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Managing a Serologic Weak D Phenotype

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BACKGROUND: Red blood cells (RBCs) from an estimated 0.2 to 1.0% of Caucasians express serologic weak Rh(D) blood types. Individuals with some of these types are capable of making anti-D antibody when exposed to the Rh(D) antigen.[1] Policies have long existed to interpret patients' and blood donors' weak D phenotypes as "Rh-negative" and "Rh-positive," respectively, thereby preventing exposure to Rh(D) of women of childbearing potential and other patients whose weak D types put them at risk for forming anti-D.

The availability of commercially-marketed blood group genotyping systems has made it possible to determine which patients' serologic weak D phenotypes express a molecular genotype that should be managed as Rh-negative and which can be managed safely and more accurately as Rh-positive. Clinicians and hospital labs are encouraged to arrange for *RHD* genotype testing of patients with serologic weak D typing results.

Key Points

- It is standard practice to Rh type blood donors using a sensitive antiglobulin test or other method to detect serologic weak D phenotypes and interpret them as Rh-positive.
- While some hospital laboratories Rh type their patients using a sensitive antiglobulin test or other method, most do not do so; thus, the serologic weak D types of most patients will go undetected, causing them to be managed as Rh-negative.
- *RHD* genotyping can determine which patients with serologic weak D phenotypes can be managed safely as Rh-positive, thereby avoiding unnecessary injections of Rh immune globulin in pregnant women and transfusions of Rh-negative RBCs in those who can safely receive Rh-positive RBCs.

LABORATORY SCIENCE AND POLICY: In 1946, a case report described RBCs that typed as Rh-negative by initial testing with anti-D, but as Rh-positive when retested using a more sensitive antihuman globulin method.[2] The associated Rh blood type, initially named D^u, is presently termed a "serologic weak D phenotype." If RBCs from such individuals are interpreted to be Rh-negative and transfused to an Rh-negative recipient, the recipient's immune system may identify the transfused RBCs as expressing a weak D antigen and form anti-D. If an Rh-negative woman forms anti-D after such a blood transfusion and becomes pregnant with an Rh-positive fetus, the fetus is at risk of Rh hemolytic disease.

In 1958, AABB (formerly the American Association of Blood Banks) issued a standard intended to protect Rh-negative individuals from Rh alloimmunization (i.e., forming anti-D) by inadvertent transfusion of RBCs that are labeled as "Rh-negative," but actually express serologic weak D. That standard, which has remained in effect until the present time, requires laboratory testing of all *blood donors'* RBCs for a serologic weak D and, if positive, interpreting the result as Rh-positive. There is no requirement for such testing of *patients'* RBCs. As a result, the RBCs of most patients with a serologic weak D are not tested by a weak D antiglobulin or other, similarly sensitive, method and these patients are managed as Rh-negative.[3]

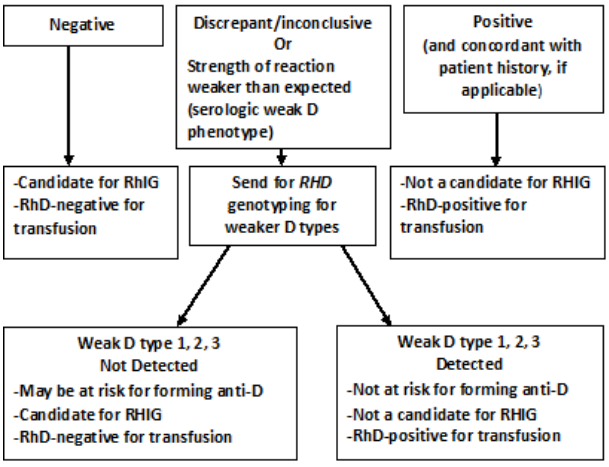
IMPACT OF CURRENT Rh TYPING STANDARD: The practice of typing blood donors, but not patients or pregnant women by a sensitive weak D antiglobulin method has in some ways been highly successful. That is, it has prevented Rh hemolytic disease in an estimated 98.4 to 99% of at-risk pregnancies.[4] However, a policy that requires Rh typing of blood donors by a sensitive method but does not require use of the same sensitive method for the Rh typing of patients and pregnant women has consequences. One important issue is that an estimated 13,360 pregnant women in the United States are not identified as having a serologic weak D phenotype and, thus, 27,400 unnecessary

injections of Rh immune globulin are administered annually.[5] Further, an estimated 17,520 transfusion recipients are not identified as having a serologic weak D phenotype and are transfused with 47,700 units of Rh-negative RBCs annually, when more accurate molecular-based Rh typing would determine that they could be safely transfused with Rh-positive RBCs (thereby conserving the often-scarce supply of Rh-negative RBCs).[5] A relatively less serious consequence is the confusion that may arise if a young woman with a serologic weak D is informed that her prenatal test results performed by a hospital or reference laboratory indicate that she is Rh-negative. If she had been a blood donor previously, she is likely to have a blood donor card indicating that she tested as Rh-positive.

RECOMMENDED PRACTICE: An AABB College of American Pathologists-organized Work Group on *RHD* Genotyping has recommended that *RHD* genotyping be performed whenever a discordant Rh phenotyping result and/or a serologic weak D phenotype is detected in patients, including pregnant women, newborns, and potential transfusion recipients.[5] In 2015, a Joint Statement was endorsed by AABB, America's Blood Centers, the American Red Cross, the Armed Services Blood Program, the College of American Pathologists, and the College of Obstetricians and Gynecologists. It recommended *RHD*

Figure 1: Algorithm for Managing a Serologic Weak D Phenotype

The algorithm illustrates how RHD genotyping can determine which individuals with a serologic weak D phenotype can be managed safely as Rh-positive.



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genotyping whenever a serologic weak D is detected by routine laboratory testing for pregnant women and females of childbearing potential.[6] The most effective way for serologic weak D results to be resolved by *RHD* genotyping is for those laboratories that routinely perform Rh phenotyping to recognize that a serologic weak D typing result is an incomplete laboratory test result and that reporting it—without including the results of suitable follow-up testing—is no longer appropriate. Laboratories should consider a serologic weak D test result to be an internal laboratory finding that requires *RHD* genotyping to determine the requested Rh type. The Work Group recommended an algorithm for resolving serologic weak D phenotype results (Figure 1).

One caveat to the above discussion is that facilities performing initial RhD testing by gel method may wish, upon encountering reaction strengths $\leq$ 3+, to consider tube typing to rule out a serologic weak D phenotype.[7,8]

CONCLUSIONS: Fewer than 3% of individuals whose blood samples appear, on initial screening, to be Rh-negative will be shown to have a serologically weak D phenotype if retested with an antihuman globulin method.[5] Thus, leaders of hospital-based laboratories will wish to decide whether or not performing *RHD* genotyping in-house—which, even for some relatively large facilities, may represent a low-volume proposition—is operationally and financially practical. Nonetheless, such genotypic testing, irrespective of where it is performed, should be performed. The reader is encouraged to contact his/her hospital's transfusion service and/or local ABC member blood center to learn where such testing is offered.

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