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Association for the Advancement of Blood & Biotherapies

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To: AABB Members

From: Jose Cancelas, MD, PhD – President
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Re: Transfusion-Related Alpha-Gal Syndrome

Association Bulletins provide a mechanism for publication of documents that have been approved by the Board of Directors for distribution to individual and institutional members, such as:

- Standards that were adopted after publication of the most recent edition of *Standards.*
- Statements of AABB policy intended for distribution to members.
- Guidance, recommendations, and reports that have been developed by AABB Committees or National Office staff for distribution to members.

This Bulletin provides:

1. Background on:
   - Alpha-Gal Syndrome (AGS), including pathophysiology, epidemiology, and diagnosis.
   - Transfusion-Related Alpha-Gal Syndrome (TRAGS), including observational cases of presumed TRAGS and hemovigilance data.
2. Recommendations for hospital transfusion services and blood suppliers regarding:
   - Evaluating and identifying TRAGS.
   - Managing transfusion risk for patients with a TRAGS diagnosis.
   - Assessing regional AGS prevalence to inform implementation of additional risk reduction strategies.
   - Managing blood inventories to support patients with a TRAGS diagnosis.

Background

1. Alpha-Gal Syndrome

AGS is an acquired food allergy.[1-3] AGS is distinguished from most IgE-mediated food allergies by a characteristic delay between ingestion and symptom onset, commonly 2-6 hours after consuming mammalian meat.[1,2,4] Clinical manifestations range from mild urticaria and gastrointestinal symptoms to severe anaphylaxis with hypotension and respiratory compromise. Patients with AGS may also have severe allergic reactions to dairy products, gelatin, and cetuximab, a monoclonal antibody used to treat certain cancers.[1,6]

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Pathophysiology of AGS

The oligosaccharide galactose-α-1,3-galactose (alpha-gal) is widely expressed by all mammals except for humans, apes, and Old World monkeys.[1,2] All humans have naturally occurring immunoglobulin (Ig)M, IgG, and IgA antibodies to alpha-gal. Humans do not normally form IgE antibodies to alpha-gal. The bites of certain tick species, however, can induce alpha-gal IgE formation.[7]

Once formed, alpha-gal IgE binds to high-affinity receptors (FcεRI) on mast cells and basophils.[8,1] Subsequent exposure to alpha-gal epitopes cross-links the cell-bound alpha-gal IgE, triggering degranulation and release of mediators such as histamine, which produce the clinical manifestations of AGS. The delay between mammalian meat ingestion and symptom onset reflects the biological handling of dietary alpha-gal.[8,9] In contrast, delivering alpha-gal epitopes intravenously (eg, cetuximab infusion) provokes more immediate reactions because gastrointestinal processing is bypassed.

Epidemiology and Risk Factors for AGS

AGS occurs predominantly in regions where hard ticks are endemic.[7] In the United States (US), sensitization is mainly associated with *Amblyomma americanum* (the lone star tick), with suspected cases concentrated in the Southeast and parts of the Midwest and Mid-Atlantic regions (see Figure 1).

