RBC administration during trauma resuscitation of a young female

Mark Yazer, MD
University of Pittsburgh

My disclosures

- Grífols: Scientific advisory board & speakers bureau
- Macopharma: Scientific advisory board
- Octapharma: Scientific advisory board
- Terumo: Speakers bureau
- Haemonetics: Speakers bureau
- Cook Biomedical: Scientific advisory board
- Verax Biomedical: Scientific advisory board

Terrible car accident

- A 19 year old female was involved in a terrible car accident
- Transported to an ICU at an adult hospital
- Splenic laceration, broken femur and pelvis, unconscious
- Hemodynamically unstable, hypoxic, tacchycardic
- Estimated to have lost about 2000 ml of blood

Pre-transfusion testing not complete!

- Pre-transfusion sample drawn but not sent to blood bank
- ABO and RhD type unknown
- Crystaloid fluids administered
- She deteriorated further and required an urgent RBC transfusion…

What would you do?

1. Withhold the transfusion until pre-transfusion testing complete?
2. Immediately use recombinant activated factor VIIa (rfVIIa, NovoSeven) and other hemostatic agents while waiting for crossmatched RBCs?
3. Use O+ RBCs from uncrossmatched RBCs in ICU refrigerator?
4. Call blood bank and request STAT uncrossmatched O- RBCs?
5. Be grateful you were not on call that night?

Really not much of a decision

- She clearly needed RBCs
- 2 O+ RBC units were quickly removed from refrigerator on trauma ward
- There are 2 potential issues here:
  1. Antibody mediated hemolysis from uncrossmatched RBCs
  2. Possible anti-D alloimmunization leading to potential for hemolytic disease of fetus and newborn following D+ RBC transfusion
- How to proceed?

1. What is the risk of hemolysis after uncrossmatched?

1. Unknown?
2. High risk because she could have been pregnant and thus become alloimmunized?
3. Medium risk because she is likely to have bled some of her plasma volume before receiving uncrossmatched RBC transfusion?
4. Low risk because uncrossmatched RBCs are from “universal donor” blood group
5. Low risk as demonstrated in a variety of studies

Low alloimmunization rate

- Uncrossmatched RBCs are generally group O
- The risk of unexpected antibodies is directly proportional to the probability that the recipient was exposed to RBCs

Age (years)	Number of patients	Males % clin sign (95% CI)	Females % clin sign (95% CI)
Indeterminant	76	0.00	0.00
< 30	4974	0.83 (0.38–1.57)	0.62 (0.40–0.92)
30–39	3308	1.09 (3.40–2.35)	1.56 (1.13–2.10
40–49	1526	1.47 (0.67–2.77)	2.74 (1.77–4.01)
50–59	1491	1.41 (0.73–2.44)	3.14 (1.93–4.80)
≥ 60	4591	2.34 (1.78–3.02)	4.59 (3.74–5.56)
Totals	15966	1.66 (1.34–2.03)	2.03 (1.77–2.32)

