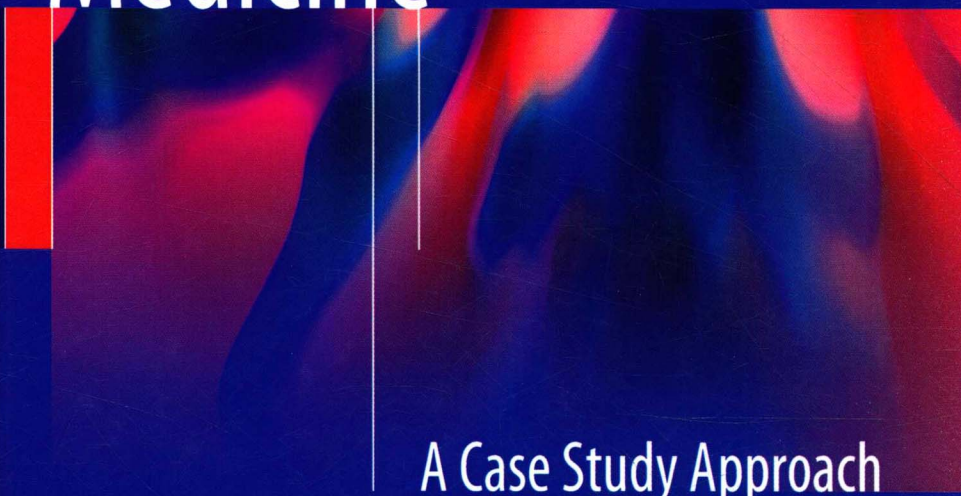
Immunohematology and Transfusion Medicine



A Case Study Approach

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Preface

Pre-transfusion testing, including ABO/Rh typing, identification of unexpected antibodies, and compatibility testing, is an important measure in the provision of blood that may be transfused to the patient in the safest possible manner. This brief introduction is not intended to give the trainee a detailed instruction on solving immunohematology cases; rather, it is intended to give an overview on how to approach the immunohematology problems (Chaps. 1–28) of this workbook. The authors of this workbook presume that the reader has had at least basic instruction in immunohematology before engaging in these cases.

Although one may be tempted to jump right to the antibody panel after noting a positive antibody screen in the presented cases, it is recommended to review the clinical history for important clues that may be helpful in solving the case. For example, a history of prior transfusions suggests that the patient could have made clinically significant alloantibodies (i.e., warm-reactive IgG alloantibodies capable of causing hemolytic transfusion reactions or hemolytic disease of the fetus or newborn). Alternatively, the use of phrases such as "routine clinic visit" may suggest that the patient is clinically stable despite significant anemia. In these practice cases, as in the real medical world, obtaining clinical history is an important step not to be overlooked, though in some of these cases (as sometimes occurring in actual practice), scant history is provided.

After reviewing the medical history, the next step is to interpret the ABO/Rh typing results. In most cases, this will be straightforward, though one should be alert to any discrepancy in the forward and reverse typing results. For example, noting a positive result with the A_1 cell in the back type may be the result of anti-A_1 antibody in an individual of A_2 blood type or the result of a cold allo- or autoantibody.

Next, one should review the antibody screen. It should be noted that in this workbook, we present a two-cell screen in either standard tube or gel (column agglutination) methods. Although typically, the antibody screen is interpreted simply as positive or negative, limited additional information can be gleaned by noting differences in reactions between the two cells (i.e., whether both cells or only one cell reacting) or differences in the testing phases (i.e., if tube method is used, differences in reactions between 37 °C vs. AHG phase). Additionally, the antigen profiles of

the antibody screen cells are listed in the beginning which may also provide useful information when ruling out antibodies.