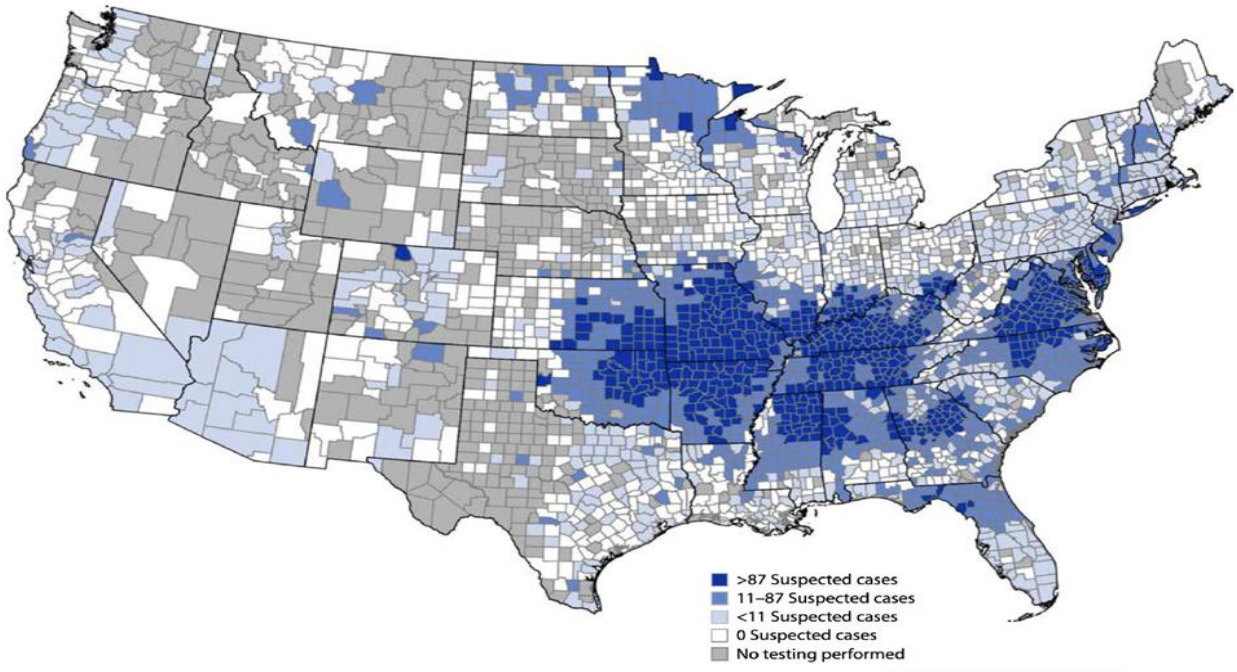

Figure 1. Suspected cases of Alpha-Gal Syndrome per 1 million population per year.[10]

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Other tick species (eg, *Ixodes scapularis* and *Ixodes pacificus*) have also been implicated. The US Centers for Disease Control and Prevention (CDC) estimates that up to 450,000 persons in the US may have been affected by AGS since 2010.[10] Based on 3,000 residual blood donor samples collected during 2024-2025 from 10 states, the estimated alpha-gal IgE seroprevalence ranged from 1.1% in Washington to 31.2% in Arkansas. Overall, the combined estimated seroprevalence in the five states with the highest seroprevalence was 24.0%.[11] Risk factors include outdoor occupational or recreational exposure in tick-endemic areas, and repeated tick bites appear to increase both sensitization rates and alpha-gal IgE levels, whereas IgE wanes with tick avoidance. Outside the US, AGS has been linked to other tick species, including *Amblyomma testudinarium* in Japan, *Ixodes holocyclus* in Australia, and *Ixodes ricinus* in Europe (see Figure 2).[12,13]