Saverimuttu J et al. *Emergency Medicine* 2003:239

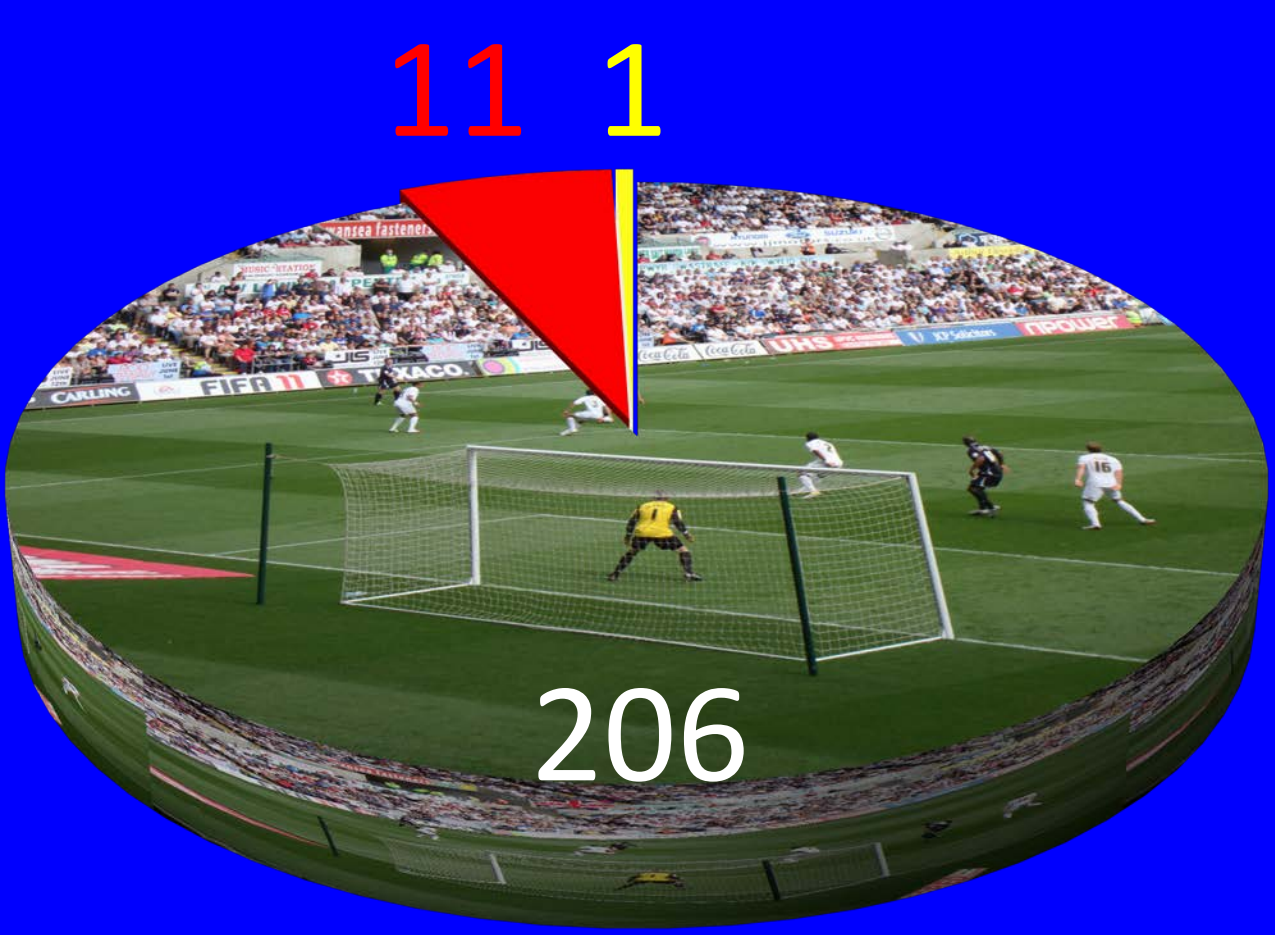
The Pitt experience with uncrossmatched RBCs

- 218 recipients of at least 1 uncrossmatched RBC
  - 1065 uncrossmatched units in total
- 65% male
- Mean age: 54 ± 21
- Mean number of uncrossmatched RBC units:

  4.9 ± 4.9
  - Range 1-24
- Units issued to…
  - ED 48%
  - OR 24%
  - ICU 23%
  - Medicine, radiology, L&D 5%

Radkay L et al. *Immunohematology* 2012:39-44

What is the risk of using uncrossmatched RBCs?



No antibodies

Antibodies: No hemolysis (6 active on day of uncx transfusion)

Antibodies: Hemolysis

Risk of hemolysis: 1/218 (0.5%)

More experience with uncrossmatched RBCs

262 recipients of uncrossmatched RBCs

17/262 (6.5%) patients had clinically significant antibodies

12/218 (5.5%)

7/17 were transfused with incompatible RBC units

Only 1/7 hemolyzed!

Risk of hemolysis: 1/262 (0.4%)

1/218 (0.5%)

Goodell PA et al., *AJCP* 2010:202

The literature's experience with uncrossmatched RBCs

Study	Number of Recipients	Number of Uncrossmatched Erythrocyte Units Issued	Rate of Hemolysis	Rate of New Antibody Formation
Mulay, 2012[17]	1,407	4,144	1/1,407 (0.02%)	7/232* (3%)
Radkay, 2012[6]	218	1,065	1/218 (0.5%)	4/218 (1.8%)
Miraflor, 2011[15]	132	1,570	1/132 (0.8%)	1/132
Goodell, 2010[18]	262	1,002	1/262 (0.4%)	Not reported
Ball, 2009[19]	153	511	0	Not reported
Dutton, 2005[14]	161	581	0	1/161 (0.6%)
Unkle, 1991[20]	135	Not reported	0	3/135 (2.2%)
Lefebre, 1987[21]	133	537	0	Not reported
Schwab, 1986[22]	99	410	0	Not reported
Gervin, 1984[23]	160	875	0	Not reported
Blumberg, 1978[24]	46	221	0	Not reported
Total	2,906	10,916	4/2,906 (0.1%)	16/878 (1.8%)

