Policies and Procedures Related to Weak D Phenotype Testing and Rh Immune Globulin Administration

Results From Supplementary Questions to the Comprehensive Transfusion Medicine Survey of the College of American Pathologists

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Objective.—To determine and evaluate policies and procedures related to weak D phenotype testing and terminology and the administration of Rh immune globulin in selected clinical situations.

Design, Setting, and Participants.—Institutions participating in the College of American Pathologists 1999 J-A Comprehensive Transfusion Medicine Survey program were asked to respond to a series of supplementary questions related to weak D phenotype testing and Rh immune globulin administration. More than 3500 institutions and transfusion services participated.

Results.—Most supplementary questions elicited more than 3000 responses. Despite no clinical or regulatory mandate, 58.2% of transfusion services routinely perform an antiglobulin test for the weak D phenotype in patients who test negative with anti-D reagents. Significant differences were found concerning the transfusion of blood components to patients with the weak D phenotype and the administration of Rh immune globulin to these individuals. At least one patient with the weak D phenotype with anti-D alloantibody formation was observed during a 12-month period by 31.8% of transfusion services.

Conclusions.—Significant variability concerning policies and procedures related to weak D typing and terminology was found in this survey. Transfusion of blood components to patients with the weak D phenotype and the administration of Rh immune globulin also demonstrated variations. Anti-D alloantibody formation by patients with the weak D phenotype may not be as rare as previously thought. Additional study related to the clinical significance of these results is warranted.

With the discovery of the Rh antigen and its relationship to hemolytic disease of the newborn in 1939 and 1940, it soon became a recognized standard of care to make every attempt to avoid transfusing Rh(D)-positive red blood cells to Rh(D)-negative individuals.1,2 This was particularly true for Rh(D)-negative women of childbearing age. As early as 1943 and 1944, a weakly reacting form of the Rh(D) antigen, which gave “intermediate” reactions with anti-D typing sera, was recognized and described by Wiener.3 In 1946, Stratton4 coined the term Dw for the phenotypic weak expression of the Rh(D) antigen. More recently, the term weak D has been proposed as a more appropriate characterization for the quantitative or qualitative differences observed for weakened expression of the Rh(D) antigen.5

The number of D antigen sites on the Rh(D)-positive red blood cell is normally in the range of 9900 to 33,000.6,7 The weak D phenotype appears to be a quantitative variation in the number of D antigen sites on the red blood cell (ie, 110 to <9000 per red blood cell).6,7 In contrast, the partial D phenotype may represent qualitative and, sometimes, quantitative differences in the D antigen.6,7 In routine serologic tests with anti-D reagents, the weak D red blood cell will initially type as Rh(D) negative but will react positively in the indirect antiglobulin phase. Most partial D red blood cells will demonstrate direct agglutination in routine serologic tests and thus type as Rh(D) positive. The incidence of the weak D phenotype in the general population has been reported to be approximately 0.23%,6 although in a hospital population undergoing pretransfusion and Rh(D) testing the incidence may be closer to 1% to 3%.5,9 These observed differences in the incidence of weak D may also reflect changes in available reagents. Monoclonal, better standardized reagents have been more recently available.

More than a half century has passed since weak expression of the Rh(D) antigen was initially observed. Confusion has continued to plague issues surrounding weak D terminology and its clinical significance. A suggestion was made in 1984 to abandon the term Dw and to use the more appropriate weak D designation.10 A further proposal was made in 1992 to standardize terms for weak D.3 Practice guidelines related to testing for the weak D antigen and recommendations related to the administration of Rh immune globulin have also been recently published.10,11 A nationwide survey of policies and procedures related to weak D testing, terms, and reporting, as well as to Rh
immune globulin administration in certain clinical situations, has never been performed. In an effort to obtain data on actual policies and practices, supplementary questions were asked of participants who subscribed to the College of American Pathologists (CAP) Comprehensive Transfusion Medicine Survey program in the first quarter of 1999. This report presents and discusses the results obtained from those supplementary questions.

MATERIALS AND METHODS

Supplementary questions related to weak D terms and testing and to the administration of Rh immune globulin in selected clinical situations were included in the 1999 J-A Transfusion Medicine (Comprehensive) and Educational Survey Set of CAP. The questions were designed to explore several aspects related to current policies and practices related to Rh immune globulin use, weak D testing, and Rh(D) typing of the pregnant patient.

