NHS Blood and Transplant

Paediatric Serious Hazards of Transfusion and Blood component selection

Helen New

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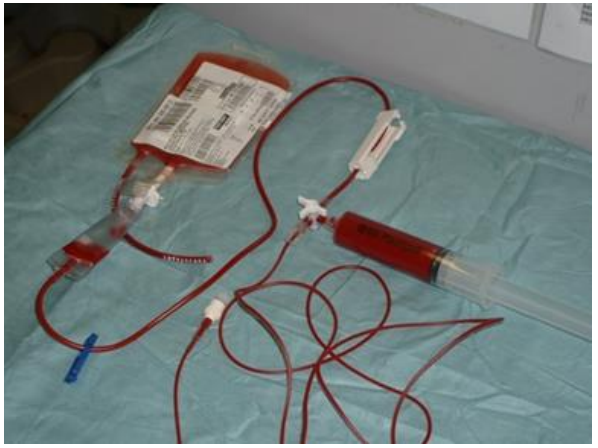
Chair, UK Standing Advisory Committee on Blood Components

SEC RTC Educational meeting Feb 26 2020

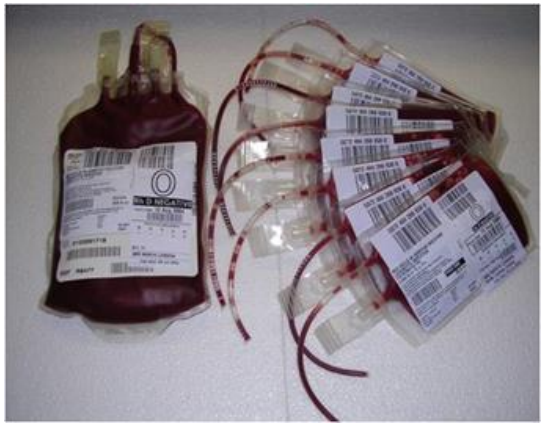
Imperial College London

What is different for neonates and children?

Vulnerability/physiological differences



Complex administration



Specific blood components

Components for paediatrics in UK

- Red cells
  - neonatal top-up ‘paedipaks’
  - neonatal exchange
  - large volume for neonates and infants
- Plasma:
  - neonatal/infant specification for neonatal plasma
    - small volume packs
  - *no longer recommended to be imported or pathogen inactivated for recipients born on/after Jan 1st 1996*
- Platelets
  - neonatal/infant specification for neonatal platelets
    - apheresis, small volume packs, 20% platelet additive solution
  - *no longer: apheresis for older recipients born on/after Jan 1st 1996 where possible*

SaBTO 2019:
https://www.gov.uk/government/publications/risk-reduction-measures-for-variant-creutzfeldt-jakob-disease-pcwg-report

Fetal/neonatal/infant specification red cells
'special' components – vulnerable recipients

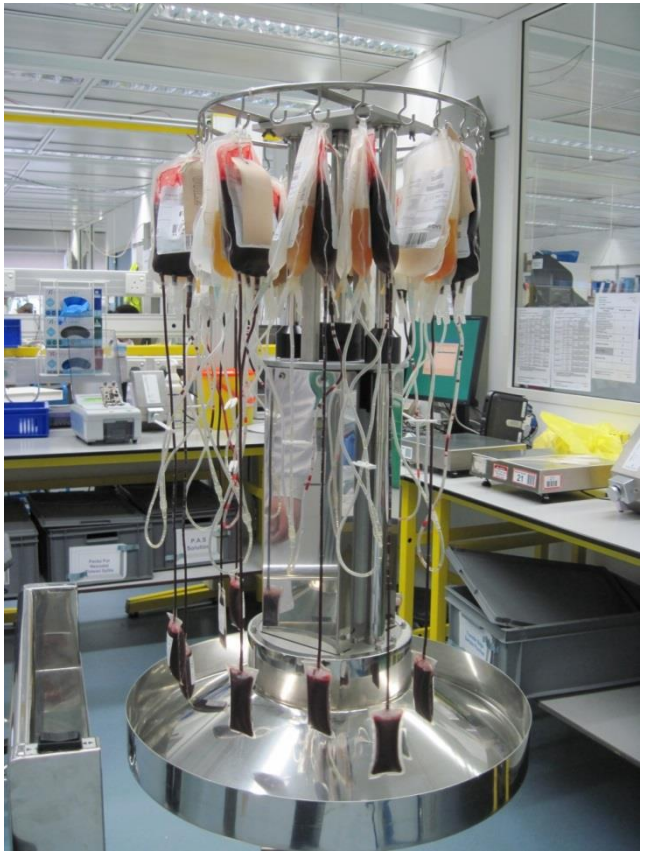
- infection risk reduction:
  - 'second time donors', CMV neg, (HEV neg)
- haemolysis risk reduction
  - 'PANTS' tested, high titre anti-A, B negative
- Kell neg, sickle neg
- red cell haematocrit
  - specific for IUT, neonatal exchange
- storage medium
  - SAGM vs Citrate Phosphate Dextrose
- large volume red cells < 5 days old – potassium (24 hr post irradiation)
  - processed within 12 hrs - higher 2,3-DPG

Varies between countries: New et al, 2009 *Vox Sang* 96, 62–85

Neonatal exchange units

NHS Blood and Transplant

- Usually group O
  - compatible with maternal antibodies
- Hct 0.5-0.55 (NHSBT)
- CMV negative
- Anticoagulant: citrate, phosphate, dextrose
- < 5 days old - reduce risk of hyperkalaemia
- Irradiated, especially if previous IUT
  - shelf life 24 hours



Approx 8000 units manufactured per annum

Kept in 'stock holding units' between manufacturing centres and hospitals.

- Irradiated and issued to hospitals on request (approx. 600 pa)

If not issued, remanufactured into standard red cell units (SAGM)

> 7000 units pa

Urgent situations: hierarchy of component requirements

- Local concessionary release policy for acceptable alternatives in emergency
- Example:
  1. ABO compatibility with mother and infant
  2. Antigen-negative for maternal antibodies
  3. Age of unit
  4. Irradiation status
  5. CMV negativity
  6. Neonatal spec – HT neg red cells