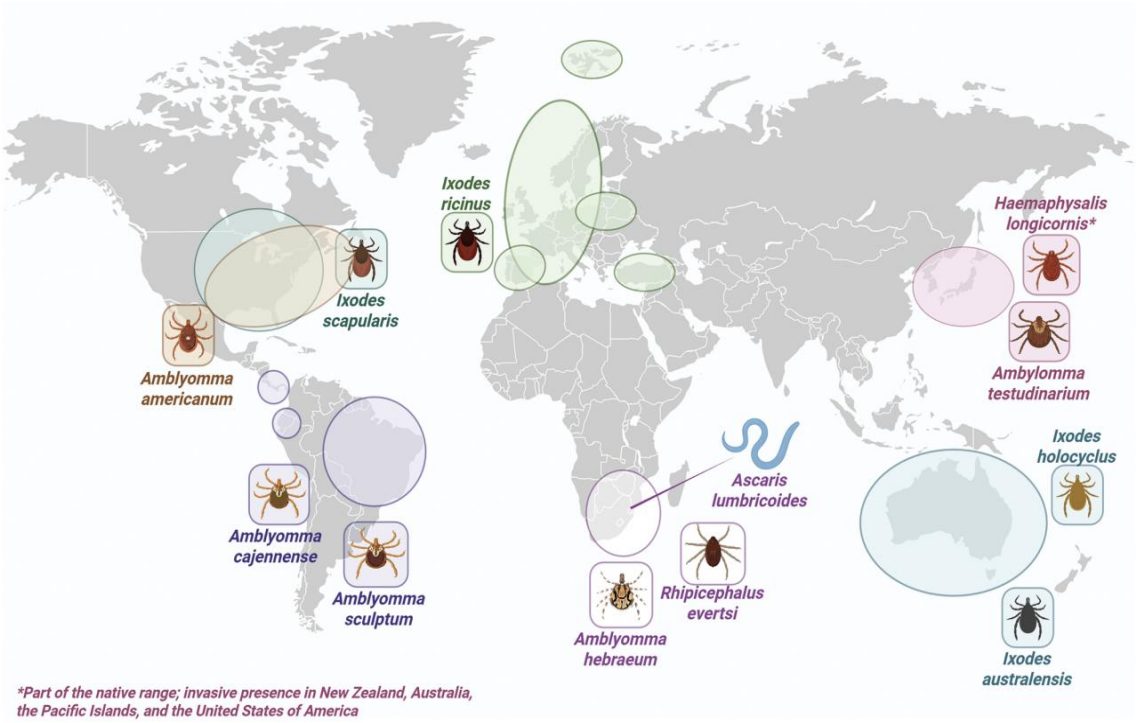

Figure 2. Geographic distribution of tick species associated with Alpha-Gal Syndrome.[11]

Diagnosis of AGS

Diagnosis is based on a compatible clinical history plus serologic confirmation of alpha-gal IgE (≥0.1 kU/L).[1,3] The alpha-gal IgE level does not predict clinical severity,[1] and asymptomatic sensitization is common. Therefore, results should be interpreted in the context of exposures and symptoms.

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2. Transfusion-Related Alpha-Gal Syndrome: Background and Pathophysiologic Rationale

There is mounting evidence to support the recognition of TRAGS as a distinct form of allergic transfusion reaction.[14-16] TRAGS is hypothesized to occur when recipients with preformed alpha-gal IgE receive B antigen-containing platelets or plasma components, triggering a severe allergic or anaphylactic reaction.[14-16] The proposed mechanism is based on structural similarity between alpha-gal and the ABO blood group B antigen. This similarity permits cross-reactivity of recipient alpha-gal IgE antibodies with B antigen in transfused components.

Major ABO-incompatible platelet and plasma units are often issued in bleeding emergencies and to minimize product wastage.[27] Although this practice is generally considered safe, ABO-incompatible platelet transfusion has been associated with a 1.5- to 2-fold increase in allergic transfusion reactions.[18] TRAGS may account for a subset of these reactions. An international multi-site survey demonstrated that on average, group O recipients received group B or AB products in 5.6% of platelet transfusions and 13.1% of plasma transfusions.[27] Although these components contain minimal residual red cells, B antigen is expressed not only on red cells but also on platelets and in soluble form in the plasma of donors with the secretor phenotype.

Other blood donor- and patient-specific factors may be important. For example, only FUT2-positive secretors should have the B antigen present in their plasma. Also, the density of the B antigen on platelets may be a factor. These details may be elucidated in future studies.

Published Cases of Presumed TRAGS

As of July 5, 2026, nine cases of presumed TRAGS have been reported in the literature.[3,14-16,19] Features of these cases:

- Most patients were men (7/9; one case no gender provided).
- All were blood group O.
- Median age was 59 years (range 29 to 83).
- All experienced anaphylactic reactions to group B or AB platelets and/or plasma
    - One death occurred as a result of anaphylaxis.

Of the six cases reporting tick exposure history, five had known tick bites. Alpha-gal IgE levels were measured in patients (including one who denied tick exposure), and all were elevated. Two patients carried a formal diagnosis of AGS at the time of transfusion and two patients had histories suggestive of mammalian meat allergy.

In one reported case, in-vitro testing demonstrated that the patient's IgE to alpha-gal cross-reacted with B antigen and mediated basophil activation in the presence of either alpha-gal or B antigen, providing mechanistic support for the TRAGS hypothesis.