After review of the clinical history, ABO/Rh typing, and antibody screen, one is ready to move on to the antibody panels if performed in the case (see Fig. 1). Although traditionally one is taught to interpret the antibody panels through a process of crossing out antigens, it is prudent to first take a moment to get a "landscape" view of the panel reactions. That is, one should look to see whether there are reactions at cold temperatures (i.e., 4 °C, RT, IS) or warm temperatures (37 °C, IgG), whether there are many cells that are positive (perhaps all cells are positive as in a panagglutinin reaction) or only few and whether the autocontrol is positive or negative. Such consideration may help to narrow the possible specificities of the present antibodies. In that light, for example, if reactions are only evident at 4 °C in the panel, then warm-reactive antibodies (such as anti-D, -K, -Jk^a, etc.) can promptly be excluded. Finally, after this initial review, one should then move on to the methodical exclusion of antibody specificities. This is traditionally taught as "crossing out" antigens in which the reactions are negative with attention toward dosage (i.e., homozygous vs. heterozygous antigen expression). Figure 2 demonstrates crossing out with respect to negative reactions, dosage, and the patient's RBC antigen phenotype. The effect of enzyme treatment (e.g., papain or ficin) may also be of value as antibody reactivity to some antigens may be enhanced or destroyed. Ultimately, after consideration of all of the clinical information and antibody identification testing, the identity of the antibody or antibodies may be determined so that the most compatible blood can be provided for the patient in case transfusion is necessary.

In the end, these cases are not necessarily meant to be difficult (though they do become more challenging as one progresses through the workbook) but are selected based on principle to introduce the practical concepts of and methods used in immunohematology antibody identification. Once the learner has grasped these basic techniques, he/she can apply them to more interesting cases that may be presented to them within the actual clinical practice of the transfusion service.

Finally, Chaps. 29–35 are designed to engage the learner in other aspects of transfusion medicine including use of massive transfusion, therapeutic apheresis, factor concentrates, and blood management.