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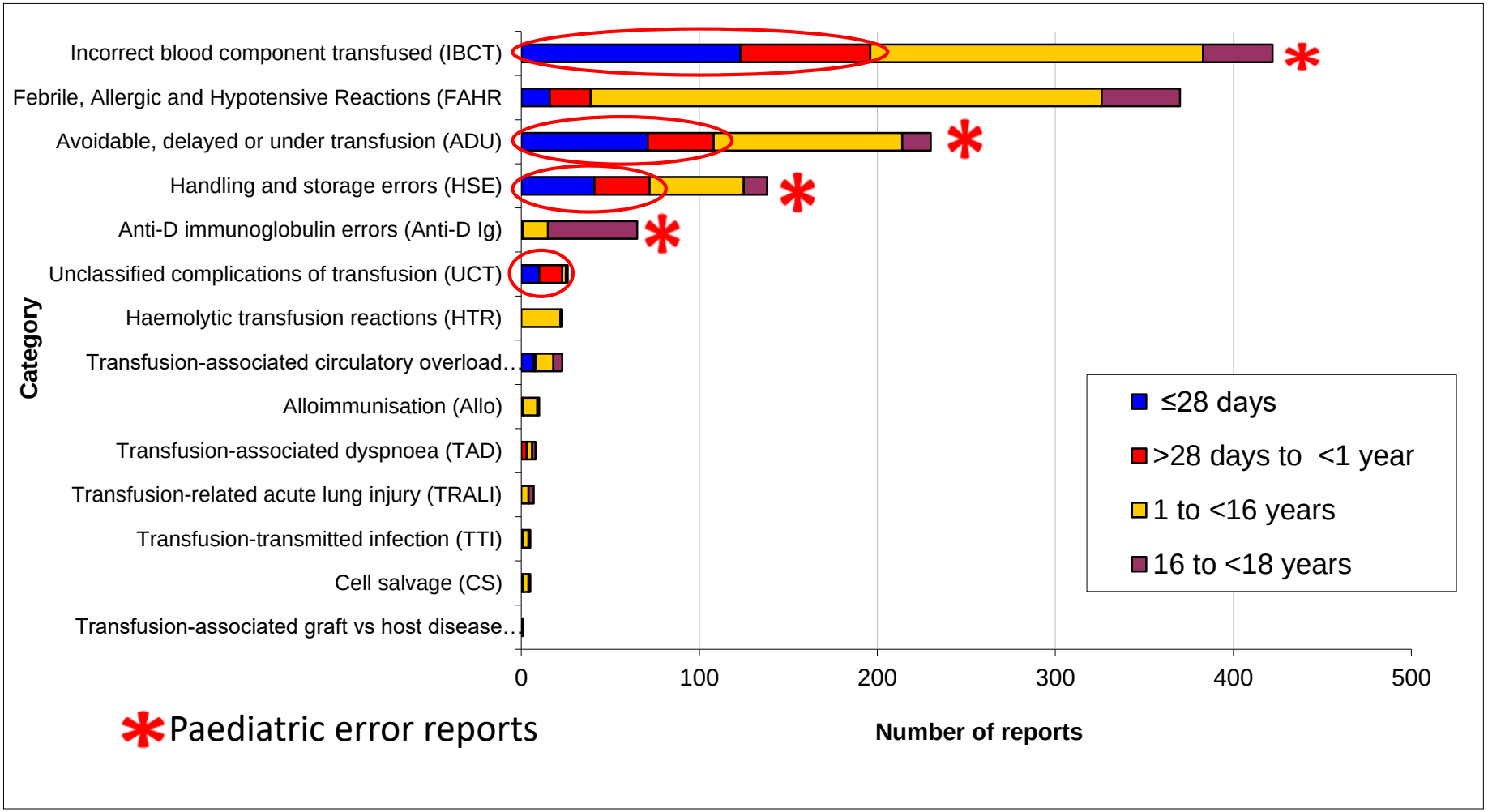
SHOT reports 2008-18: paediatric vs adult

1,333 paediatric/17,204 total (7.7%)

1. There is evidence of a disproportionately high number of reports following paediatric transfusions compared to adults
2. Approximately two thirds of paediatric reports are errors, which should be preventable, and the rest are pathological reactions which in many cases are not preventable.
3. Paediatric reports are particularly over represented in three of the error categories, reflecting the increased complexity of paediatric transfusion:
    - Incorrect blood component transfused (IBCT-WCT)
    - Specific requirements not met (IBCT- SRNM)
    - Avoidable, delayed or under/over transfusion (ADU)
4. Febrile, allergic and hypotensive reactions (FAHR) are approximately a quarter of both paediatric and adult reports
5. TACO is a smaller percentage of paediatric reports:
    - it is important for pulmonary complications (TACO and TRALI) to be considered in neonates and paediatrics as in older patients

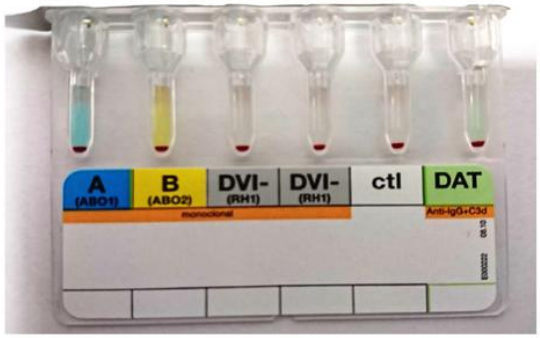
Reports for neonates and infants are mainly in the 'error' categories

SHOT cumulative data 2008-2018 – reports in recipients < 18 years



Themes of recurrent errors

- lab errors in neonatal testing
- selection of wrong component for neonates
  - obstetric ‘emergency O neg’
- specific requirements not met
  - understanding, communication (shared care)
- volume calculations
  - ‘units’ not ‘mL’
- administration
  - Pumps, 3-way taps



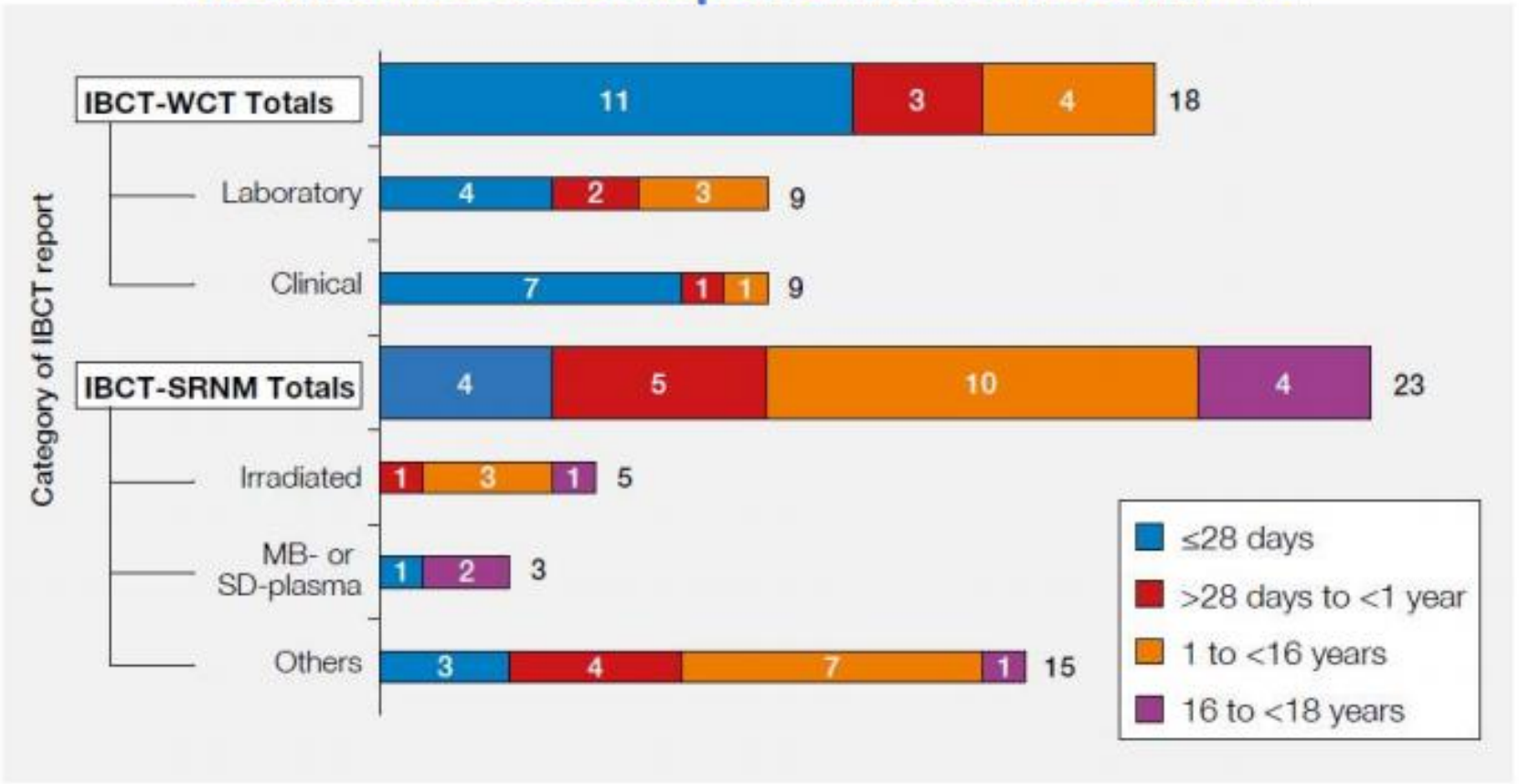
SHOT 2016

Total 21 cases of over or undertransfusion

- 11 (52%) were paediatric
- consistent with the complexity of transfusion administration and prescription calculations for neonates and children.’

