# *Who's afraid of incompatible plasma? The use of A plasma and O whole blood in massive bleeding*

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## Background

TRANSFUSION PRACTICE

**A possible new paradigm? A survey-based assessment of the use of thawed group A plasma for trauma resuscitation in the United States**

*Nancy M. Dunbar,[1,2] and Mark H. Yazer,[3,4] on behalf of the Biomedical Excellence for Safer Transfusion (BEST) Collaborative[5]*

TRANSFUSION 2016;56:125–129

- 34/59 (58%) US level 1 trauma centers use thawed group A plasma for trauma patients of unknown ABO group
- 21/34 (62%) have NO limit on the number of A units
- 27/34 (79%) do NOT titer anti-B

## Disclosures

- ❑Grifols: Honoraria & SAB
- ❑Macopharma: Scientific advisory board
- ❑Octapharma: Scientific advisory board
- ❑Terumo: Honoraria
- ❑Haemonetics: Honoraria
- ❑Cook Biotech: Scientific advisory board
- ❑Verax Biomedical: Scientific advisory board
- ❑New Health Sciences: Scientific advisory board

## ABO incompatible plasma? Seriously?

Yes!

- Begs some questions that need to be answered:
  - What is a safe titer threshold?
  - How often should donors be titered?
  - Is it a safe practice?

## The puzzle of incompatible plasma

- Ideally everything would be ABO compatible, I guess
- Not practical, especially for platelets
  - Maybe with 7 day PLTs the supply will be better
- Group AB donors are rare and their plasma is precious
  - A bad trauma can really deplete the city's inventory
- Is there an alternative for massively bleeding patients?

## What is a safe titer threshold?

- I don't know
- Probably doesn't exist
- Question really is – below what titer threshold is hemolysis *unlikely*
- Risk is always there, but can we minimize it?

## Hemolysis happens primarily at high titer

| Author, Year | Recipient Age | Recipient ABO group | Platelet Product Type | Platelet Product ABO group | Isohemagglutinin Titer Saline | Isohemagglutinin Titer AHG | Isohemagglutinin Titer Hemoglobin Drop (%) |
|---|---|---|---|---|---|---|---|
| Zoes, 1977[25] | 44 | AB | Random donor pool | O | anti-A: 256<br>anti-B: 64 | NR | NR |
| McLeod, 1982[26] | 45 | A | Apheresis | O | 1,280 | 10,240 | 42.8 |
| Conway, 1984[27] | 15 | A | Apheresis | O | 8,192 | NR | NR |
| Pierce, 1985[28] | 2.5 | A | Apheresis | O | 512 | 32,000 | 50.4* |
| | 58 | B | Random donor | O | 512 | 16,384 | 42.6 |
| Ferguson, 1988[29] | 66 | A | Random donor | O | 256 | > 4,000 | 26 g/L |
| Reis, 1989[30] | 56 | B | Apheresis | O | NR | 4,096 | 53.9 |
| Murphy, 1990[31] | 30 | A | Apheresis | O | 256 | 1,024 | 47.3 |
| Mair, 1998[32] | 28 | A | Apheresis | O | 128 | NR | 30.9 |
| MacManigal, 1999[33] | 72 | AB | Apheresis | O | NR | NR | NR |
| Larsson, 2000[34] | 44 | A | Apheresis | O | 16,384 | NR | 29.8† |
| Valbonesi, 2000[35] | 51 | A | Apheresis (dry platelet) | O | > 8,000 | NR | 37.2 |
| | 18 | A | | | | | 39.7* |
| Anonymous, 2002[36] | 36 | A | Apheresis | O | NR | 2,048 | 22.5 |
| | 45 | A | Apheresis | O | NR | 4,096 | 15.3 |

Lozano and Cid *TMR* 2003;17:57-68

## How often should donors be titered?

- Anti-A and/or –B in 56 healthy Danish people q 3 months
- Automated solid phase
- Expressed as $\log_2$ titer steps
  - Titer 32 = 5 titer steps


| No. | Volunteers | Anti-A, IgM | Anti-A, IgG | Anti-B, IgM | Anti-B, IgG |
|---|---|---|---|---|---|
| O | 19 | 4.7 (0.45) | 4.9 (0.39) | 4.3 (0.50) | 3.5 (0.30) |
| A | 27 | | | 3.5 (0.41) | 0.1 (0.31) |
| B | 10 | 4.0 (0.37) | 0.3 (0.58) | | |
| Overall | 56 | 0.42 (n = 29, 0.87) | 0.47 (n = 29, 0.96) | 0.45 (n = 46, 0.91) | 0.30 (n = 46, 0.62 |

