These are coagulation parameters; as this patient appears to have suffered an anaphylactic transfusion reaction, they would not provide guidance regarding future transfusion strategies.

C. Culturing the patient and blood products may provide information on TAS/BaCon (see discussion titled Clinical Pearls: Differential and approach to a high-risk febrile reaction above). However, given that this is likely an anaphylactic transfusion reaction, this would not be the next appropriate step.

D. These serologic investigations are not helpful in providing further guidance in the setting of an allergic or anaphylactic reaction. This presentation is unlikely to reflect RBC incompatibility/hemolysis,

He recovers and is extubated on POD1.
He is discharged home on POD7 after an uneventful post-operative course.
Laboratory testing reveals evidence of IgA deficiency (on a pre-transfusion specimen) and post-reaction detection of anti-IgA IgG in the patient's serum.
Two years later he is back, needing a hip replacement.

8. Which strategy would you adopt for this case?
    - **A.** bloodless surgery
    - **B.** cancel surgery
    - **C.** fractionated blood substitutes
    - **D. stock 2u washed or IgA deficient RBCs**

A. This is not a practical solution; while patient blood management (PBM) principles should be applied, it is not true that he cannot be transfused. Banning blood may be detrimental to him in both (A) & (B).

B. Cancelling surgery would not be ideal given that other options are available in this case.

C. This option may not be safe. Firstly, we do not have licensed RBC substitutes. Secondly, although plasma can be contrived by its purified protein products (eg PCC, fibrinogen, albumin), these are not guaranteed to be as free of IgA as components donated from individuals who are known to be IgA deficient.

D.CORRECT. If we assume that IgA deficiency is the basis of his previous reaction, we would favour safe-for-IgA deficiency products. If there was a need for plasma (unlikely in hip surgeries, but may be needed in other types of surgery), we would also stock IgA deficient plasma; this can be brought to the hospital, and only thawed if needed.

CLINICAL PEARL: Understanding IgA deficiency

The bigger question is the relevance of IgA deficiency in any given anaphylactic reaction.

Individuals with a reassuring exposure history (ie- many uneventful transfusions, with one anaphylaxis event) may be re-exposed without testing; if a reaction recurs, then testing & special management are justified, but if a reaction does not recur, then the patient has proven themselves tolerant.

However, in someone who has reacted early (and especially serially) into their blood product exposure history, the precautionary principle would be to assume that IgA deficiency may be at play. In the setting of anaphylatic reactions or multiple (at least two) severe allergic reactions, if tests reveal IgA deficiency, then managing with IgA deficient or washed blood products is justified. If there is no IgA deficiency (or IgA sensitization), then exposures to unmodified products may resume, although if reactions recur, then modifications (such as washing to remove other mediators in the plasma) may be required.

If this was not a reaction case, but we were told that the patient was incidentally noted to be IgA deficient, (as may occur on pre-operative chart review), it is NOT necessary to test for anti-IgA IgG, nor to provide IgA-free products.

The risk of testing in a patient who has not had a previous reaction is that up to 1/3rd of IgA deficient individuals may be found to be sensitized (having anti-IgA IgG). Though having anti-IgA IgG may be a predictor of the experience of anaphylaxis, the positive predictive value is poor (ie- twice as many examples of non-reactors as reactors in a scoping review of exposures [Rachid & Bonilla, J Allergy Clin Immunol 2012]). However, if anti-IgA IgG is tested for, and it is absent, then some reassurance may be gained on unmodified exposures.

Contingencies/Options for Transfusion Support & Challenges

	Give un-altered/ routine products & observe what happens	"plasma" (supernatant) volume reduction (PVR)	Washing	Sourcing from IgA deficient donors	Solvent-detergent-treated
Platelets	*(riskiest of these options)*	*(though performed at some blood banks, will not deplete IgA)*	*(few banks offer, and action strips product)*	Usually at least 1 dose available in national inventory at any given time, but not guaranteed, and delivery may not be immediate	Not an option
Plasma	*(riskiest of these options)*	*Not applicable! (PVR = no plasma left!)*	*Not applicable* *(washing = no plasma left!)*	Frozen stock usually available but may be scarce & need to be transported in	SDP (eg Octaplas) may help in recurrent (non-IgA-deficient) reactors

RBC	*(risky, but less so than platelets or plasma, due to low plasma content in the product [2-20cc]; this may arguably be the safest "unmodified starter/re-exposure" product)*	*(though performed at some blood banks, will not deplete IgA)*	Feasible at some blood banks, or may be ordered as such from CBS	Feasible, but IgA deficient donors will be favoured for apheresis plasma and platelet donations; RBC stock may take more time to amass, especially if there are also RBC antigen matching needs	Not an option

If IVIG is needed, there is a known spectrum for IgA content:

	Gammagard S/D (Shire)	Privigen (CSLB)	Gamunex/ IGIVnex (Grifols)	Pfizer Panzyga	Gammagard Liquid (Shire)	Octagam (Octpaharma)
IgA content	≤ 2.2 µg/mL	<25 µg/mL	46 µg/mL	100 µg/mL	140 µg/mL	≤ 400 µg/mL

If scIg is needed, the spectrum of IgA content is as follows:

	Hizentra (CSLB) 20%	IGIVnex/Gamunex (Grifols) 10%	Cuvitru (Shire) 20%	Cutaquig (Octapharma) 16.5%
IgA content	< 50 µg/mL	< 84 µg/mL	< 280 µg/mL	≤ 400 µg/mL

Suggested reference:

https://professionaleducation.blood.ca/en/transfusion/publications/anaphylactic-transfusion-reactions-and-iga-deficiency

*Please note that the above contains a helpful algorithm for how and when to test for IgA deficiency