SHOT 2017

Incorrect blood component transfused n=41



IBCT-WCT=incorrect blood component transfused-wrong component transfused; IBCT-SRNM=IBCT-specific requirements not met; MB=methylene blue-treated; SD=solvent-detergent treated

SHOT Paediatric laboratory errors

47% of paediatric errors in 2018 (mainly IBCT-WCT, -SRNM, and ADU)

Key Paediatric SHOT message:

- Laboratory staff should be fully trained on, and be aware of the BSH guidelines regarding pre-transfusion compatibility testing and red cell selection for neonates and infants up to 4 months old.

- Previous transfusions of group O red cells need to be taken into account when interpreting neonatal grouping results.

Lab examples: IBCT – WCT

Neonatal/infant grouping/compatibility testing (2016)

- A baby who had received group O IUT grouped as O at birth.
  - should not have been reported as the baby's true group could not be determined due to the prior IUT.
- A 1-month-old baby, group A, with necrotising enterocolitis (NEC), who had received multiple transfusions with group O red cells was grouping as O in the laboratory
  - given group O fresh frozen plasma (FFP)
  - failure to check the historical record.
- An infant aged 4 months and 10 days was issued red cells using the original sample taken at birth
  - from 4 months of age compatibility testing should be undertaken as for adults.

Lab examples: IBCT – WCT

Incorrect component selection (SHOT 2016)

- A 1-month-old group A D-negative baby girl was transfused with O D-positive red cells due to incorrect component selection, only discovered later at another hospital
  - the hospital decided to only stock D-negative neonatal red cells in the future.
- A 4-day-old D-positive baby with haemolytic disease of the fetus and newborn (HDFN) due to maternal anti-D inappropriately underwent exchange transfusion with O D-positive units
  - resulting in prolonged haemolysis requiring further exchange transfusion

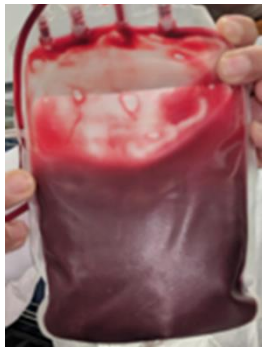
Lab examples: IBCT – SRNM

Failure to use phenotyped blood (SHOT 2017)

- A neonate transfused with O D neg red cells without checking maternal sample
  - Mother had anti-f antibodies: antigen neg units crossmatched against maternal sample should have been used.
- Blood issued for 2 infants without crossmatch when there was evidence of maternal anti-D
- Three children sickle cell disease received Rh-unselected units
  - one developed allo anti-C

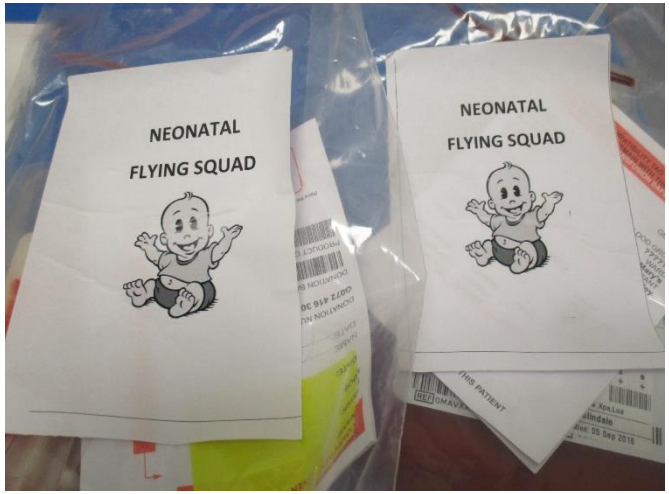
IBCT-WCT
Inappropriate use of adult O D-neg units

- In 2015, 12 cases of incorrect blood component transfused, adult O D-negative emergency units were used inappropriately to resuscitate neonates/infants despite availability of neonatal emergency packs.



SHOT recommendation

Adult O D-negative units are unsuitable for neonatal emergency use. Dedicated neonatal O D-negative units should be available. Local measures should be in place to help guide staff to select the correct component in emergency situations



Rachel Moss

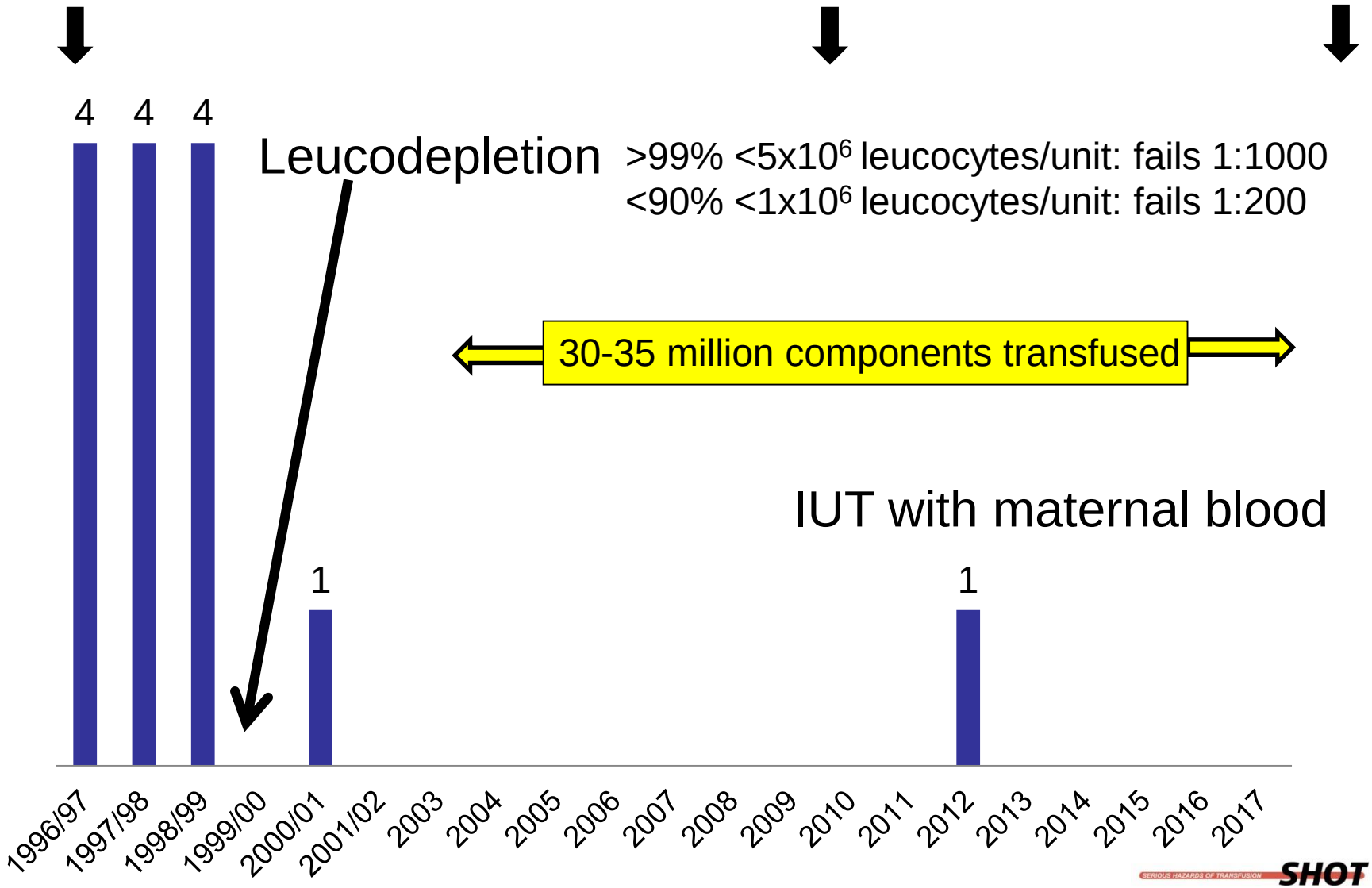
Irradiation to prevent TAGvHD: what have we learned from paediatric SHOT?