The survey was sent to more than 3500 participating institutions and transfusion services. Individual responses to the questions were summarized as percentages of the total responses for each possible response or question. All participants did not necessarily answer every question, and missing responses were not included in the analysis of results. Overlap in the data is possible in those institutions that received more than one survey, but because of the specific nature of the survey questions, any dual reporting would be expected to be minimal. Survey results were centrally collected, formatted, and tabulated by CAP staff.

RESULTS

Ten questions were asked, and more than 3000 responses were received for 9 of the 10 questions. When asked if a test for weak D (D−) is routinely performed in patients who test negative with anti-D reagents on direct agglutination (ie, without anti-human globulin), 58.2% (2087/3588) responded in the affirmative. A total of 15.8% (568/3588) indicated that a test for weak D is performed only on women of childbearing age, whereas 15.2% (547/3588) do not perform weak D testing on patients.

When asked how the patient's Rh type would be reported if found to be positive for weak D, 50.7% (1775/3498) of responding institutions indicated “Rh(D) positive.” A total of 20.9% (730/3498) indicated that the patient's type would be reported as a “Rh(D)-positive, weak D (D+ or D mosaic) positive/variant,” whereas 20.1% (704/3498) indicated that the patient's type would be reported as “Rh(D)-negative, weak D (D+ or D mosaic) positive/variant.” Interestingly, 3.3% (114/3498) indicated that the patient's Rh type would be reported as “Rh(D) negative.”

If a patient is found or known to have the weak D phenotype, 43.5% (1487/3417) of institutions indicated that their policy would dictate transfusion with Rh(D)-negative blood components, whereas 42.4% (1449/3417) indicated that Rh(D)-positive blood components would be transfused. In 10.2% of institutions (347/3417), Rh(D)-negative blood components would be transfused in the case of a childbearing woman.

Institutions were asked how many patients (or donors) with the weak D phenotype were also found to have an anti-D alloantibody (transfusion or pregnancy related) in the past 12 months. Responses are detailed in Table 1.

Transfusion services were asked if they routinely recommend the administration of Rh immune globulin to those patients found or known to have a weak D phenotype and who receive various Rh(D)-positive blood components. Responses are detailed in Table 2.

<table>
<thead>
<tr>
<th>No. of Patients (or Donors) Identified</th>
<th>Percentage of Transfusion Services*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>68.1</td>
</tr>
<tr>
<td>1</td>
<td>10.9</td>
</tr>
<tr>
<td>2</td>
<td>6.4</td>
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<tr>
<td>3</td>
<td>3.7</td>
</tr>
<tr>
<td>4</td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
<td>1.6</td>
</tr>
<tr>
<td>&gt;5</td>
<td>7.4</td>
</tr>
</tbody>
</table>

* Total number of responses received was 3235.

<table>
<thead>
<tr>
<th>Type of Patient Treatment Recommended for</th>
<th>Rh(D)-Positive Platelet Components,*</th>
<th>Rh(D)-Positive Plasma Components,†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>15.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Only female patients</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Only female patients of childbearing age</td>
<td>31.6</td>
<td>6.8</td>
</tr>
<tr>
<td>No patients</td>
<td>41.0</td>
<td>85.6</td>
</tr>
<tr>
<td>Other</td>
<td>11.1</td>
<td>5.8</td>
</tr>
</tbody>
</table>

* Total number of responses received was 3193.
† Total number of responses received was 3185.

For patients who are determined to be Rh(D) negative (ie, not weak D), transfusion services were asked if they routinely recommend the administration of Rh immune globulin to those Rh(D)-negative patients who undergo transfusion with Rh(D)-positive platelets or plasma blood components. Responses are detailed in Table 3.

Institutions were asked if Rh immune globulin is dispensed from the transfusion service, the pharmacy, or both. A total of 75.4% (2476/3282) indicated that Rh immune globulin is dispensed from the transfusion service, 16.2% (533/3282) from the pharmacy, 3.2% (105/3282) from both, and 5.2% (171/3282) did not respond or did not know.