- Maximum titer step variation was 1.5 (IgG anti-A) and 1 (all 3 others)

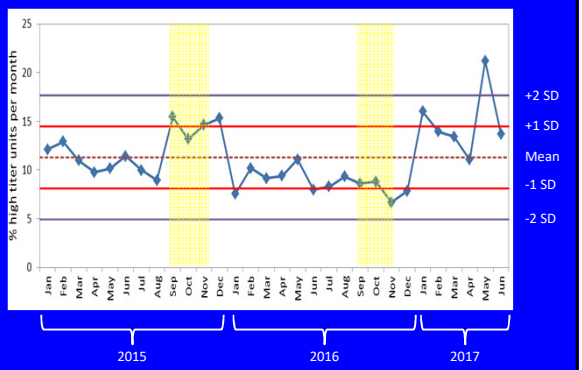
Sprogøe U et al. *JTACS* 2017;82:S87-590

## Hemolysis happens primarily at high titer

| Reference, year | Recip. ABO | Plt type | Plt ABO | Saline titer | AHG titer | Outcome |
|---|---|---|---|---|---|---|
| Lundberg and McGinniss | AB | RDP | O | 64 | 128 | Survived |
| Zoes et al. [36] | AB | RDP | O | 64/256 | NR | Survived |
| McLeod et al. [37] | A | RDP | O | 32/64 | 10,240 | Survived |
| Siber et al. [38] | A | RDP | O | NR | 8192 | Survived |
| Ferguson [39] | A | RDP | O | 256 | >4000 | Survived |
| Reis and Coovadia [40] | B | ADP | O | NR | 4096 | Survived |
| Murphy et al. [17] | O | ADP/ | O | 512/ | 2048/ | Survived |
| | | ADP | O | 256 | 1,024 | |
| Mair and Benson [4] | A | SDP | O | 128 | NR | Survived |
| SHOT Steering Group [41] | A | SDP | O | 0 | 20,000 | Survived |
| McManigal and Sims [42] | AB | SDP | O | Not tested | Not tested | Survived |
| Larsson et al. [5] | A | SDP | O | 16,384 | NR | Survived |
| Valbonesi, et al. [29] | A | SDP | O | >8000 | 128 | Survived |
| SHOT Steering [43] | A | RDP, RDP, SDP respectively | O | NR x 3 cases | NR x 3 cases | Survived |
| SHOT Steering [44] | A | SDP | O | >1024 | >8192 | Survived |
| Josephson et al. [21] | A | SDP | O | NR/ | 1024/ | Survived |
| | A | | O | 256 | 8192 | |
| Fauzie [46] | A | SDP | O | 32 | 32 | Survived |
| Reinhardt et al. [34] | AB | SDP | O | 512 | NR | Survived |
| Sadani et al. [22] | A | SDP | O | 1280 | 160 | Survived |