1. Infants born post IUT
   - 18 cases 2007-17 where irradiation was missed for infants
2. DiGeorge syndrome
   - recurrent reports of irradiation missed/caused delays to provision of blood pre-surgery

- most patients with DiGeorge not immunodeficient
  - often inconclusive diagnosis of immunodeficiency pre cardiac surgery
- excessive use and waste of irradiated blood?
  - increased costs
  - shorter shelf-life may make harder to re-allocate
- associated risks/errors
  - hyperkalemia, delay in component provision, missed irradiation
    - repeated reports to SHOT of delays/errors

SHOT lessons: Irradiation and TA-GvHD

Cases of TA-GvHD reported to SHOT



SERIOUS HAZARDS OF TRANSFUSION SHOT

Planned paediatric updates to BSH irradiation guidelines 2020

- Neonates and infants with suspected cardiac immunodeficiency syndromes eg DiGeorge:

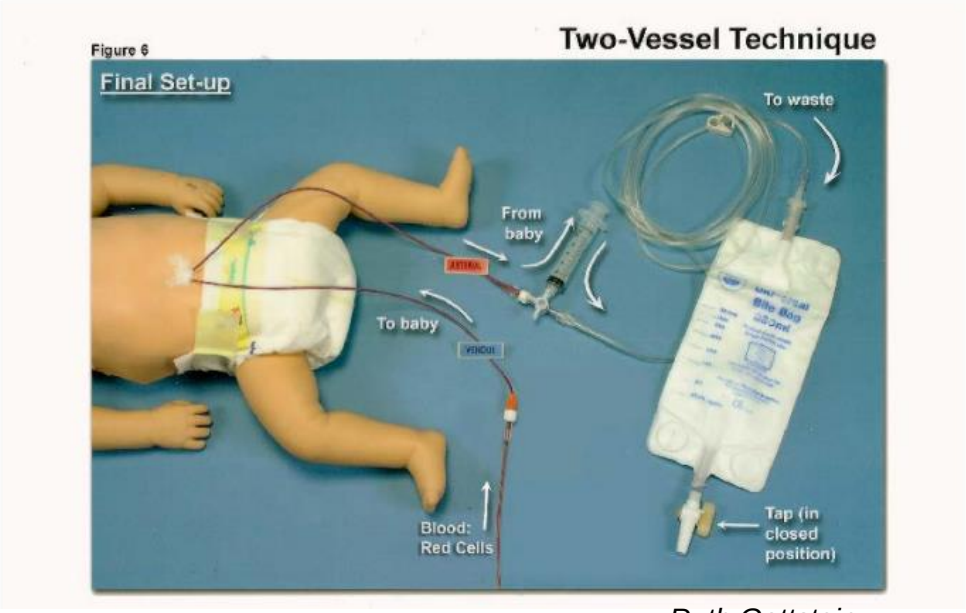
  T lymphocyte counts prior to cardiac surgery

  - *No need to irradiate* if T cells >400 cells/microliter, of which ≥ 30% are naive T cells
  - If not possible to undertake T cell investigations before surgery, give irradiated components until immunological investigations have been undertaken
- Use of irradiated components is **not indicated** for small volume 'top up' transfusions for neonates after intrauterine transfusion
- *No change*: IUT, neonatal exchange transfusion, severe congenital T-cell immunodeficiencies

Foukaneli et al, BSH irradiation guideline (in preparation)

Neonatal exchange blood transfusions – repeated SHOT error reports (lab/clinical)

- invasive procedures relatively rarely performed
- recipients by definition vulnerable; urgent situations
- special components with short shelf-life with which staff may be unfamiliar

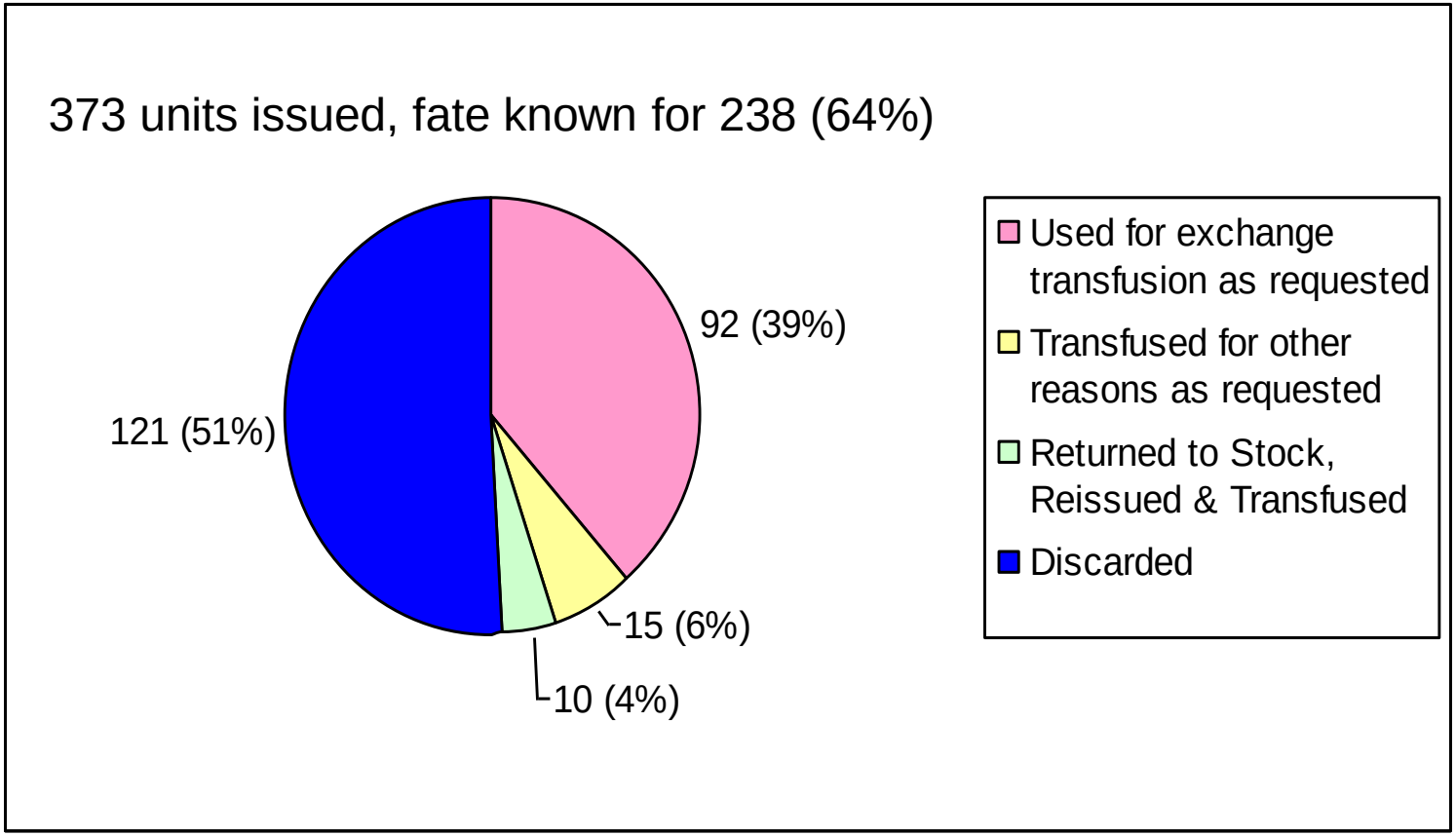


Ruth Gottstein

SHOT 2015 recommendation

Particular attention should be provided for laboratory staff training regarding the specification and ordering of components for neonatal exchange in hospitals with neonatal intensive care units.