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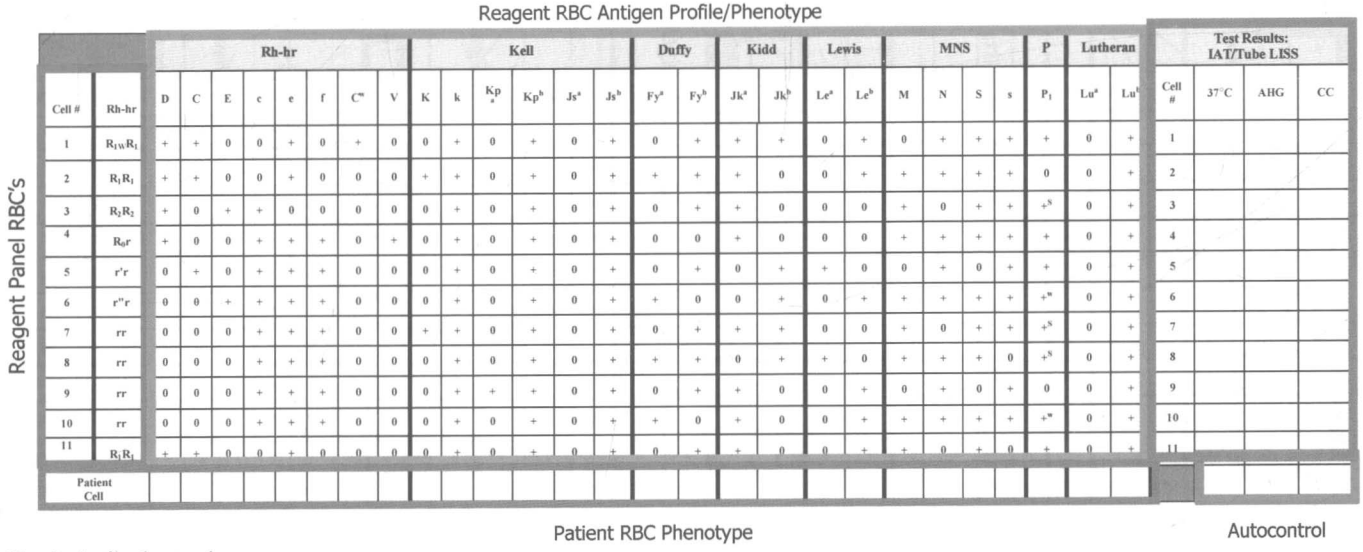
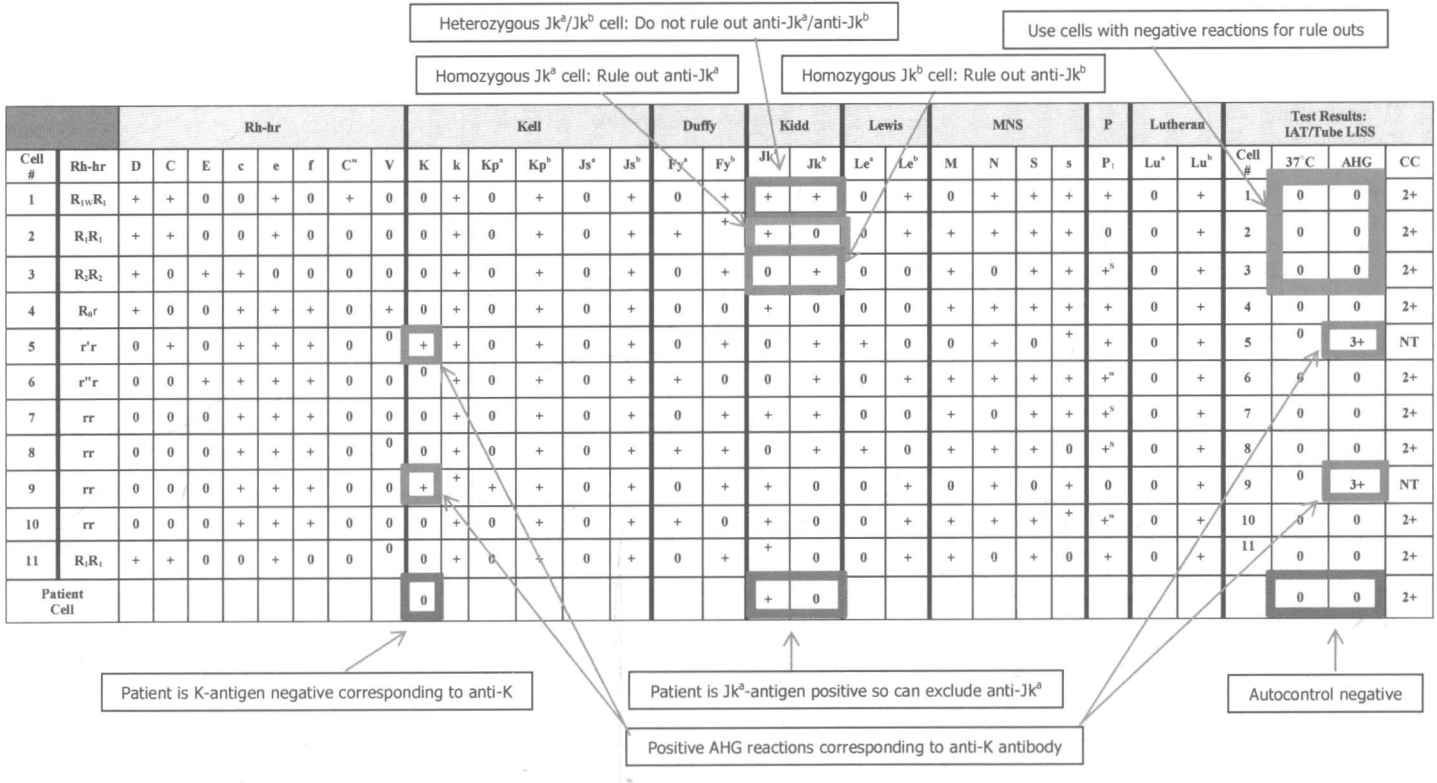