Josephson et al. *Transfusion and Apheresis Science* 2010;42:83-88

## No periodicity of high titer group A plasma units



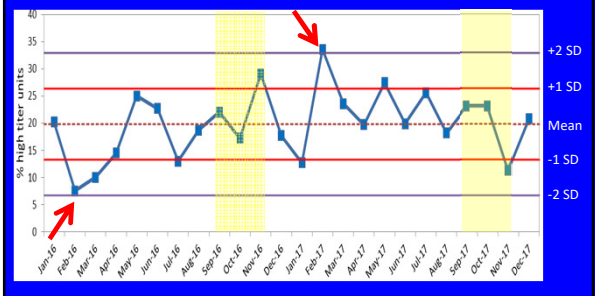

Courtesy of Dr. Sarah Harm and the BEST collaborative

## Examples of titer thresholds

| Product | Source | Method | Critical titer: Direct agglutination, indirect agglutination |
|---|---|---|---|
| *Group O Apheresis platelets* | Josephson et al.[41] | Gel | ≥64, ≥256 |
| | Cooling et al.[6] | Gel | NT, ≥128 |
| | Quillen et al.[42] | Gel | ≥250, NT |
| | Karafin et al.[19] | Gel | ≥512 |
| | Pittsburgh, USA[16] | Tube | ≥100, NT |
| | UK national guidance[43] | Automated<br>Tube | ≥100, NT<br>≥128, NT |
| | Scottish National Blood Transfusion Service[29] | Automated | ≥50, NT |
| | Italy[44] | Gel | ≥64, 256 |
| | Germany[44] | Tube | ≥64, NT |
| | Norway[44] | Gel | NT, ≥250 |
| | Sweden[44] | Tube | ≥100, ≥400 |
| | Japan[44] | Gel | NT, ≥512 |
| *Group A Plasma* | STAT study[7]<br>3 centers<br>1 center<br>13 centers | <br>Tube<br>Tube<br>NT | <br>≥50, NT<br>≥100, NT |
| *Whole Blood* | Mayo Clinic, USA[33] | Tube | ≥200, NT |
| | Pittsburgh, USA[34] | Tube | ≥50, NT |

Yazer et al. *Transfusion* 2018:532

## No periodicity of high titer whole blood units




Courtesy of Dr. Sarah Harm and the BEST collaborative

*Is emergency issued group A plasma associated with increased risk of mortality in group B and AB trauma patients compared to A recipients?*

**S**afety of the Use of **T**hawed Group **A** Plasma in **T**rauma (STAT Study)

Dunbar and Yazer, *Transfusion* 2017;57:1879

## Conclusions on STAT study

- Survival was not significantly different between those who received incompatible group A plasma and those for whom it was identical
  - Supports use of thawed group A plasma in the initial resuscitation of patients of unknown ABO group

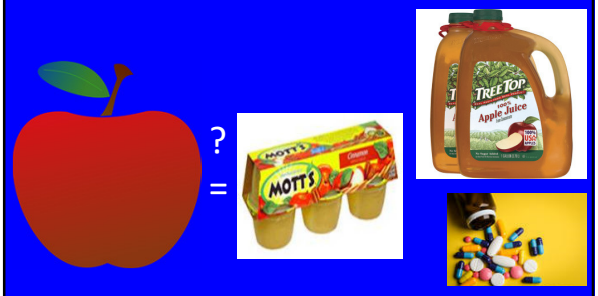
**JUST DO IT.**

## Patient demographics

| | Group A | Group B, AB | |
|---|---|---|---|
| | Identical (n = 809) | Incompatible (n = 354) | p value |
| Sex | | | |
| Female | 215 (27) | 90 (25) | 0.72 |
| Male | 594 (73) | 264 (75) | |
| Age (years) | 48 (15-99, 22) | 48 (11-96, 22) | 0.70 |
| Mechanism of injury | | | |
| Blunt | 641 (79) | 239 (68) | <0.0001† |
| Penetrating | 168 (21) | 115 (32) | |
| TRISS probability of survival (%) | 64 (0-100, 36) | 66 (0-100, 66) | 0.62 |
| Blood products transfused | | | |
| Total RBC units transfused | 9 (0-105, 13) | 9 (0-96, 13) | 0.53 |
| Total group A plasma transfused | 7 (1-116, 11) | 4 (1-58, 5) | <0.0001† |
| Total all plasma units transfused | 8 (1-116, 12) | 7 (1-90, 11) | 0.51 |
| Total PLT doses transfused | 1 (0-23, 2) | 1 (0-16, 2) | 0.50 |
| Total cryoprecipitate pools transfused | 1 (0-17, 1) | 1 (0-9, 1) | 0.81 |

Dunbar and Yazer, *Transfusion* 2017;57:1879

## What's old is new again…Whole blood revisited




Courtesy Col (Dr.) Alan Murdock

## Results: Overall Survival

| | Identical (n = 809) | Incompatible (n = 354) | p value |
|---|---|---|---|
| In-hospital mortality | | | |
| Survival to discharge | 572 (71) | 253 (71) | 0.83 |
| In-hospital death | 237 (29) | 101 (29) | |
| Early mortality (<24 hr) | | | |
| Yes | 114 (14) | 59 (17) | 0.28 |
| No | 695 (86) | 295 (83) | |
| Hospital LOS (days) | 14 (0-111, 17) | 14 (0-128, 18) | 0.89 |