2010 NHSBT 6 month audit on fate of neonatal exchange red cell units issued to hospitals



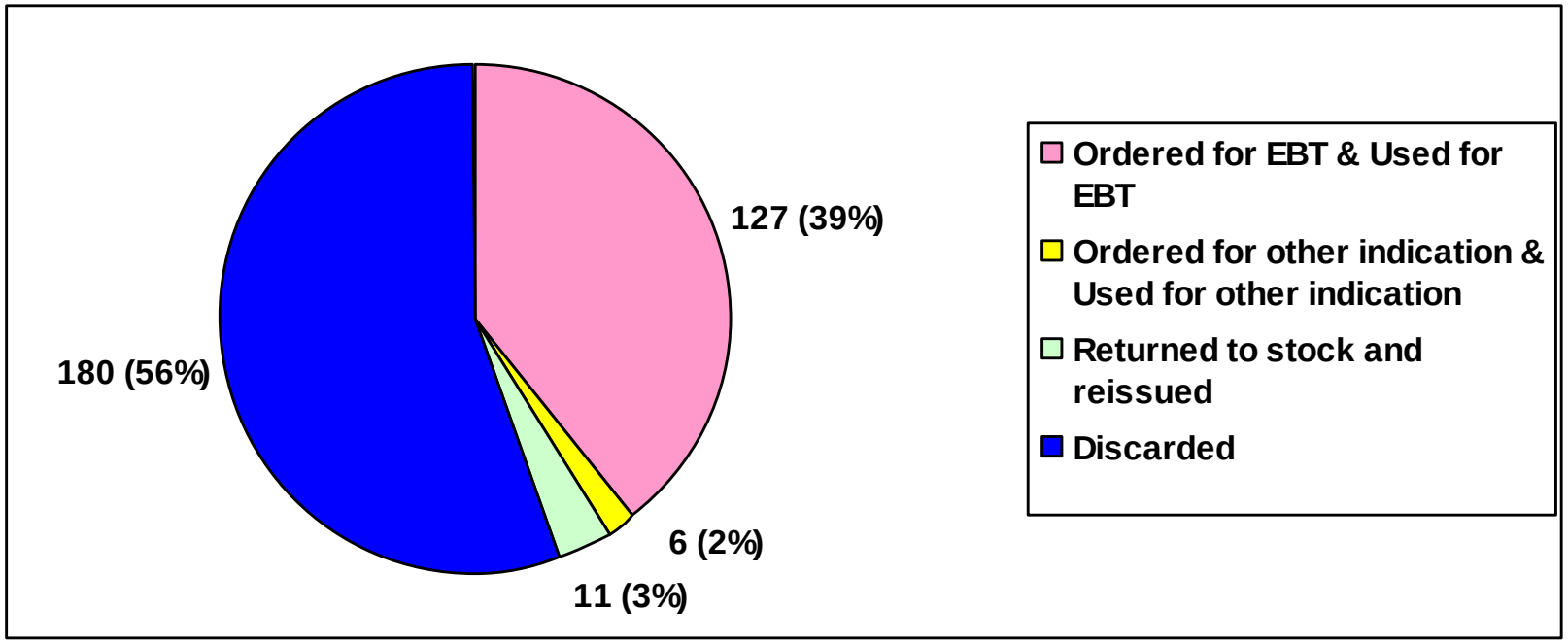
If ordered for EBT for maternal antibody alone (8%), only 24% transfused

2010 audit recommendations

- exchange units should only be only ordered for neonatal exchange transfusion
- if not required for EBT they may be reissued for patients born before Jan 1st 1996.
- hospitals were asked to review indications for ordering to see if ordering may be avoidable to reduce wastage, particularly if order is on the basis of maternal antibody alone.

6 month re-audit 2015 – very similar!

404 units issued, fate known for 324 (80%)



If ordered for EBT for maternal antibody alone (10%), only 14% transfused

Can this wastage be reduced yet retain adequate availability?

- If not required for EBT, units may be reissued for other patients (of any age) within shelf life. Larger volume and with more more plasma (Group O), than standard red cells in SAGM, therefore use for Group O recipients, where TACO not a concern.

ADU - SHOT 2012
Massive over-transfusion of 1 year old child

- 10 kg child brought into A&E after vomiting blood.
- Hb 98 g/L. Wrongly diagnosed with acute arterial bleed
- O RhD neg blood prescribed in units, not mL/kg
- Given a total of 4 units (1122 mL), the first 3 given at a rate of a unit per 20 minutes, and subsequently continued to receive the 4th unit *despite normalisation of his heart rate and blood pressure.*
- Post transfusion Hb 270g/L
- Attempted venesection difficult. Required transfer to a paediatric intensive care unit and made a full recovery.

What red cell volume to prescribe?

UK 'NICE' Transfusion guidelines 2015:

- 'Restrictive' approach
- Clinically reassess and check Hb **after each unit of red cells**, unless bleeding/chronic **[approx. 3-4 ml/kg]**

Children? *Pragmatic, no evidence – extrapolated from adults*

BSH paediatric guidelines 2016

Transfusion volumes for non-bleeding infants and children, excluding those on chronic transfusion programmes, ***should generally be calculated to take the post-transfusion Hb to no more than 20 g/L above the transfusion threshold*** *usually a maximum of one unit.*

- **ie approx. 8 ml/Kg**

'Transfusion formula', mL NOT 'units'

$$\text{Volume to transfuse (mL)} = \frac{\text{Desired Hb (g/L) - actual Hb (g/L) x weight (kg) x Factor (4)}}{10}$$

- factors between 3-5 have been recommended
- assess on an individual patient basis

Neonates: 15ml/kg *– not evidence based*

SHOT and paediatric prescribing

Key Paediatric SHOT messages:

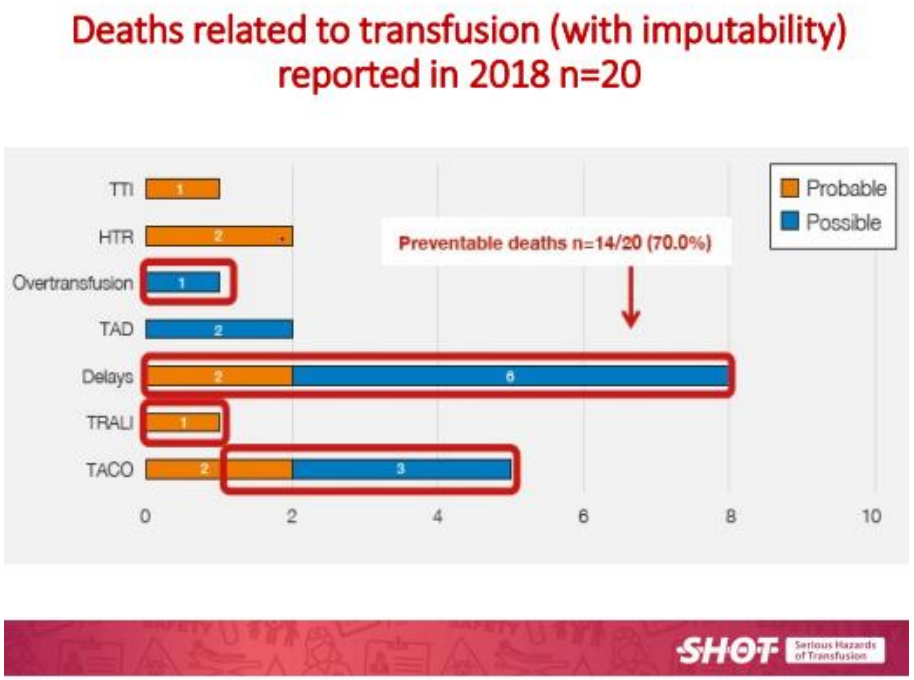
- Blood components should be prescribed in volumes for children related to their weight, but not more than the standard accepted dose for an adult.
- Clinical staff who prescribe blood for paediatric patients should not do so unless they have been given training in weight-based prescribing of blood components.