Fig. 1 Antibody panel



		Rh-hr								Kell						Duffy		Kidd		Lewis		MNS				P	Lutheran		Test Results: IAT/Tube LISS		
Cell #	Rh-hr	D	C	E	c	e	f	C^w	V	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	M	N	S	s	P1	Lu^a	Lu^b	Cell #	37°C	AHG	CC
1	$R_{1w}R_1$	+	+	0	0	+	0	+	0	0	+	0	+	0	+	0	+	+	+	0	+	0	+	+	+	+	0	+	1	0	0	2+
2	R_1R_1	+	+	0	0	+	0	0	0	0	+	0	+	0	+	+	+	+	0	0	+	+	+	+	+	0	0	+	2	0	0	2+
3	R_2R_2	+	0	+	+	0	0	0	0	0	+	0	+	0	+	0	+	0	+	0	0	+	0	+	+	+^s	0	+	3	0	0	2+
4	R_0r	+	0	0	+	+	+	0	+	0	+	0	+	0	+	0	0	+	0	0	0	+	+	+	+	+	0	+	4	0	0	2+
5	r'r	0	+	0	+	+	+	0	0	+	+	0	+	0	+	0	+	0	+	+	0	0	+	0	+	+	0	+	5	0	3+	NT
6	r''r	0	0	+	+	+	+	0	0	0	+	0	+	0	+	+	0	0	+	0	+	+	+	+	+	+^w	0	+	6	0	0	2+
7	rr	0	0	0	+	+	+	0	0	0	+	0	+	0	+	0	+	+	+	0	0	+	0	+	+	+^s	0	+	7	0	0	2+
8	rr	0	0	0	+	+	+	0	0	0	+	0	+	0	+	+	+	0	+	+	0	+	+	+	0	+^s	0	+	8	0	0	2+
9	rr	0	0	0	+	+	+	0	0	+	+	+	+	0	+	0	+	+	0	0	+	0	+	0	+	0	0	+	9	0	3+	NT
10	rr	0	0	0	+	+	+	0	0	0	+	0	+	0	+	+	0	+	0	0	+	+	+	+	+	+^w	0	+	10	0	0	2+
11	R_1R_1	+	+	0	0	+	0	0	0	0	+	0	+	0	+	0	+	+	0	0	+	+	0	+	0	+	0	+	11	0	0	2+
Patient Cell										0								+	0										0	0	2+

Fig. 2 Antibody panel rule out

List of Abbreviations

ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AHG	Antihuman globulin
aHUS	Atypical hemolytic uremic syndrome
AML	Acute myeloid leukemia
CC	Coombs control/Check cells
CCI	Corrected count increment
C_3d	Complement component 3d
CHF	Congestive heart failure
CMV	Cytomegalovirus
CPDA	Citrate–phosphate–dextrose–adenine
CPOE	Computer physician order entry
C-section	Cesarean section
CT	Computed tomography
DAT	Direct antiglobulin test
DIC	Disseminated intravascular coagulation
DTT	Dithiothreitol
EDTA	Ethylenediaminetetraacetic acid
EGA	EDTA glycine acid
ELISA	Enzyme-linked immunosorbent assay
FFP	Fresh frozen plasma
FMH	Fetal-maternal hemorrhage
GERD	Gastroesophageal reflux disease
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDFN	Hemolytic disease of the fetus/newborn
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPA	Human platelet antigen
HTLA	High titer/low avidity
IAT	Indirect antiglobulin test
IgA	Immunoglobulin A

IgG	Immunoglobulin G
IgM	Immunoglobulin M
IS	Immediate spin
ITP	Idiopathic (immune) thrombocytopenic purpura
IV	Intravenous
IVIG	Intravenous immune globulin
KB	Kleihauer–Betke
LISS	Low ionic strength solution
m	Microscopic
mf	Mixed field
MICU	Medical intensive care unit
NHSN	National Healthcare Safety Network
NOACS	Novel anticoagulants
NT	Not tested
PBM	Patient blood management
PCC	Prothrombin complex concentrate
PEG	Polyethylene glycol
PTP	Posttransfusion purpura
RBC	Red blood cell
RESt	Rabbit erythrocyte stroma
RhIg	Rh immune globulin
RT	Room temperature
S	Strong
SC1	Screen cell 1
SC2	Screen cell 2
SCD	Sickle cell disease
Tryp	Trypsin
TTP	Thrombotic thrombocytopenic purpura
vWF	von Willebrand Factor
W	Weak
WAIHA	Warm autoimmune hemolytic anemia
WBC	White blood cell

Table of laboratory normal values

Laboratory test	Normal range
Hemoglobin (Hgb)	12.5–17.0 g/dL
Hematocrit (Hct)	34–46%
Mean corpuscular volume (MCV)	80–100 fL
Platelets	150–450 K/μL
Haptoglobin	30–200 mg/dL
Lactate dehydrogenase (LDH)	300–600 U/L
Total bilirubin (T Bili)	0.2–1.3 mg/dL
Prothrombin time (PT)	11–14 s
International normalized ratio (INR)	1.0–1.2
Activated partial thromboplastin time (aPTT)	32–40 s
Creatinine	0.6 –1.3 mg/dL