- Logistic regression for in-hospital mortality and 24-hour survival and plasma compatibility was not a significant predictor

Dunbar and Yazer, *Transfusion* 2017;57:1879

## Why intervene early with plasma?

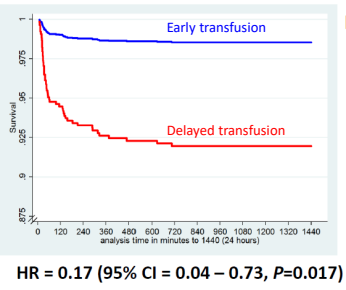
- Many injured combat victims requiring MT are coagulopathic at presentation

| | N=247 MT | N=311 No MT |
|---|---|---|
| Age (y), mean ± SE | 27 ± 1 | 28 ± 1 |
| Gender, woman, n (%) | 4/247 (2) | 14/317 (4) |
| Blunt mechanism, n (%) | 18/247 (7) | 73/311 (23) |
| INR, mean ± SE | 2.0 ± 0.1 | 1.2 ± 0.1 |
| PT (s) , mean ± SE | 19.0 ± 0.9 | 11.9 ± 0.2 |
| PTT (s) , mean ± SE | 47.3 ± 3.5 | 31.4 ± 1.5 |
| HGB (g/dL) , mean ± SE | 10.5 ± 0.2 | 13.7 ± 0.1 |
| Platelets × $10^{-3}$/L, mean ± SE | 218 ± 8.7 | 257 ± 5.0 |

Schreiber MA et al. *J Am Coll Surg*, 2007

## Early initiation of transfusion saves lives

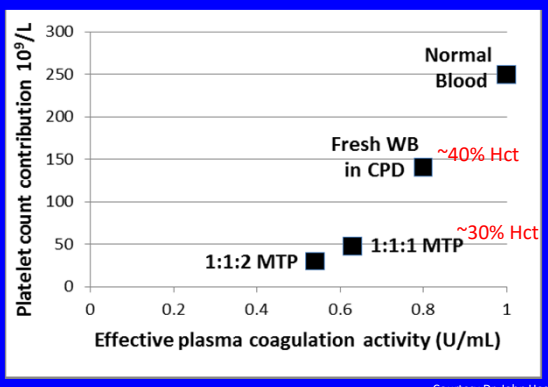
- Adjusted, retrospective US military data on 502 pre-hospital RBC recipients



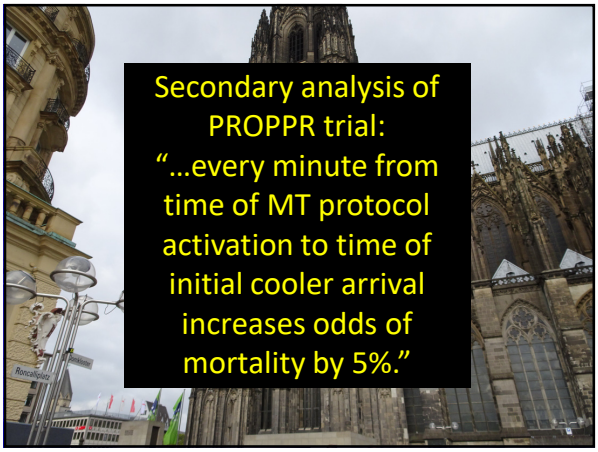

**HR = 0.17 (95% CI = 0.04 – 0.73, *P*=0.017)**

Shackelford SA et al. JAMA. 2017 24;318:1581-1591

## 1:1:1 is not the same as WB



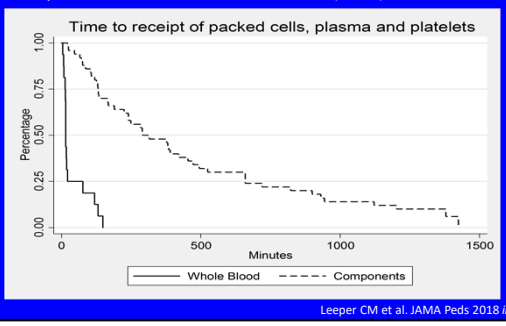

Courtesy Dr. John Hess




| | Volume of CPD | Volume of AS | Total |
|---|---|---|---|
| | 47 | 0 | 47 |
| | 10 | 110 | 120 |
| APLT | 36 | 0 | 36 |
| WB PLT | 13 | 0 | 13 |
| | 70 | 0 | 70 |