Boisen M et al. *Anesthesiology* 2015

Low alloimmunization rate

Age (years)	ED total	ED % clin sign (95% CI)	Trauma total	Trauma % clin sign (95% CI)	Haem/onc total	Haem/onc % clin sign (95% CI)
Indeterm.	70	0.0	29	0.0	0	0.0
< 30	1860	0.5 (0.22–0.92)	772	0.5 (0.14–1.32)	124	0.0
30–39	1019	1.8 (1.05–2.78)	333	0.8 (0.49–3.40)	136	4.4 (1.64–9.36)
40–49	664	2.6 (1.50–4.07)	223	1.3 (0.27–3.88)	157	7.0 (3.55–12.19)
50–59	588	2.6 (1.43–4.17)	194	1.0 (0.13–3.67)	166	3.6 (1.34–7.70)
≥ 60	1797	3.9 (3.05–4.90)	554	3.8 (2.36–5.74)	607	6.3 (4.47–8.49)
Totals	5998	2.2 (1.80–2.55)	2105	1.7 (1.16–2.30)	1190	5.1 (3.94–6.54)

Saverimuttu J et al. *Emergency Medicine* 2003:239

Remember this…

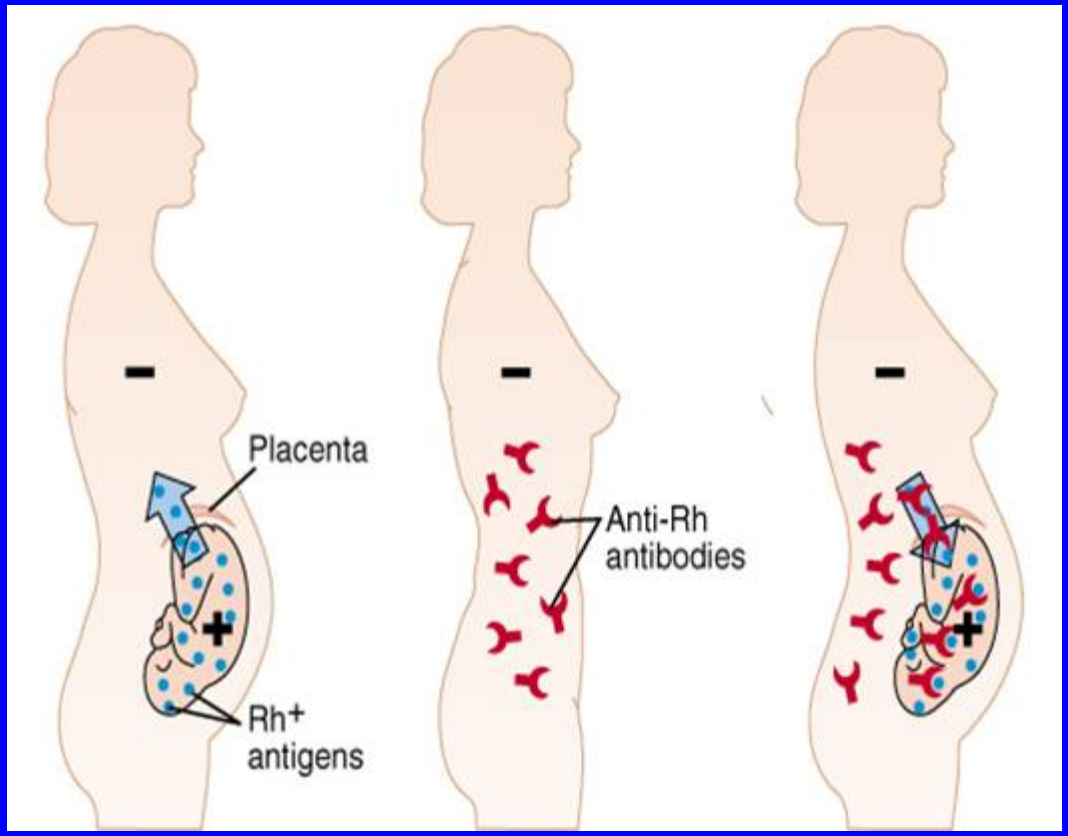
- Do not hesitate to use uncrossmatched RBCs in an unstable patient without ABO group
- Overall probability that they have an antibody is low
- Even if they do, probability of hemolysis is tiny
- Uncrossmatched RBCs are not a substitute for crossmatched RBCs in otherwise stable patients