Table of RBC antigen frequencies

	Antigen	Frequency (%)		
		Caucasian	African-American	Asian
Rh	D	85	92	99
	C	68	27	93
	c	80	96	47
	E	29	22	39
	e	98	98	96
Kell	K	9	2	–
	k	>99	>99	–
Duffy	Fy^a	66	10	99
	Fy^b	83	23	18.5
Kidd	Jk^a	77	92	73
	Jk^b	74	49	76
MNS	M	78	74	–
	N	72	75	–
	S	55	31	–
	s	89	93	–

Screening Cell (SC) Antigen Profiles

		Rh-hr								Kell						Duffy		Kidd		Lewis		MNS				P	Lutheran	
Cell #	Rh-hr	D	C	E	c	e	f	C^w	V	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	M	N	S	s	P_1	Lu^a	Lu^b
SC1	R_1R_1	+	+	0	0	+	0	0	0	0	+	0	+	0	+	+	0	+	+	+	0	+	+	+	+	+	0	+
SC2	R_2R_2	+	0	+	+	0	0	0	0	+	+	0	+	+	0	+	+	+	0	0	+	+	+	+	+	+	0	+

Authors' Note

This case-based immunohematology workbook has been developed over many years and was created in response to the need to teach learners in the practical art of interpreting red cell antibody studies. Though there have been many textbook resources, both in print and more recently online, which have been published for learning facts about blood banking and transfusion medicine, there are few available resources for studying and practicing immunohematology cases. The cases presented in this workbook are based on realistic clinical scenarios that one may encounter in the blood bank laboratory and transfusion service. Thus, this workbook is an excellent companion to reference texts for the practical application of learned immunohematology techniques to case-based studies in the identification of red cell antibodies and in the clinical management of patient transfusions. The questions accompanying each case are presented in an open-ended format rather than in the traditional single-best-answer multiple-choice format; though some may prefer the latter format for convenience, it is wise to remember that patients do not come with multiple choices. Furthermore, the open-ended style should hopefully encourage learners to engage in further reading and discussion of the subject matter. Over the years, many clinical pathology trainees have benefitted from the use of this type of workbook problem-solving learning, both in the preparation for their board certification exam as well as for their careers. Finally, the authors are indebted to Oanh Nguyen and Olga Kruty for their technical review in the preparation of this workbook.

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Contents

Chapter 1
Basic Single Antibody Identification: How Hard Can It Be?

Clinical History

A 52-year-old male with a history of hypertension, type 2 diabetes mellitus, and three-vessel coronary artery disease is admitted to the hospital for a coronary artery bypass graft surgery. An ethylenediaminetetraacetic acid (EDTA) anticoagulant sample is submitted to the blood bank for type and crossmatch of four red blood cell (RBC) units. No transfusion history is given.

ABO/Rh/Antibody Screen

ABO/Rh (tube method)				
Patient RBCs (forward type)			Patient plasma (reverse type)	
Anti-A	Anti-B	Anti-D	A_1 cells	B cells
0	0	3+	4+	4+
Antibody screen (tube LISS method)				
	37°C	AHG	CC	
SC1	0	0	2+	
SC2	3+	4+	NT	

Reaction scale = 0 (no reaction) to 4+ (strong reaction)
RBC red blood cells, *LISS* low ionic strength solution, *AHG* antihuman globulin, *CC* check cells, *NT* not tested, *SC* screen cell