Table 1. Number of Patients (or Donors) With the Weak D Phenotype and Anti-D Alloantibody Identified by Transfusion Services in the Past 12 Months

Table 2. Percentage of Transfusion Services That Routinely Recommend the Administration of Rh Immune Globulin to Patients With the Weak D Phenotype

Table 3. Percentage of Transfusion Services That Routinely Recommend Rh Immune Globulin Administration to Rh(D)-Negative Patients Who Receive Rh(D)-Positive Platelet or Plasma Components
from both the transfusion service and the pharmacy, and 5.1% (168/3282) from "other."

Finally, institutions were asked about their policy to perform Rh(D) typing on pregnant patients at the time of delivery. A total of 39.8% (1256/3156) indicated that their policy is to perform Rh(D) typing in every pregnant patient at the time of delivery, whereas 32.3% (1019/3156) indicated that Rh(D) typing is performed at the time of delivery only if no typing is already on record. Rh(D) typing is not performed in every pregnant patient at the time of delivery by 13.8% (434/3156) of institutions, and 14.2% (447/3156) indicated "other."

**COMMENT**

Terms and policies related to the weak D phenotype and Rh immune globulin administration have been recommended and debated for decades.5-7 This is the first nationwide survey to gather data from a large number of transfusion services to assess actual current practices. The data are limited by the fact that actual techniques for determining the weak D phenotype were not assessed and additional follow-up and clarification questions could not be pursued.

Despite the fact that testing for weak D phenotype is not required by the American Association of Blood Banks (AABB), except during pregnancy,8-10 58.2% of responding institutions in this survey indicated that they routinely perform an antiglobulin test for the weak D phenotype on patients who test negative with anti-D reagents. The American College of Obstetricians and Gynecologists also agrees with the AABB's policy on weak D phenotype testing of pregnant patients.11 Testing pregnant or nonpregnant patients for the weak D phenotype is also not required by the CAP Laboratory Accreditation Program.12 An antiglobulin test for the weak D phenotype is performed only for women of childbearing age by 15.8% of institutions.

In general, individuals with the weak D phenotype who undergo routine Rh(D) typing will be typed as Rh(D)-negative, unless an antiglobulin test is also performed. For purposes of transfusion, this would dictate that these "mistyped" patients would receive only Rh(D)-negative red blood cell-containing components. Also, such patients might potentially receive Rh immune globulin following an Rh(D)-positive red blood cell exposure. In this regard, 50.7% of responding institutions would record a weak D patient's Rh(D) type as "Rh(D) positive," whereas 41% would record it as either "Rh(D)-positive or -negative, weak D variant." Only 3.3% would record the patient's Rh(D) type as "Rh(D) negative." For purposes of transfusion, the transfusion of Rh(D)-positive or Rh(D)-negative red blood cells to weak D patients is about equally divided (42.4% and 43.5%, respectively).

It is unclear why transfusion services are equally divided between transfusing Rh(D)-positive and Rh(D)-negative red blood cells to patients with the weak D phenotype, and the survey was not designed to gather additional information in this regard. However, speculation would suggest that such policy distinctions might be made to avoid overusing harder-to-find Rh(D)-negative red blood cells, because, in most instances, weak D patients are able to tolerate Rh(D)-positive red blood cells without forming an anti-D alloantibody. Additionally, patients with the weak D phenotype are generally not considered candidates for Rh immune globulin administration. This author is not aware of any data examining the cost-effectiveness of testing all patients for the weak D phenotype to avoid transfusing Rh(D)-negative red blood cells to those few patients who would be found to be positive for the weak D phenotype. Data are also lacking concerning the positive or adverse consequences of "overadministering" Rh immune globulin to patients in this setting.

In the case of a woman of childbearing age with the weak D phenotype, 10.2% of institutions would transfuse Rh(D)-negative blood components. This implies that approximately 90% would routinely transfuse Rh(D)-positive components in this situation. It has been recommended that obstetric patients who are clearly positive for the weak D phenotype (ie, demonstrate ≥2+ macroscopic reactivity with anti-D reagent by the antiglobulin technique) can be safely considered to be Rh(D) positive and undergo transfusion with Rh(D)-positive blood components.13 Contrary to this recommendation, however, 58.2% of transfusion services indicated that they routinely recommend the administration of Rh immune globulin to patients of childbearing age who are positive for the weak D phenotype and who receive Rh(D)-positive blood components. Likewise, despite recommendations to the contrary for those pregnant patients with the weak D phenotype and with a possible Rh(D)-positive fetus,11-13 71.1% of transfusion services would recommend the administration of Rh immune globulin in this clinical situation. Rare cases of hemolytic disease of the newborn in pregnant patients with the weak D phenotype have been reported14-17 and may be one of the underlying reasons for the relatively high percentage who would administer Rh immune globulin in this clinical setting.