2. Potential for D alloimmunization

- She's A – !!!
- Received 2 O+ RBCs
- She also received 12 more O neg RBCs
- Also plasma and platelets
- She is now more stable and so we can think

The problem with anti-D

- The patient is a 19 year old woman
- "…Of childbearing age"
- If she becomes anti-D alloimmunized then her fetus could be affected by HDFN



< 25% of hospitalized D- patients make anti-D

- 445 D+ units transfused to 98 D- recipients
- 82% of D+ RBCs issued to ER, OR, ICU or medicine ward

Recipient characteristics	Anti-D formers (n = 22)	Non–anti-D formers (n = 76)
Number of units of D+ RBCs transfused		
Mean	3.3	4.9
Median	2.5	3
Range	1-10	1-24
Number of recipients who received any LR D+ RBCs		
Mean	3	10
Median	4	4
Number of units	4	3.5
Range	2-6	1-10
Number of recipients reexposed to D+ RBCs	1	8

Yazer and Triulzi, *Transfusion* 2007

What about D alloimmunization in all patients?

- American study of 268 patients who received uncrossmatched RBCs
- Eight D- patients survived ≥7 days and had an antibody screen thereafter

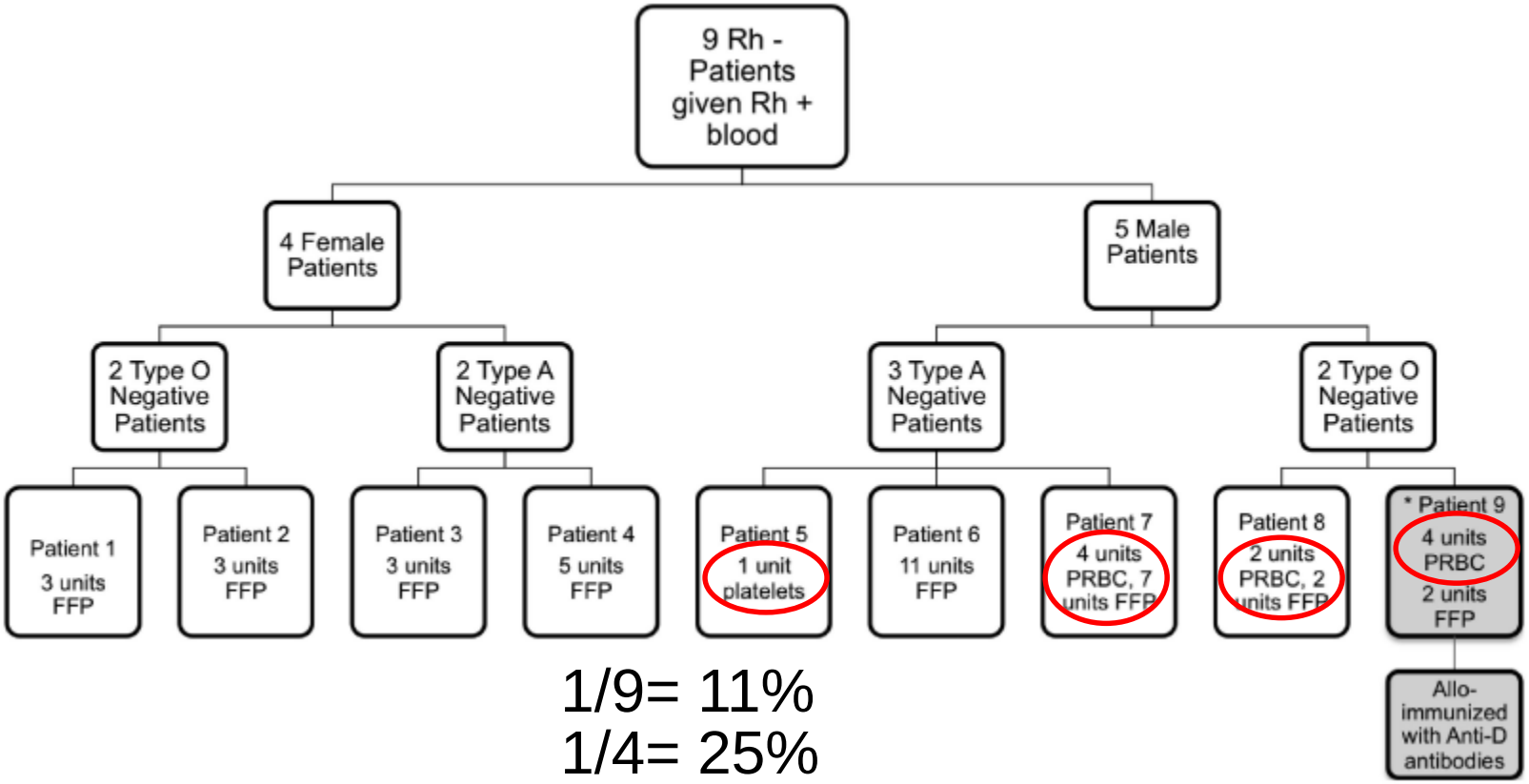
Age (years)	Sex	ABO type	Admission service	Number of ED-released O– RBC units transfused in ED	Number of O+ RBC units transfused outside ED	Antibody screen on admission	Length of serologic follow-up (days)	Antibody screen result on follow-up	Length of stay (days)	Mortality (during study period)/died from injuries suffered on admission
38	Male	O	Trauma	2	20	Negative	164	Positive (WAA, anti-D, C, E)	202	Alive/NA
47	Male	B	Trauma	2	27	Negative	26	Negative	29	Died/yes
90	Female	B	Gastrointestinal	2	6	Negative	10	Positive (anti-E)	14	Alive/NA
31	Male	O	Trauma	4	1	Negative	2003	Negative	24	Alive/NA
54	Female	A	Trauma	2	25	Negative	142	Negative	146	Died/no
74	Male	O	Vascular surgery	2	3	Negative	65	Negative	14	Alive/NA
50	Male	A	Gastrointestinal	1	2	Positive (anti-D)	280	Positive (anti-D)	36	Alive/NA
63	Male	O	Vascular surgery	1	14	Negative	16	Negative	40	Alive/NA