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Additional Observational and Hemovigilance Data

Other reports may reflect previously unrecognized TRAGS. Joubeh et al described two group O patients who experienced anaphylaxis following the transfusion of pathogen-reduced group B or AB platelets.[20] The investigators initially hypothesized that the reactions were due to psoralen allergy. However, both patients subsequently tolerated multiple transfusions with pathogen-reduced group O and A platelets.[3] Rossi et al reported institutional data demonstrating higher allergic reaction rates in group O patients receiving group B platelets and notably suggested a possible association with AGS.[4]

In a multicenter, retrospective, observational cohort study, group O recipients of group B or AB plasma or platelet transfusions were found to be at a fourfold higher risk of an acute transfusion reaction compared with group O recipients of group O units in AGS high-prevalence regions exclusively. Compared with patients at AGS low-prevalence sites, patients at AGS high-prevalence sites had an absolute risk of 11 more moderate-severe reactions per 10,000 transfusions.[5]

A nationwide hemovigilance analysis by the Établissement Français du Sang (EFS) reviewed approximately 1.5 million plasma and platelet transfusions over three years. Severe allergic transfusion reactions were significantly more frequent when group B or AB platelets or plasma were transfused to group O recipients, but not when transfused to group A recipients, compared with all other ABO combinations.[22]

A small French observational study found that in patients who had experienced severe allergic transfusion reactions, group O recipients of group B/AB units were significantly more likely than controls to have formed alpha-gal IgE.[6]

This epidemiological evidence suggests that in AGS high-prevalence regions, the risk of TRAGS is greater than in low-prevalence regions. Because the direct evidence for TRAGS is limited to nine reported cases, an estimate of TRAGS risk is not currently possible. The recommendations in this bulletin are based on indirect and limited direct evidence; thus, other potential mechanisms should be considered for severe allergic reactions.

Recommendations for Hospital Transfusion Services

1. Evaluate Patients with Severe Allergic Transfusion Reactions to Identify TRAGS Cases

Group O recipients:
A diagnosis of TRAGS should be considered when a group O recipient develops a severe allergic transfusion reaction (eg, respiratory symptoms, hypotension, and/or throat or facial swelling) following transfusion of group B antigen-containing platelets or plasma. The patient's

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serum should be tested for alpha-gal IgE.[27] A serum alpha-gal IgE level ≥0.1 kU/L is considered compatible with TRAGS.[1]

Non-group O recipients:

- Group B or AB patients are known to be at reduced risk for AGS[24,25] and are similarly expected to be at markedly lower risk for TRAGS reactions.
- The relative susceptibility of group A patients for TRAGS warrants further study. If a group A patient has a severe allergic reaction to a group B or AB blood component, it would be reasonable at this time to measure serum alpha-gal IgE.

Additional tests that may help to confirm a diagnosis of TRAGS:

- Serum tryptase (might be elevated in the setting of a severe allergic reaction, although the test has 40-70% sensitivity; tryptase level normally returns to baseline within 24 hours). Serum tryptase can remain elevated in some medical conditions (eg, hereditary alpha tryptasemia; myeloid leukemias).
- Serum IgA (as an initial test to exclude IgA deficiency as a possible cause of severe allergic reaction).

2. If a Patient Is Diagnosed with TRAGS

- Ensure that the patient does not receive group B antigen-containing platelets or plasma in the future.
- Consider referring the patient to allergy/immunology personnel for formal AGS evaluation. Of note, TRAGS can occur in patients who have alpha-gal IgE but have no history of mammalian meat allergy.
- Unlike conventional allergic transfusion reactions, it is unclear at this time whether plasma reduction strategies (eg, washing, platelet additive solution) can help to prevent or mitigate TRAGS reactions.
- Report the case to hemovigilance agencies.

3. Assess Regional AGS Prevalence to Inform Implementation of Additional Risk Reduction Strategies

- Hospital transfusion services should assess AGS prevalence within their geographic service area and primary patient catchment regions. For the US, the best prevalence data are available from a 2023 publication by Thompson et al (table 1 therein).[9] A wide global distribution of ticks associated with AGS is described in a scoping review by Owens-Pickle (table 2 therein).[12]
- **AGS low-prevalence regions**: Routine changes in transfusion practice are generally not warranted. However, awareness should be maintained given the possibility of patients visiting or moving from higher-prevalence areas. Restricting group O patients with a history of meat allergy and/or patients testing positive for IgE alpha-gal from receiving group B or AB platelets or plasma is appropriate.