The ability of patients with the weak D phenotype to form an anti-D alloantibody has rarely been reported since 1953,18 and data on the frequency of this phenomenon have not been published. However, if the data obtained from this survey are representative, it does not appear to be that rare of an occurrence, since 31.8% of respondents reported seeing at least one such case in the previous 12 months and 20.9% reported seeing at least 2 cases (Table 1). Additional information on these cases, such as age and sex of the patients, transfusion-versus pregnancy-related anti-D alloantibody formation, and Rh(D)-positive red blood cell exposure history, and laboratory techniques used by the individual transfusion services to determine weak D typing and anti-D alloantibody formation were not obtained as part of this study. During a 2½-year study period, this author observed 4 cases of anti-D alloantibody formation following the transfusion of Rh(D)-positive blood components in patients determined to have the weak D phenotype by a standard serologic technique.9 This was an incidence of approximately 0.8% to 2.1% of all patients positive for the weak D phenotype who were seen by one transfusion service. One of these 4 cases occurred in a young woman, 2 cases were women aged 52 and 60 years, and 1 case was a 59-year-old man whose only Rh(D)-positive red blood cell exposure was 8 U of Rh(D)-positive fresh frozen plasma.9 Thus, the incidence of anti-D alloantibody formation in patients with the weak D phenotype may not be that rare and may partially explain some of the discrepancies noted in this study related to the transfusion of Rh(D)-positive red blood cells and the administration of Rh immune globulin in patients who have the weak D phenotype. The significant rate of anti-D alloantibody formation in patients with the weak
D phenotype as reported herein highlights the need for additional study in this area.

It is encouraging to see that in 75.4% of institutions Rh immune globulin is dispensed by the transfusion service rather than by the pharmacy (16.2%). Pharmacies do not have a proven record of being able to link specific product lot numbers to specific patients or perform appropriate lookbacks to the extent that blood banks and transfusion services can.

Table 3 details the policies related to Rh immune globulin administration to Rh(D)-negative (ie, not weak D phenotype) patients who undergo transfusion with Rh(D)-positive platelet or plasma blood components. Since the administration of platelet and plasma components can clearly contain enough red blood cell contamination to cause Rh(D) immunization, the AABB standards state that the transfusion service shall have a policy addressing Rh immune globulin administration in this setting. Only 15.7% recommend Rh immune globulin administration to Rh(D)-negative patients who receive Rh(D)-positive platelets, 31.6% make the recommendation only in the case of female patients of childbearing age, and 0.6% make the recommendation for all female patients (Table 3). Thus, more than half (52.1%) of transfusion services apparently do not even recommend Rh immune globulin prophylaxis to Rh(D)-negative women of childbearing age who might receive Rh(D)-positive platelet components. This percentage is even higher (91.4%) in the case of Rh(D)-positive plasma transfusion (Table 3). This would clearly seem to be an area where transfusion medicine specialists could take a proactive approach to advocate for the administration of Rh immune globulin in those clinical situations where it is clearly indicated. Additional study in this area is warranted.

The AABB standards state that “the Rh type of pregnant women shall be determined”; the AABB also states that after initial ABO/Rh(D) typing “no repeat ABO/D typing is necessary (unless required for some other purposes such as for transfusion).” The results from this survey indicate that in 39.8% of responding institutions, Rh(D) typing is performed on every pregnant patient at the time of delivery (whether or not a type is already on record). Given that 40% of transfusion services routinely perform Rh(D) typing at the time of delivery, it would be interesting to know more details about the cost-effectiveness of this policy, the incidence of discordant results when compared with historical records, and other clinical outcome data.

The information gathered from this survey indicates that after 50 years significant variability continues to exist concerning policies and procedures related to weak D typing, interpretation, and terminology. Variability also exists concerning the transfusion of Rh(D)-positive and Rh(D)-negative blood components to patients with the weak D phenotype and the administration of Rh immune globulin. Additional study of these issues related to the weak D phenotype is warranted and, in conjunction with molecular studies, might prove beneficial in standardizing policies related to transfusion and Rh immune globulin prophylaxis and further defining the weak D phenotype.

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References