1/7 = 14%

Meyer and Uhl, *Transfusion* 2015

What about D alloimmunization in trauma?

- Another American study of trauma patients
- 132 patients received an uncrossmatched RBC transfusion
- Nine patients were D- and received D+ “blood products”



Miraflor et al, *J Trauma* 2012

What about D alloimmunization in trauma?

- Yet another American study of trauma patients
- 161 patients received an uncrossmatched RBC transfusion
- Ten patients were D- and received D+ RBCs
  - "1" / 10 (10%) developed anti-D
- But was it really just one?

One male of type A- who received 6 units of Rh+ UORBC had an initial (sero)conversion, but no antibody to the Rh factor on subsequent crossmatching 5 months later

Actual rate was really 20%

Dutton et al, *J Trauma* 2005

What about D alloimmunization to PLTs?

- ADAPT study
- Largest retrospective study to date
- 485 D- "all comers" who had not received D+ RBCs
- Received at least 1 dose of D+ PLTs, had screen ≥28 days later

Platelet product type	D+ (*n*)	D− (*n*)	Total (*n*)
Whole blood-derived platelets	1180	1505	2685
Apheresis platelets	1970	694	2664
Total number	3150	2199	5349

- 55% hematology/oncology patients

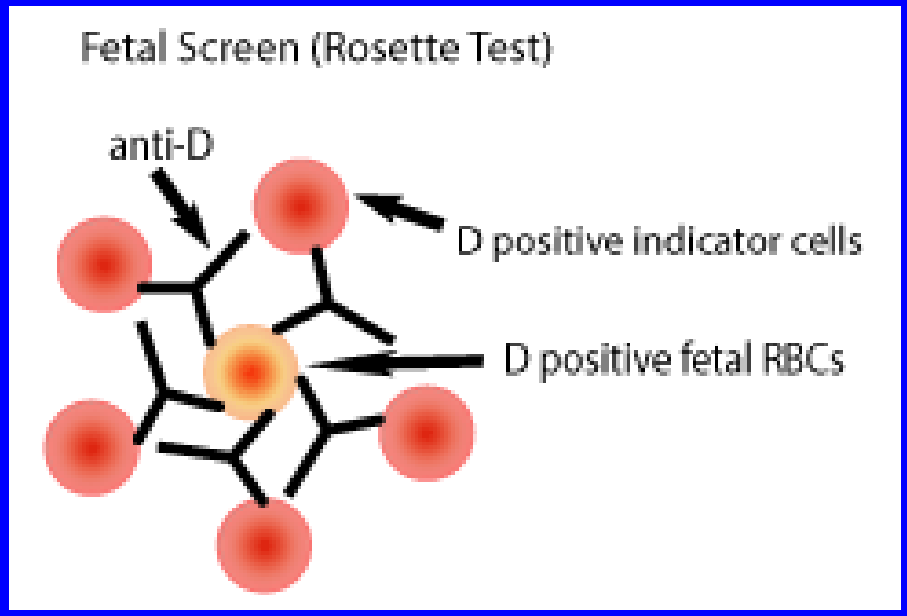
Cid et al. *Br J Haem* 2015: 598

What should we do about the 2 D+ RBCs?