## WB makes it easier to (initially) provide balanced resuscitation

- Time from ED admission until administration of WB (n=18) or at least 1 RBC, plasma, and PLT in historical cohort (n=50)



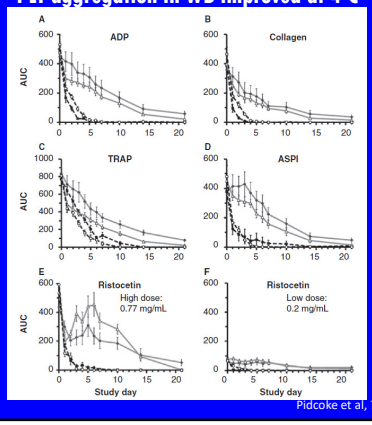

Leeper CM et al. JAMA Peds 2018 *in press*

## A lot of extra fluid in reconstituted WB

Imagine a 10 unit massive transfusion

- 1:1:1 = 1800 mL of CPD/AS
- 1:1:2 = 2270 mL of CPD/AS
- 10 RBC, 10 plasma, 2 APLT = 1742 mL CPD/AS
- WB 700 mL CPD

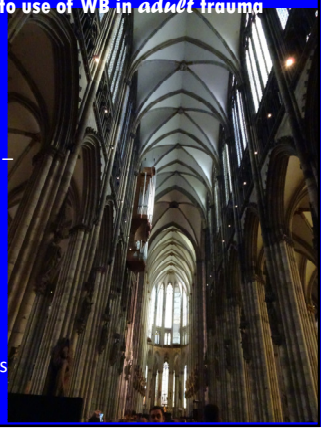
## PLT aggregation in WB improved at 4°C



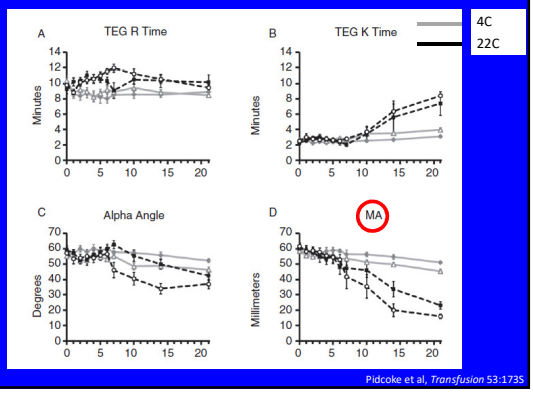

Pidcoke et al, *Transfusion* 53:173S

## The Pittsburgh approach to use of WB in *adult* trauma

- Group O + WB units
  - Collected with PLT sparing inline leukoreduction filter
  - Titer of both anti-A and –B <50
  - Titers performed on every unit every time
  - Male only donors for TRALI risk mitigation
- Stored as WB for 14 days
  - On day 15 WB units are processed into RBC units with 21 day outdate

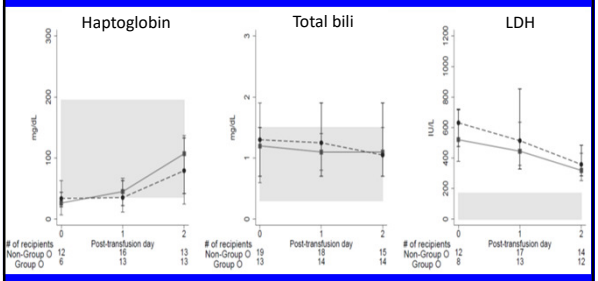


## TEG parameters in WB improved at 4°C




Pidcoke et al, *Transfusion* 53:173S

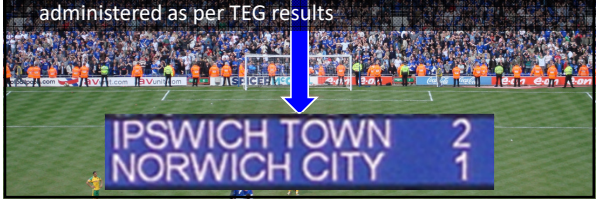
## No haemolysis amongst recipients of 3 and 4 WB units




