Transfusionists Talk – Transfusion Made Bloody Easy

INTRAVENOUS IMMUNE GLOBULIN (IVIG): WHAT'S SO UNIQUE?

Responses for the Additional Q&A

1. **In the presence of signs and symptoms of hemolysis in a group O recipient, is post-IVIG hemolysis automatically excluded?**

"Hemolysis:

IVIg administration commonly results in a positive direct antiglobulin test (DAT) and, in up to 3% of cases, contributes to clinically significant hemolytic events.[22, 23] IVIg-associated hemolysis has been defined by the IVIg Hemolysis Pharmacovigilance Group of Canada as:

A drop in hemoglobin of at least 10 g/l and a positive DAT within 10 days following IVIg infusion with supporting evidence of hemolysis as indicated by at least two of:

increased reticulocyte count,
increased lactate dehydrogenase level,
low haptoglobin level,
increased unconjugated bilirubin level,
hemoglobinemia,
hemoglobinuria,
or the presence of significant spherocytosis and no alternate etiology for the anemia.[24]

Many case series have described IVIg-associated hemolysis as having a higher occurrence rate in patients receiving high doses.[23, 25, 26] The lower prevalence in group O patients appears to implicate isohemagglutinins.[27] Some manufacturers are now providing IVIg products that are isohemagglutinin-depleted to minimize risk. The risk of hemolysis appears highest when a product with a high isohemagglutinin titre is administered at doses of 2 g/kg or higher to a blood group A or AB recipient;[28] some Canadian jurisdictions have implemented prospective hemolysis monitoring processes for these patients."

Reference:

Canadian Blood Services (CBS). Clinical guide to transfusion chapter 4. Immune globulin products [Internet]. Ottawa (CA); CBS: 2019 [cited 2023 Mar 23]. Available from: https://professionaleducation.blood.ca/en/immune-globulin-products

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Significant hemolysis in blood group O patients who have received IVIG should prompt investigation for other causes of hemolysis. Its occurrence could not be explained by the presence of isoagglutinins. In a publication by Bellac et al, 373 cases of severe IVIG-associated hemolysis were analyzed, including three cases of blood group O patients. For each of these three patients, however, there were other factors that could explain the hemolysis, and there was no evidence that IVIG was implicated.

As for the presence of other (non-ABO) blood group antibodies in IVIG, a small

percentage of blood donors may have those antibodies but since IVIG is manufactured from a large pool of donors those would be diluted out so much that the resulting low titres would not be clinically significant. By comparison, the majority of blood donors are group O, A or B and their plasma contains isoagglutinins. Although many of these are IgM which is mostly removed in IVIG production, IgG class isoagglutinins will still be present in IVIG.

Reference:

Bellac CL, Hottiger T, Jutzi MP, Bögli-Stuber K, Sänger M, Hanschmann KM, Keller-Stanislawski B, Funk MB. The role of isoagglutinins in intravenous immunoglobulin–related hemolysis. Transfusion. 2015 Jul;55(S2):S13-22.

Additional Reference:

Pendergrast J, Armali C, Callum J, Cserti-Gazdewich C, Jiwajee A, Lieberman L, Lau W, Lin Y, Parmar N, Pavenski K, Riden LS, Shehata N, Willie-Ramharack K, Tomlinson G, Tong TN, Binnington B, Branch DR; QUEST Research Program. A prospective observational study of the incidence, natural history, and risk factors for intravenous immunoglobulin-mediated hemolysis. Transfusion [Internet] 2021 [cited 2023 Mar 23]; 61(4):1053-1063. Available from: https://doi.org/10.1111/trf.16232

2. **Any specific considerations for the pregnant patient?**

Summary IVIG Product Monographs:

It is unknown whether IVIG can cause fetal harm if given to a pregnant woman or can affect reproduction capacity. IVIG products cross the placenta and are also excreted into breast milk. IVIG should be given to a pregnant and lactating woman with caution and only if clearly necessary.

Anecdotal practice:

For IVIG given for Fetal/ Neonatal alloimmune thrombocytopenia, the woman's pre-pregnancy weight was used for dosing weight.

Additional Reference:

Newfoundland Labrador Blood Coordinating Program. Clinical transfusion resources IVIG [Internet]. St. John's (CA); Newfoundland Labrador Blood Coordinating Program 2021 [cited 2023 Mar 23]. Available from: https://www.gov.nl.ca/hcs/bloodservices/resources/ivig/

7.1. pregnant women,

Note: Because of hemodilution naturally occurring during pregnancy, higher doses of IgG should be considered in pregnant recipients with Common Variable Immune Deficiency.