Transfusion Associated Circulatory Overload (TACO)

- A leading cause of transfusion-related mortality and morbidity reported to SHOT
- international definition recently revised

- Revised TACO criteria
  - onset up to 12 hrs after transfusion
  - at least one required criterion
    - total of 3 criteria

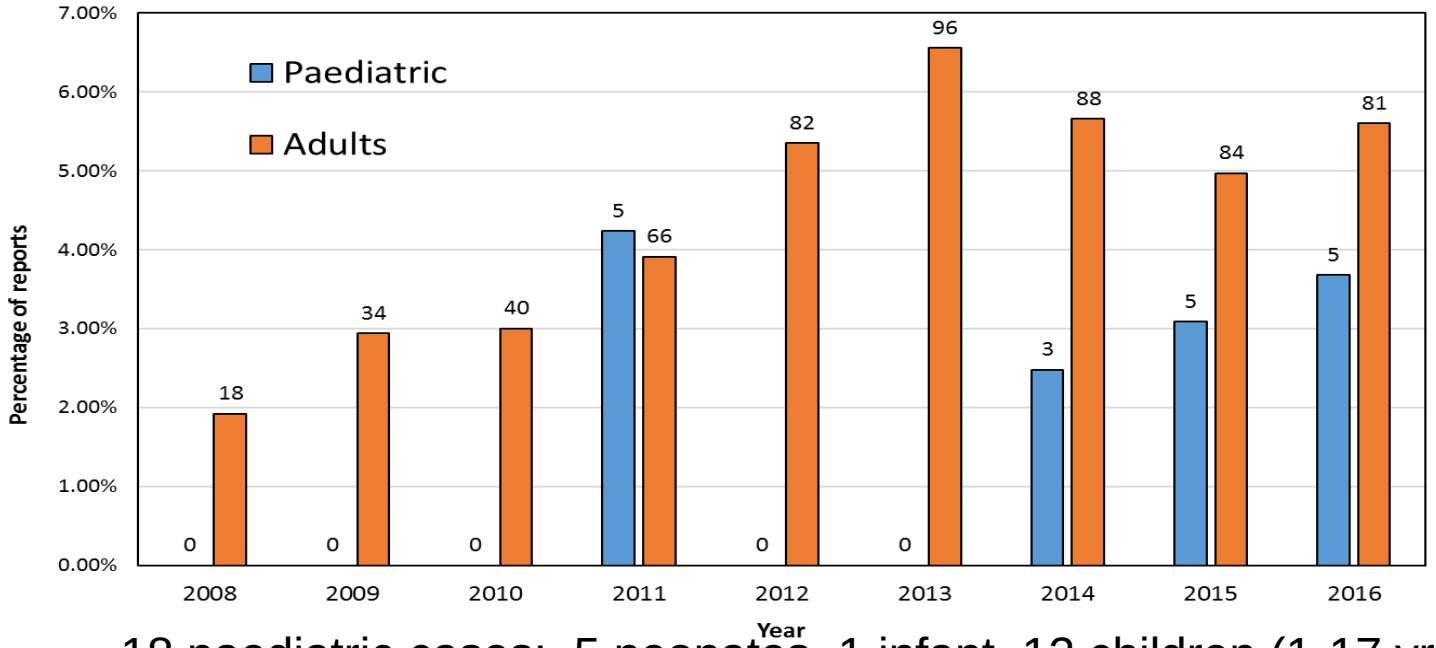
1. required criteria:
   - A. Acute or worsening respiratory compromise and/or
   - B. Evidence of acute or worsening pulmonary oedema based on: • clinical physical examination, and/or • radiographic chest imaging and/or other non-invasive assessment of cardiac function
2. additional criteria
   - other CVS changes
   - fluid overload evidence
   - relevant biomarker eg BNP



https://www.shotuk.org

Wiersum-Osselton et al. *Lancet Haematol* 2019

SHOT Paediatric TACO reports 2008-2016 - are we getting a representative picture?



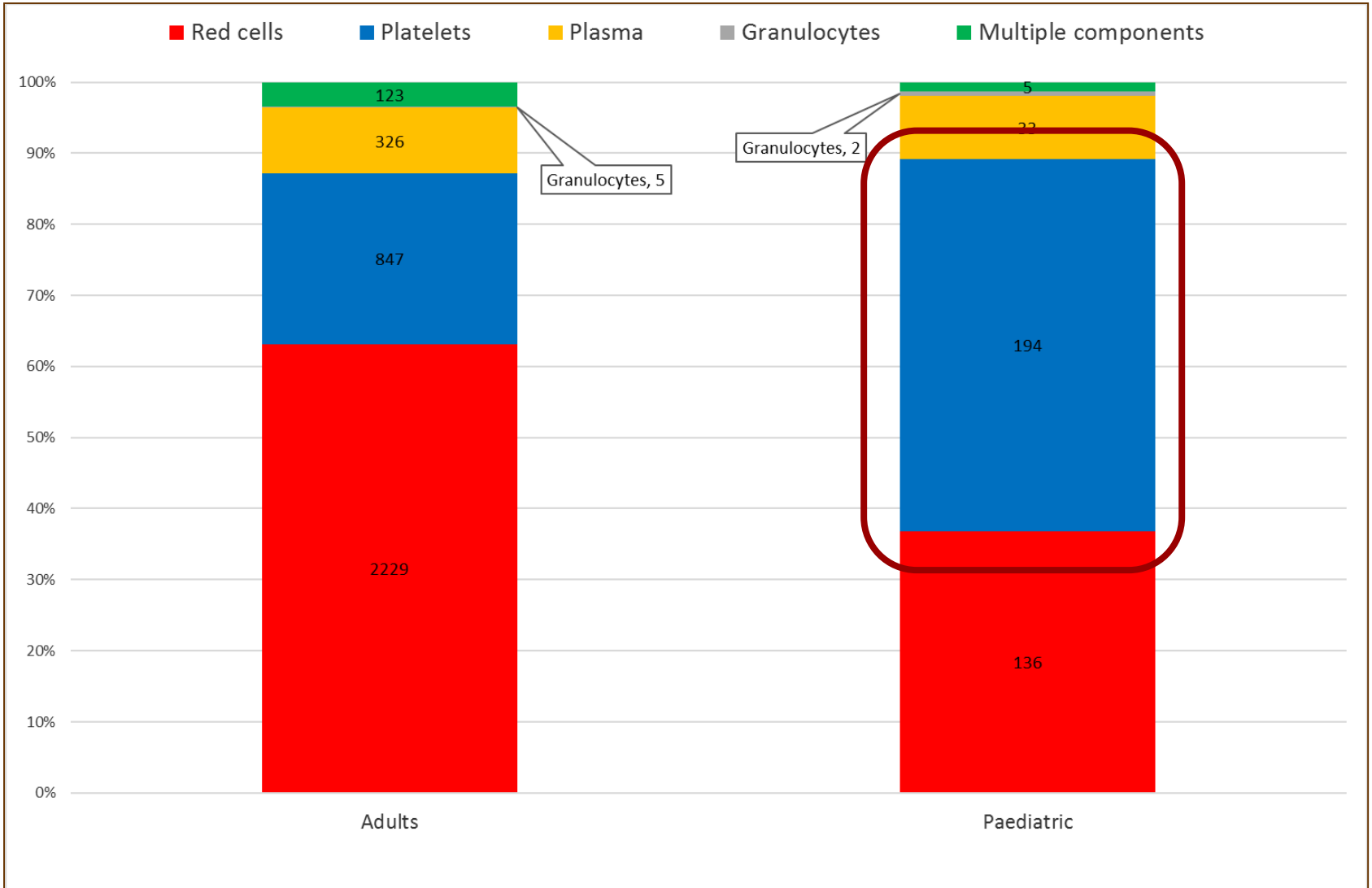
18 paediatric cases: 5 neonates, 1 infant, 12 children (1-17 yrs)

Paediatric definitions of pulmonary complications uncertain

De Cloedt et al, *Transfusion* 2018

- Retrospective observational study, PICU, 136 transfused patients
- ISBT TACO criteria, comparing two definitions of abnormal, up to 24 hrs post transfusion
- *Incidence of TACO varied 1.5% to 76% depending on definition*

Febrile, Allergic and Hypotensive reactions: Adult vs Paediatric FAHRs related to component type (cumulative data 2008-2018)



Platelets for Neonatal Transfusion Study 2 (PlaNeT-2/Matisse)

-a randomised controlled trial of platelet transfusion thresholds

25 vs 50 x 10^9/L

PlaNeT-2

PlaNeT2 Trial

Aim

To compare two different platelet count thresholds for *prophylactic* platelet transfusion to preterm neonates (<34 wks gestation):

- is transfusion at <50x10^9/L superior to <25x10^9/L?