1. Nothing, it was only 2/14 RBCs and they have surely bled out by now
2. Nothing, her risk of making anti-D is quite low
3. Administer RhIg
4. Do a Kleihauer-Betke test for D+ RBCs
5. Do a fetal bleed screen (rosette test) to detect D+ RBCs
6. Perform urgent RBC exchange as soon as possible to avoid alloimmunization

What we did next…

- We did a rosette test to detect D+ RBCs
- Commonly performed on post-partum D- women to detect the presence of > 30 ml of D+ RBCs
- K-B test is not useful in this setting as it detects hemoglobin F, not specifically D+ RBCs



Results

- The fetal bleed screen was positive
- Indicates that > 30 ml of RBCs still present in recipient
- Unfortunately it does not tell us how many D+ RBCs are still present!
- What to tell the family?

What do we say to the family?

1. The administration of the D+ RBCs was necessary to save her life
2. She still has some D+ RBCs in circulation
3. Her risk of making anti-D is 25%
4. Her risk of having a fetus affected by severe HDFN is 25%
5. The overall risk of a bad fetal outcome is thus ~ 5%
6. Not recommended to use RhIg if patient received >1 D+ RBC unit
7. All the above

We talked to the family

- We explained the low risk of a bad fetal outcome
- Father felt that she intended to have children
- Wanted us to “do everything”
- Femoral line inserted
- She weighed 102 kg
- For a fraction of remaining (FCR) of 10% we calculated that we needed to exchange 18 RBC units
- How should we prepare these RBCs?

How to select RBCs for exchange

1. ABO, D compatible
2. ABO, D, K matched
3. ABO, D, C, c, E, e, K matched
4. Matched for ABO and all minor antigens

Selecting RBCs for exchange

- We tried to antigen match the RBCs
- Her RBC phenotype was negative for:
  D C E K Fy^a Jk^a s
- Thus we would have had to screen many many units to find 18 antigen matched
- We decided to match only for Rh and K

Antigen system	Antigen	Total antibodies*
Kell	K	131 (22.7)
	Kp^a	3 (0.5)
	Js^a	2 (0.4)
Rh	D	53 (9.2)
	C	28 (4.9)
	c	27 (4.7)
	E	111 (19.2)
	e	2 (0.4)
	C^w	8 (1.4)
	V	3 (0.5)

Tormey et al. *Transfusion* 2008:2069

RhIg is required

- We calculated that there would be 10% of the recipient's own RBCs left after the exchange
- If each RBC unit contained 230 ml of RBCs, then potential for 46 ml of residual D+ RBCs
- Each 1500 IU vial of RhIg covers 15 ml of packed RBCs
- We thus administered 6 vials of RhIg

RhIg is required

- Antibody screen performed 6 hours later was negative
- So 6 more vials were administered
- Antibody screen became positive
- Now we'll wait and see if she produces anti-D

Summary

1. Don’t withhold lifesaving RBCs regardless antibodies, RhD, age…or anything else!
2. Risk of making anti-D is 25%
3. Risk of having a fetus affected by severe HDFN is 25%
4. The overall risk of a bad fetal outcome is thus ~ 5%
5. Not recommended to use RhIg if patient received >1 D+ RBC unit
6. Talk to the family