Seheult J et al. Transfusion *in press*

## The Pittsburgh approach to use of WB in *adult* trauma

- Started in December 2014
- Only for male trauma patients with hypotension
- 2 WB units kept in the ED fridge *for immediate use*
  - At least 2 more kept in the blood bank
- Initially maximum of 2 WB units per patient
  - Now maximum of 6 units
- After these 6 units administered, conventional products administered as per TEG results




## Some outcomes in adult trauma

| | Component therapy (n=90) | WB (n=46) | p |
|---|---|---|---|
| Age | 43 (15-89), n=90 | 32 (18-90), n=43, 3 unk | 0.03 |
| ISS | 22 (1-75), n=90 | 22 (1-43), n=35 | 0.97 |
| Admission SBP | 92 (0-220), n=85 | 98 (0-180), n=35 | 0.75 |
| Lowest SBP | 83 (0-186), n=84 | 78 (0-124), n=34 | 0.29 |
| Admission HR | 100 (0-160), n=88 | 112 (0-155), n=37 | 0.12 |
| Admission GCS | 15 (3-15), n=89 | 14 (3-15), n=37 | 0.38 |
| Hospital LOS | 12 (0-59), n=90 | 10 (0-118), n=41 | 0.59 |
| ICU LOS | 4 (0-58), n=90 | 2 (0-29), n=43 | 0.003 |
| ICU free days | 4 (0-38), n=90 | 4 (0-107), n=41 | 0.45 |
| Days on Ventilator | 2 (0-47), n=90 | 1 (0-24), n=35 | 0.46 |
| Vent. Free days | 9 (0-43), n=90 | 8 (0-114), n=35 | 0.80 |
| % mortality | 26/90 (29%) | 13/39 (33%) | 0.68 |

Yazer et al. *Journal of Trauma* 2016;81:21-26

## If you like ratios

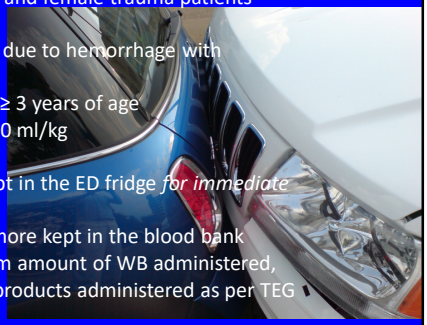
- Mean Plasma:RBC ratio
  - WB group (n=216): 1.04 ± 0.55
  - Control (n=90): 0.75 ± 0.71
  - P<0.0001
- Mean PLT:RBC ratio
  - WB group (n=216): 0.93 ± 0.70
  - Control (n=90): 0.51 ± 0.74
  - P<0.0001


## Conclusions

- What was considered incompatible 10 years ago is fine now
- Unit deferrals will depend on titer threshold and method
- Frequency of unit titering depends on your tolerance of risk
- All evidence to date indicates safety
- Efficacy remains to be seen, especially for WB

## The Pittsburgh approach to use of WB in *paeds* trauma

- Started in June 2016
- For **both** male and female trauma patients
- O neg WB
- Signs of shock due to hemorrhage with hypotension
- ≥ 15kg and/or ≥ 3 years of age
- Maximum of 30 ml/kg
- 1 WB units kept in the ED fridge *for immediate use*
  - At least 1 more kept in the blood bank
- After maximum amount of WB administered, conventional products administered as per TEG results



## WB in paeds trauma!

- 18 patients have received WB for trauma resuscitation
- Mean age 10.6 ± 4.9 years old
- 8 group O, 10 non-O (all A)
  - Two especially sick group O patients
- 8 female, 10 male
- Mean # units per patient: 1.2 ± 0.4 units
  - Total of 19 WB units (in whole or in part) used
  - Mean age of WB: 10.2 ± 3.1 days

Leeper CM et al. JAMA Peds 2018 *in press*