Primary Outcome

Composite of mortality and major bleeds at or before 28 days after randomisation

Secondary Outcomes

- subsidiary efficacy outcome measures
- adevelopmental follow-up validated parent questionnaire at a corrected age of 2 years

Results - Primary outcome

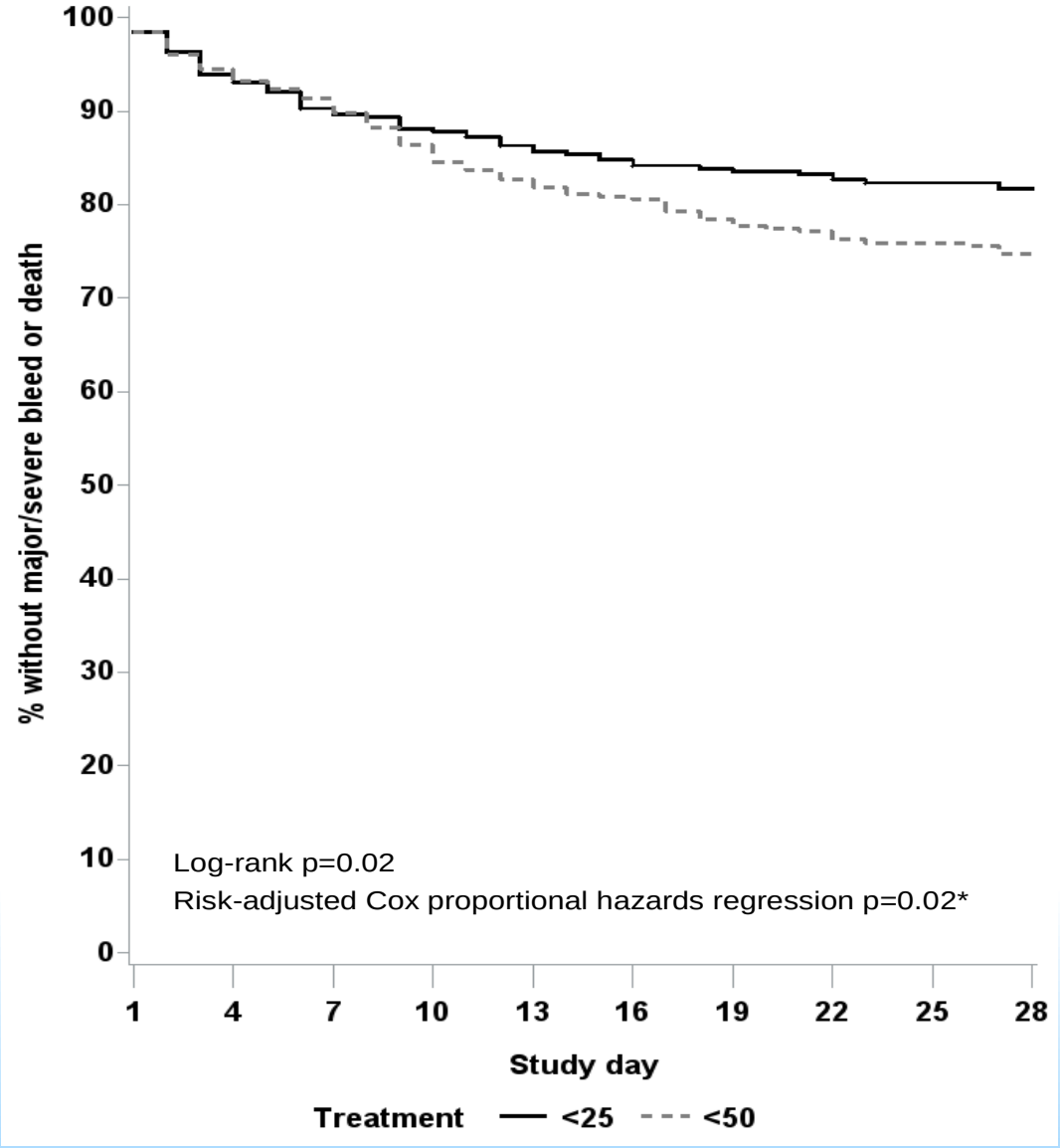
	<25 (n=331)	<50 (n=329)	Odds ratio (95% CI)	p-value
Major/severe bleed or mortality by day 28	61/329 (19%)	85/324 (26%)	1.57 (1.06 - 2.32)†	0.02

Number needed to harm = 100/(26-19)
= 14.3

For every 14.3 patients treated with <50 strategy, 1 extra MB or death would be expected

† Adjusted for gestational age, presence of IUGR and centre

Major bleed /mortality survival curve



* The model was adjusted for IUGR and gestational age as covariates and centre as a random effect

Conclusions

- Among preterm infants with severe thrombocytopenia, use of a platelet count threshold for prophylactic platelet transfusion of $50x10^9$/L resulted in a higher rate of mortality or major bleeding compared to a restrictive threshold of $<25x10^9$/L in the subsequent 28 days.

- Reducing the transfusion trigger from $<50x10^9$/L to $<25x10^9$/L may prevent death or major bleeding in **7 out of 100** preterm neonates with severe thrombocytopenia.

- Other wider implications

Curley, Stanworth, Willoughby., Fustolo-Gunnink, et al. *NEJM*, 380, 242-251 2019

What is the mechanism of harm?

- platelets have recognized immunological and inflammatory effects
- adult platelets in a neonatal haemostatic system
  - developmental mismatch?
- haemodynamic shifts related to transfusion volume/rate
  - relatively higher volume (and dose) transfused than for adults
    - commonly transfused platelet volume: 10-20ml/kg for neonates
    - approx 2-4ml/kg for adults (1 pack apheresis platelets)
- platelet-derived reactive oxygen species and proangiogenic factors
- vessel occlusion by platelet microthrombi
- platelet donation characteristics?
  - storage age, blood group matching, donor

UK Neonatal platelet components

- ‘neonatal’ donors, split apheresis packs
- suspended in plasma, 7 day shelf-life
- quality monitoring: pH at end of shelf-life
  - low pH correlates with worse in vivo platelet recovery and survival
  - revised specification: 90% > pH 6.4
  - 2018-19 performance dropped to 80%
- Quality improvement project
  - addition of 20% Platelet Additive Solution (SSP+) prior to splitting
  - laboratory studies, operational validation
  - Implemented from Jan 14th 2020

Communications to users

- likely 20% reduction in the platelet dose transfused for a given volume (ml/kg)
- considered not clinically significant, particularly for prophylaxis for non-bleeding neonates
- in bleeding settings such as cardiac surgery, where transfusion volume is less of a consideration, clinicians may choose to transfuse higher volumes
  - utilise the additional volume in the new neonatal platelet packs.
- *Note* neonatal platelet doses relatively higher than for adults

In view of considerations around transfusion associated circulatory overload (TACO) it is suggested that neonatologists do not increase the transfused volume of the new platelet component to compensate for the 20% dilution in non-bleeding neonates.