- **AGS medium-to-high-prevalence regions**: Because the incidence of TRAGS remains undefined and the inventory implications of broad ABO restriction strategies may be substantial, regional risk-reduction approaches should be implemented cautiously and in collaboration with blood suppliers. Some risk reduction measures could include:
    - Applying informatics tools within the electronic health record to identify patients with elevated alpha-gal IgE and/or history of AGS.
    - Including questions about meat allergies/AGS when obtaining informed consent from patients who might receive blood components.
    - Restricting patients with a possible history of AGS from receiving group B/AB platelets or plasma.
    - Developing strategies in the hospital that would restrict group B/AB platelets and plasma from being given to group O patients for routine transfusions. These strategies could be quickly deployed if there is an increase in severe TRAGS cases.
        - These strategies should be developed in collaboration with blood suppliers.
        - In emergency situations, transfusions should not be withheld.
    - Using group A plasma instead of group AB plasma for emergency transfusion when the recipient's ABO group is unknown.[26,27]

Adoption of any risk reduction strategy should include evaluation of inventory impact. Close collaboration with blood suppliers will be crucial to maintain the blood supply.

Recommendations for Working with Blood Collectors

1. Adoption of any risk reduction strategy should include evaluation of inventory impact and communication with blood suppliers.
2. Collectors and hospital transfusion services should collaborate to evaluate the feasibility, clinical prioritization, and inventory impact of requests to restrict group B antigen-containing platelets and plasma for patients with known or suspected TRAGS.

Conclusion

TRAGS represents a newly recognized type of allergic transfusion reaction, which can occur in group O recipients of group B or AB platelets or plasma. These reactions can be severe or even fatal. Although the overall incidence remains undefined, accumulating mechanistic, case-based, and epidemiologic evidence supports continued vigilance.

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Hospital transfusion services in AGS high-prevalence regions should consider measures that will mitigate the risk of TRAGS. However, measures taken to mitigate the risk of TRAGS must be balanced with considerations for the wider blood supply.

Recommendations may evolve as further data clarify the epidemiology, clinical significance, and optimal prevention strategies for TRAGS.

References

1. Commins SP. Diagnosis and management of alpha-gal syndrome: Lessons from 2,500 patients. Expert Rev Clin Immunol 2020;16:667-77.
2. Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol 2009;123:426-33.
3. Binder AM, Commins SP, Altrich ML, et al. Diagnostic testing for galactose-alpha-1,3-galactose, United States, 2010 to 2018. Ann Allergy Asthma Immunol 2021;126:411-6.e1.
4. Hilger C, Fischer J, Wölbing F, Biedermann T. Role and mechanism of galactose-alpha-1,3-galactose in the elicitation of delayed anaphylactic reactions to red meat. Curr Allergy Asthma Rep 2019;19:3.
5. Kaufman RM, Hoen AG, Khan J, et al for the BEST Collaborative. Epidemiologic Study of Transfusion-Related Alpha-Gal Syndrome. JAMA Intern Med Published online August 24, 2026. doi:10.1001/jamainternmed.2026.3983.
6. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med 2008;358:1109-17.
7. Commins SP, James HR, Kelly LA, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α-1,3-galactose. J Allergy Clin Immunol 2011;127:1286-93.e6.
8. Platts-Mills TAE, Commins SP, Biedermann T, et al. On the cause and consequences of IgE to galactose-α-1,3-galactose: A report from the National Institute of Allergy and Infectious Diseases Workshop on Understanding IgE-Mediated Mammalian Meat Allergy. J Allergy Clin Immunol 2020;145:1061-71.
9. Román-Carrasco P, Lieder B, Somoza V, et al. Only α-Gal bound to lipids, but not to proteins, is transported across enterocytes as an IgE-reactive molecule that can induce effector cell activation. Allergy 2019;74:1956-68.
10. Thompson JM, Carpenter A, Kersh GJ, et al. Geographic distribution of suspected alpha-gal syndrome cases — United States, January 2017-December 2022. MMWR Morb Mortal Wkly Rep 2023;72:815-20.
11. Saunders EF, Taylor ML, Jones ES, et al. Alpha-gal immunoglobulin E seroprevalence among blood donors — 10 states, 2024-2025. MMWR Morb Mortal Wkly Rep 2026;75:315-21.