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Tube Panel

		Rh-hr								Kell						Duffy		Kidd		Lewis		MNS				P	Lutheran		Test Results: IAT/Tube LISS			
Cell #	Rh-hr	D	C	E	c	e	f	C^w	V	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	M	N	S	s	P_1	Lu^a	Lu^b	Cell #	37°C	AHG	CC
1	$R_1{}^wR_1$	+	+	0	0	+	0	+	0	0	+	0	+	0	+	0	+	+	+	0	+	0	+	+	+	+	0	+	1	0	0	2+
2	R_1R_1	+	+	0	0	+	0	0	0	+	+	0	+	0	+	+	+	+	0	0	+	+	+	+	+	0	0	+	2	0	0	2+
3	R_2R_2	+	0	+	+	0	0	0	0	0	+	0	+	0	+	0	+	+	0	0	0	+	0	+	+	$+^s$	0	+	3	3+	4+	NT
4	R_0r	+	0	0	+	+	+	0	+	0	+	0	+	0	+	0	0	+	0	0	0	+	+	+	+	+	0	+	4	0	0	2+
5	$r'r$	0	+	0	+	+	+	0	0	0	+	0	+	0	+	0	+	0	+	+	0	0	+	0	+	+	0	+	5	0	0	2+
6	$r''r$	0	0	+	+	+	+	0	0	0	+	0	+	0	+	+	0	0	+	0	+	+	+	+	+	$+^w$	0	+	6	3+	4+	NT
7	rr	0	0	0	+	+	+	0	0	+	+	0	+	0	+	0	+	+	+	0	0	+	0	+	+	$+^s$	0	+	7	0	0	2+
8	rr	0	0	0	+	+	+	0	0	0	+	0	+	0	+	+	+	0	+	+	0	+	+	+	0	$+^s$	0	+	8	0	0	2+
9	rr	0	0	0	+	+	+	0	0	0	+	+	+	0	+	0	+	+	0	0	+	0	+	0	+	0	0	+	9	0	0	2+
10	rr	0	0	0	+	+	+	0	0	0	+	0	+	0	+	+	0	+	0	0	+	+	+	+	+	$+^w$	0	+	10	0	0	2+
11	R_1R_1	+	+	0	0	+	0	0	0	0	+	0	+	0	+	0	+	+	0	0	+	+	0	+	0	+	0	+	11	0	0	2+
Patient Cell																														0	0	2+

Reaction scale = 0 (no reaction) to 4+ (strong reaction)

Questions

1. What is the patient's ABO/Rh blood type?
2. What antibodies did you identify?
3. Are the antibodies clinically significant? Why or why not?
4. How many RBC units would you need to screen in order to find four compatible (i.e., negative for the corresponding antigen) units as requested? (Refer to the table of RBC antigen frequencies, using antigen frequencies listed under Caucasian population)

Answers

1. **What is the patient's ABO/Rh blood type?** Forward or front typing of the patient's sample (i.e., using reagent anti-A and anti-B sera to detect A and B antigens on the RBCs) shows that the patient is group O type (i.e., neither A nor B antigens are detected). Back or reverse typing of the sample confirms that patient is group O since both anti-A and anti-B isoantibodies are detected in the plasma of the patient. Testing with reagent anti-D serum shows that the D antigen is present on the patient's RBC; therefore, the patient is Rh D positive.
2. **What antibodies did you identify?** Anti-E alloantibody is present; E antigen (Rh3) is a part of the Rh blood group system. Although the "rule of three" applies in the identification of antibodies, for simplicity of working up the cases in this workbook, the learner will find that the rule cannot be consistently applied. The "rule of three" states that at least three antigen-positive and three antigen-negative RBCs that react and do not react, respectively, are necessary to achieve a statistically significant p value (or probability value) of 0.05. In this case, however, only two of the panel cells are E antigen positive and so a third cell technically should be tested [1].
3. **Are the antibodies clinically significant? Why or why not?** Anti-E is a clinically significant alloantibody since it is IgG, is warm temperature reactive (i.e., 37 °C), and is capable of causing delayed hemolytic transfusion reactions as well as hemolytic disease of the newborn. In general, clinically significant antibodies are warm-reacting, immune IgG antibodies while cold-reacting IgM antibodies are not considered to be clinically significant. Antibodies to the following blood group antigens are usually IgG: Duffy, Kell, Kidd, Rh, and Ss. Antibodies to the following blood group antigens are usually IgM: Lewis, MN, and P1.
4. **How many RBC units would you need to screen in order to find four compatible (i.e., negative for the corresponding antigen) units as requested?** About 29% of the Caucasian population carries E antigen (see table of RBC antigen frequencies) on their red cells; thus, 71% are negative and the chances of finding a compatible donor red cell unit for the patient with anti-E antibody are about seven out of ten units. A total of 4 RBC units were requested for the

patient; thus, dividing 4 by 0.71 (i.e., 4/ 0.71), we find that 5.6 or, essentially, 6 RBC units need to be screened in order to find 4 E-antigen-negative, compatible RBC units for the patient.

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Recommended Reading

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