SHOT 2013 High K+ red cells: Familial pseudohyperkalaemia mutation

- D5 red cells (non-irradiated) used to prime bypass machine for cardiac surgery for 4 month old infant.
- blood gas on bypass circuit checked before attaching patient (perfusionist's normal practice)
- in circuit potassium 13.76 mmol/L
- unit supernatant K+ 41.4mmol/L
  - Day 7 median 14.0 mmol/L (97.5th centile 31.8)
- blood not transfused, no clinical impact except minor delay

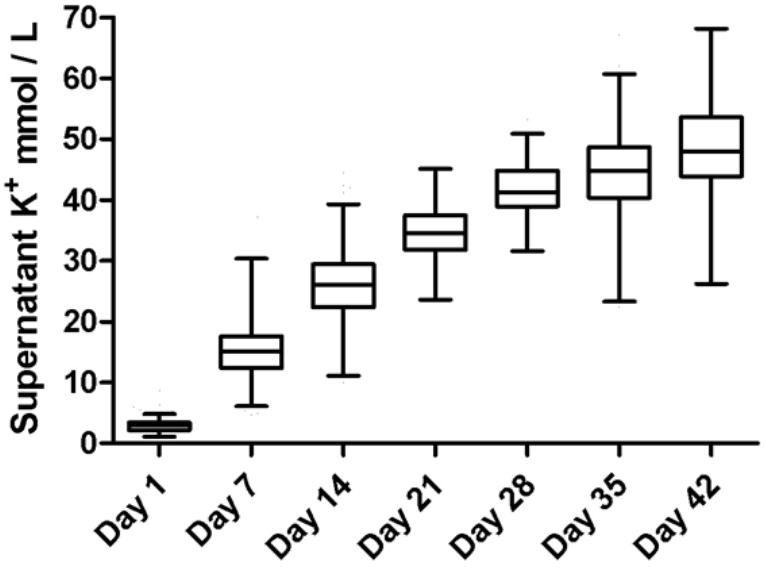
- Donor: mutation for Familial Pseudohyperkalaemia
  - dominant inheritance, asymptomatic in donor
  - red cells leaky to cations in the cold
  - mutation in approx 1:400 in UK

Bawazir et al, *Transfusion* 2014

Red cell potassium and transfusion

- high K^+ levels in Red Cell Concentrates (RCC) may cause hyperkalaemia during rapid transfusions of vulnerable recipients, with rare cases of mortality
  - Vraets et al, 2011 ; Lee et al, 2014
- measures to limit risk
  - 5 day shelf life for neonatal red cells for large volume transfusion (UK) (24 hours if irradiated)
  - K^+ levels measured in the circuit pre-bypass; ultrafiltration of red cells pre bypass
  - some countries wash older red cells
  - ? K^+ filters in the giving set

Potassium release from RCC during refrigerated storage



NHSBT Component Development Laboratory reference data

median (solid bar), 25 & 75 centiles (box), 2.5 & 97.5 centiles (whiskers); n 118 – 588 on each day

K^+ release over storage by FP red cells

- 6 FP donors, blood stored in standard conditions as for blood transfusion

- during storage FP RCC released significantly higher levels of K^+ than control ($p = 0.001$).
- initial rate of K^+ release was higher in the FP RCC: K^+ reached near maximal levels on day 7
- on day 7, the highest FP K^+ value (63.0 mmol / L) was 2.1 fold higher than the 97.5th percentile of the CDL reference data
- on day 35 the highest FP K^+ level (73.7 mmol / L) was only 1.3 fold higher than the 97.5th percentile of the CDL reference data.

CARED study group, Meli, Bruce, Cardigan et al

Clinical transfusion implications

- a 5-day shelf-life restriction of FP RCC may not be sufficient to reduce the risk of hyperkalaemia in clinical scenarios such as neonatal large volume transfusion
- at 35-day shelf-life, less impact of FP on red cell supernatant potassium
  - unlikely to be clinically significant in situations where transfusion of older red cells is acceptable
- some FP blood donors already identified
  - via clinical cases
  - others potentially via large scale genotyping studies

UK Blood Services clinical risk assessment

Conclusions

- uncertain actual level of risk from FP donations to red cell transfusion recipients
- strong case for avoiding FP donations where possible for recipients of neonatal/infant large volume transfusions
  - clinical perception that these are at highest risk of transfusion associated hyperkalaemia
  - already current recommendations to reduce risk of hyperkalaemia by using fresher red cells
- known FP donor red cells will be excluded from neonatal/infant red cells for transfusion
  - possibility of future screening for FP for neonatal/infant red cells
  - ?other patient groups at special risk

Guidance to reduce risks of paediatric transfusion associated hyperkalaemia

Key Paediatric SHOT message:

Those involved with rapid large volume red cell transfusion to children should be aware of the risk of transfusion-associated hyperkalaemia (particularly for infants or those with co-morbidities).

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BSH paediatric transfusion guidelines 2016

1. **Blood used for cardiac surgery in neonates and infants should be used before the end of Day 5**
2. **Potassium concentrations should be checked in the bypass fluid before connecting to the patient to ensure that they are within the normal range.**

Key Paediatric SHOT message: Hospitals should have clear paediatric transfusion guidelines for different patient groups, readily available in all paediatric areas.

BSH Guidelines 2016

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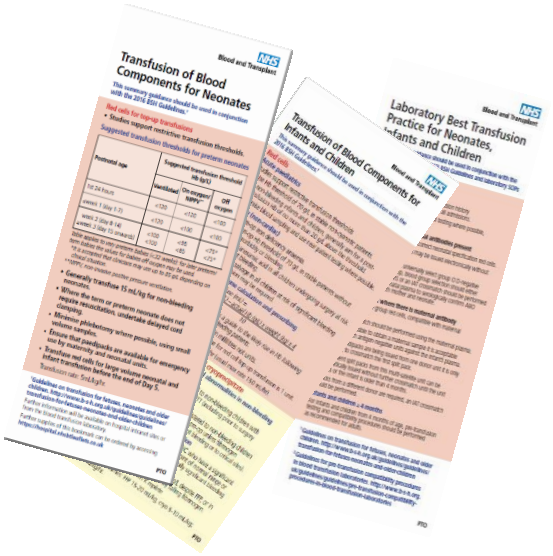
bjh guidelines

Guidelines on transfusion for fetuses, neonates and older children

Helen V. New,[1,2] Jennifer Berryman,[3] Paula H. B. Bolton-Maggs,[4] Carol Cantwell,[2] Elizabeth A. Chalmers,[5] Tony Davies,[6] Ruth Gottstein,[7] Andrea Kelleher,[8] Sailesh Kumar,[9] Sarah L. Morley[10] and Simon J. Stanworth,[11] on behalf of the British Committee for Standards in Haematology

British Journal of Haematology, 2016, 175, 784–828

http://www.b-s-h.org.uk/guidelines/guidelines/transfusion-for-fetuses-neonates-and-older-children



SHOT 'Bite' for Neonates and Paediatrics

KEY SHOT MESSAGES FOR PAEDIATRICS

- Hospitals should have clear paediatric transfusion guidelines for different patient groups, readily available in all paediatric areas
- Blood components should be prescribed in volumes for children related to their weight, but not more than the standard accepted dose for an adult. Clinical staff who prescribe blood for paediatric patients should not do so unless they have been given training in weight-based prescribing of blood components
- Laboratory staff should be fully trained on, and be aware of the BSH guidelines regarding pre-transfusion compatibility testing and red cells selection for neonates and infants up to 4 months old[1,2]. Previous transfusions of group O red cells need to be taken into account when interpreting neonatal grouping results
- Patients with suspected DiGeorge syndrome should receive irradiated cellular component until immunodeficiency is excluded, and this should be communicated to the laboratory
- Those involved with rapid volume red cell transfusion to children should be aware of the risk of transfusion-associated hyperkalaemia (particularly for infants or those with co-morbidities)
- It is important for pulmonary complications (TACO & TRALI) to be considered in neonates and paediatrics as in older patients

https://www.shotuk.org/wp-content/uploads/myimages/SHOT-Bites-No4-Paediatrics-1.pdf

Blood components App

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https://hospital.blood.co.uk/patient-services/patient-blood-management/education/

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