vodafone

1. What is the risk of hemolysis after uncrossmatched?

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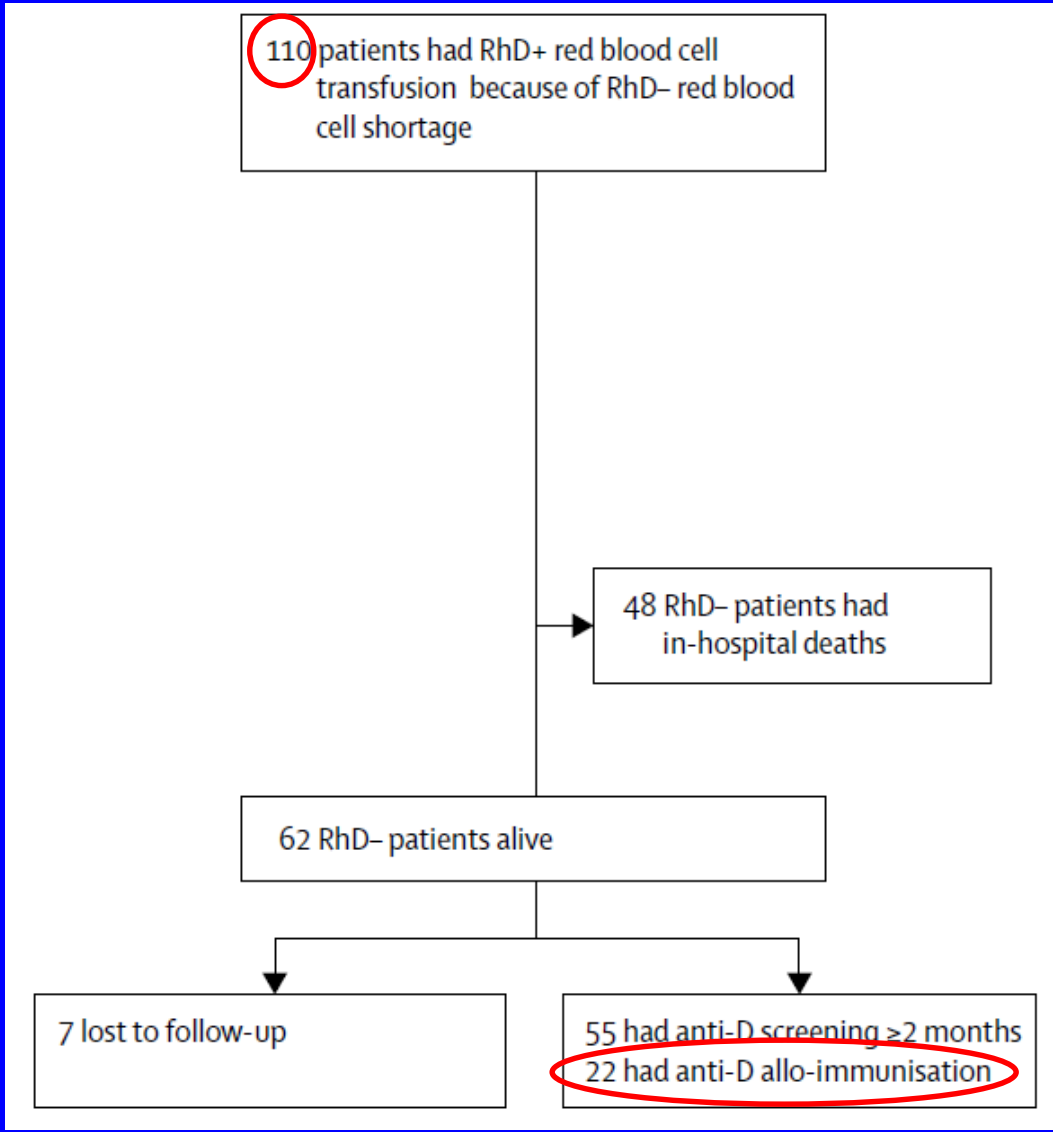
What about D alloimmunization in all patients?

- German study of patients who received D+ RBCs in A&C



Overall rate of D alloimmunization: 22/110=20%

Of those who survived and had an antibody screen: 22/55=40%

Selleng und alles, Lancet Haem 2017

What about D alloimmunization in trauma?

