recipient allogeneic Ab (alloAb), mostly natural anti-A/anti-B IgM, may fix and activate complement up to C5/C9. Formation of membrane attack complex (MAC) will create pores in transfused RBCs with resulting intravascular hemolysis, release of toxic moieties including free hemoglobin responsible for end-organ damage including renal failure, and tissue factors contributing to occurrence of disseminated intravascular coagulation (DIC). ***B.*** Alternatively, complement activation may be incomplete, as typically observed in a delayed hemolytic transfusion reaction involving neoformed allogeneic IgG. In such cases, complement activation up to C3 results in C3b-mediated opsonization of RBCs, extravascular hemolysis, and clearance through immunophagocytosis. Anemia and jaundice will be the primary clinical manifestations. ***C.*** Lastly, alloAb may not fix complement while ensuring antibody-dependent cellular cytotoxicity (ADCC)–mediated phagocytosis of targeted RBC. *(Adapted from SR Panch et al: Hemolytic transfusion reactions. N Engl J Med 381:150, 2019.)*

Prevention of hemolytic reactions relies on **pretransfusion testing** of potential recipients. Testing will include determination of the ABO RhD phenotype (and anti-ABO Abs) as well as additional typing for the other main Rh Ags (CcEe): K Ag of the Kell system and, more rarely, Duffy, Kidd and Ss Ags, depending on the clinical setting. These determinations are most often performed by serology. However, molecular typing is increasingly being used to predict RBC phenotype and facilitate the selection of a compatible component. Special care must be taken to verify the patient's identity and apply adequate tube labeling. A double ABO determination performed separately may be considered, especially in the absence of a systematic crossmatch.

Testing will also include the screening and identification of alloAbs directed against RBC Ags other than ABO. This screen is performed by mixing patient serum with type O RBCs expressing Ags from most blood group systems and whose extended phenotype is known. The specificity of the alloAb is identified by correlating the presence or absence of Ag with the induced—or not—agglutination. Special attention should be paid to patients receiving monoclonal Ab treatment that may bind to erythrocytes in vivo (such as anti-CD38 IgG treatment for multiple myeloma) and therefore interfere with alloAb screening. Such interference may be offset by sample dithiothreitol pretreatment.