12. Owens Pickle E, Dye-Braumuller K, Self S, et al. Tick to table: A scoping review on the global impact of alpha-gal syndrome. J Med Entomol 2026;63(2):tjag040.
13. Valois A, Le Forestier J, Baduel E, et al. Risk factors for α-Gal syndrome: A case-control study exploring the role of tick bites in French Guiana. Ticks Tick Borne Dis 2026;17:102607.
14. Gilstad CW, Conry-Cantilena K, Zarpak R, Eder AF. An outbreak of anaphylactic transfusion reactions to group B plasma and platelets and its possible relationship to Alpha-Gal syndrome. Transfusion 2023;63:1997-2000.
15. Jones VM, Nakahara H, Choudhary SK, et al. Immunologic investigation of an allergic transfusion reaction suspected due to alpha-gal syndrome. Transfusion 2025;65:1989-95.
16. Miller MJ, Lee P, Lee BG, et al. Consideration for alpha-gal syndrome in two critically ill persons with group O blood who received group B plasma. Transfusion 2024;64:949-51.
17. Dunbar NM, Kaufman RM, Bary KS, et al for the Collaborative BEfSTB. ABO-mismatched platelet and plasma transfusion practices and the potential for transfusion-related alpha-gal syndrome: The Biomedical Excellence for Safer Transfusion Collaborative Study. Transfusion 2025;65:1621-9.
18. Malvik N, Leon J, Schlueter AJ, et al. ABO-incompatible platelets are associated with increased transfusion reaction rates. Transfusion 2020;60:285-93.
19. Foster M, Brown M, Mueller A, et al. Transfusion-related alpha-gal syndrome: Two new cases expanding the demographic and geographic spectrum, and evidence of a diagnostic gap in allergic transfusion reaction evaluation. Transfusion 2026;66(6):1167-79.
20. Joubeh S, Lima JLO, Wooten M, et al. Allergic reaction to psoralen-treated platelets: Real or coincidence? Transfusion 2022;62:716-7.
21. Rossi S, Wendt L, Ballas Z, Knudson CM. In response to Joubeh and Singh: Allergic reactions to platelets; to B or not to B? Transfusion 2022;62:2655-6.
22. Malard L, Beuscart C, de Chaisemartin L, et al for the Collaborative BEfSTB. Association between group B major ABO-incompatible platelet or plasma transfusion and severe allergic reactions: A nationwide haemovigilance analysis suggesting a role for α-gal syndrome. A Biomedical Excellence for Safer Transfusion Collaborative study. Vox Sang 2026;121:81-6.
23. de Chaisemartin L, Nicaise-Roland P, Malard L, et al. Severe allergic transfusion reactions to B/AB plasma or platelets in group O recipients are linked to α-Gal sensitization. Blood 2026;147(25):3113-17.
24. Rispens T, Derksen NI, Commins SP, et al. IgE production to α-gal is accompanied by elevated levels of specific IgG1 antibodies and low amounts of IgE to blood group B. PLoS One 2013;8:e55566.
25. Brestoff JR, Tesfazghi MT, Zaydman MA, et al. The B antigen protects against the development of red meat allergy. J Allergy Clin Immunol Pract 2018;6:1790-1.e3.
26. Dunbar NM, Yazer MH for the BEST-Collaborative. Safety of the use of group A plasma in trauma: The STAT study. Transfusion 2017;57:1879-84.
27. Jacquot C, Jones T, Bahar B, et al. Use of group A thawed plasma in emergency transfusions at a pediatric quaternary care center. Transfusion 2024;64:1851-9.

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