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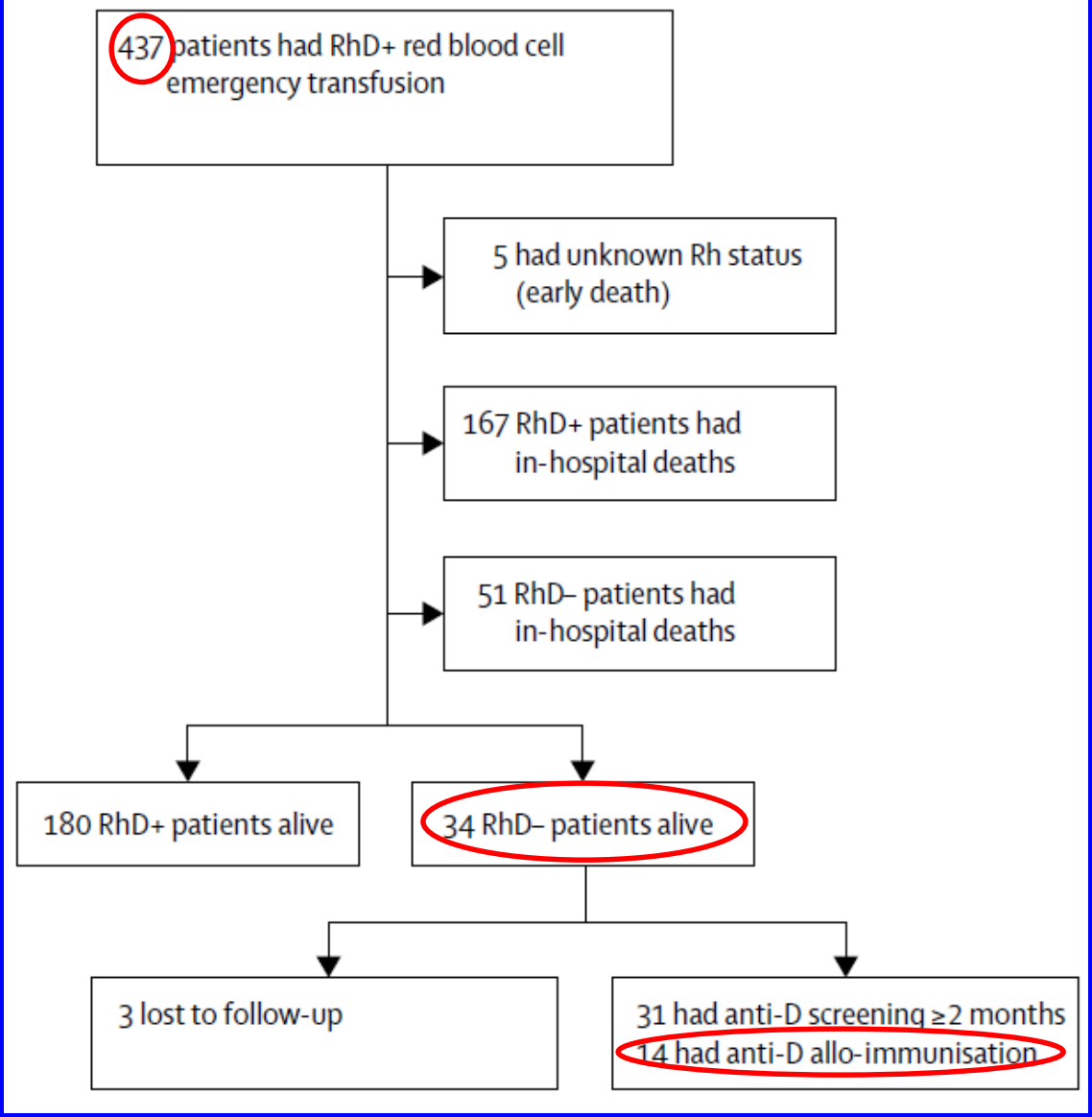

Overall rate of D alloimmunization: 14/437=3%

Rate of D alloimmunization amongst D- recipients of D+ RBC in ED: 14/31=45%

Selleng und alles, Lancet Haem 2017

What % of anti-D alloimmunized pregnancies end in severe HDN?

- > 90%
- ~ 50%
- ~ 25%
- < 10%

What to do now?

1. Do nothing, she bled so much that there's probably only 31 ml of D+ RBCs left
2. Calculate the highest possible quantity of D+ RBCs still present and give enough RhIg to clear them
3. Perform RBC exchange using D- RBCs
4. Talk to the family as patient is unconscious

What is the risk of alloimmunization following uncx?

1. Higher than that with crossmatched RBCs because pre-transfusion testing is not completed before they are issued
2. Exactly the same as with crossmatched RBCs if extended phenotyping not performed
3. Lower than with crossmatched RBCs because the patient is bleeding significantly so the transfused RBCs end up on the floor quickly

A word about alloimmunization after uncrossmatched RBCs

- Don’t forget that crossmatched RBCs are generally only matched for ABO and D
- Thus the potential to form antibodies to other antigens also exists with crossmatched RBCs
- Recipient’s inflammatory state aside, the risk of forming new alloantibodies to minor antigens is the same as with crossmatched RBCs

Why perform a fetal bleed screen?

1. If negative then likely very few D+ RBCs still present
2. If positive then an RBC exchange must immediately be performed
3. If positive then too many D+ RBCs are present for RhIg to be effective
4. If positive the patient has already become alloimmunized to D