The RH Antigen

Summary
Every clinician knows that a patient’s A1C may vary over time and between labs. Most clinicians don’t realize that a patient’s Rh or D typing may also vary from testing lab to testing lab. This is due to variations in the amount of D antigen on the red cells, or which parts of the D antigen are present or absent from the red blood cells (RBC). This is also due to the variation in the new testing reagents used by various labs. This pearl is a review of the variations in D antigen expression and effect in patient testing. When variations in test results occur, clinicians should treat patients as if they were Rh negative.

Introduction
The main Rh antigen—the one that determines whether a person is "Rh-positive" or "Rh-negative"—is known to blood bankers as the "D" antigen. In most people who are D-positive ("Rh-positive"), the antigen is expressed quite well, and routine testing readily shows the person to be D-positive when anti-D is mixed with their red blood cells. This expression shows up easily in test tubes immediately after centrifugation (in other words, at the "immediate spin" phase). Occasionally, however, individuals have significantly decreased quantities of the D antigen, such that they do not test as D-positive with routine immediate spin testing. Instead, they require an indirect antiglobulin test, or "IAT." Beyond true D negative, test results at the IAT phase can be categorized as weak D, partial D, partial weak D, and DEL.

Weak D
D-positive people who require an IAT to prove that they are indeed D-positive have what is called a "weak D" phenotype, formerly called the "D" phenotype. They are traditionally assumed to have completely normal but significantly decreased amounts of D antigen on their RBC. Today, the extremely sensitive monoclonal anti-D reagents that blood bankers have at their disposal rarely fail to react against cells that have decreased amounts of D antigen. Many of these cases would have been called weak D in the past. In fact, the only apparently D-negative individuals that need weak D testing are D-negative blood donors (to ensure that they are, indeed, D negative) and babies born to D-negative moms.

In most cases, weak D is caused by mutations in the D gene that lead to changes in the D transmembrane protein either within the membrane or inside the RBC. If the changes occur on the exterior aspects of the RBC, it is called "partial D." Weak D and partial D are in fact not as separate as we would like to think from these classic definitions. There are overlap categories with decreased quantities of D having qualitative abnormalities, which some call "weak partial D" or "partial weak D."

Partial D
A gene known as RHD on chromosome 1 codes for this large, transmembrane protein, and it is present in the majority of people across most racial lines. Occasionally, however, as a result of a mutation in the gene, a person may have amino acid substitutions affecting a part of the normal D protein. Again, when this results in changes to the parts of the antigen on the external aspect of the RBC, the patient is described as having "partial D." If someone with partial D is exposed to blood from someone with a
normal form of D, an antibody against the portions of the antigen that is lacking maybe formed. This antibody looks just like anti-D because it reacts against all "normal" D-positive cells. This situation leads to the classic presentation of a partial D patient in the transfusion service as an apparently D-positive patient who makes an anti-D. There are several different types (at least 70) of partial D, with varying strengths of reactivity with anti-D. The main thing to remember about partial D blood recipients is that they need to receive D-negative blood, even though they may appear D positive. Modern anti-D reagents, while very good at detecting weaker forms of the D antigen, are specifically designed to not detect the most common form of partial D in Caucasians (DVI), so most Caucasian partial-D patients will test as D-negative. Donors must be called RhD positive and as recipients must be called RhD negative. This can cause confusion when a patient has donated blood for themselves; the unit will be labeled D positive, but the patient type will be listed as D negative.

Partial Weak D
In partial weak D, there is an overlap between two categories with qualitative and quantitative RhD defect. When exposed to D positive cells, these patients will be susceptible to form an anti D antibody.

DEL (Del)
DEL (also called Del) is an extremely weak Rh D expression caused by different mutations and deletions. Essentially, the patient is D positive but you cannot tell they are positive with regular D testing. DEL occurs more often (though still rarely) in Asian populations, particularly in Japanese. It is impossible to detect Del serologically and these donors will be able to immunize D-neg patients.

Bibliography

Questions: Please reply to this e-mail, and your question(s) will be directed to the author of this Pearl, Dr. Zena Khalil, Regions Medical Director for Transfusion Services.

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