When should I transfuse platelets and plasma for children ?

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When should I transfuse platelets and plasma in children ?

1. Platelet Transfusion in children:
   - Background
   - Evidence & uncertainties
   - Recommendations

2. FFP use in neonates & children:
   - Background
   - Evidence & uncertainties
   - Recommendations

Platelet use in the UK

- Increasing use of a scarce resource
  - 25% increase between 2007/8 - 2014/15 (England – all ages)
- Paediatric clinical settings
  - Haematology-oncology, cardiac surgery, PICU
- Therapeutic vs Prophylactic use
  - Prophylaxis : 60%
- Efficacy
  - Historical & more recent evidence of benefit
  - Optimal use not well defined
    - Prophylaxis strategies, Thresholds, Doses
- Safety - consequences of inappropriate use
  - Adverse reactions, platelet refractoriness, blood product exposure

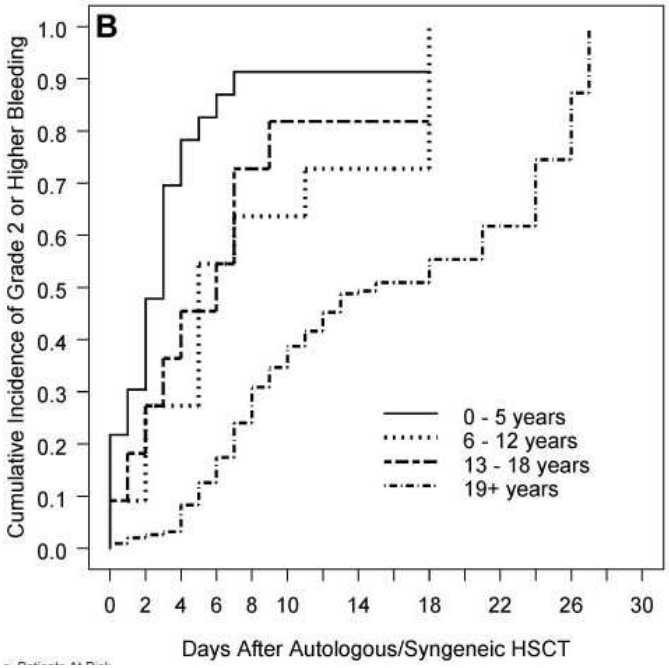
Platelet Support: Evidence

- Evidence base limited:
  - Significant extrapolation from adult studies
  - Consensus opinion

- Recent systematic reviews & other studies -
  - Prophylactic vs transfusion only strategies - support prophylaxis
  - Thresholds - may vary between individuals & disease groups
  - Platelet dose – lower dose may be as effective but may require more frequent transfusion

Platelet Support: Evidence

- PLADO study (post hoc paediatric subgroup)
  - Children (n=198) with treatment induced hypoproliferative thrombocytopenia
  - Daily haemostatic assessment



Age range	≥ Grade 2 bleeding
Child 0-5 yrs	86%
Child 6-12 yrs	88%
Child 13-18 yrs	77%
Adult	67%

- Higher risk of bleeding in children vs adults
- More days with ≥ Grade 2 bleeding
- Risk highest in the autologous HSCT group
- Bleeding occurred at a range of counts

Josephson, Blood 2012

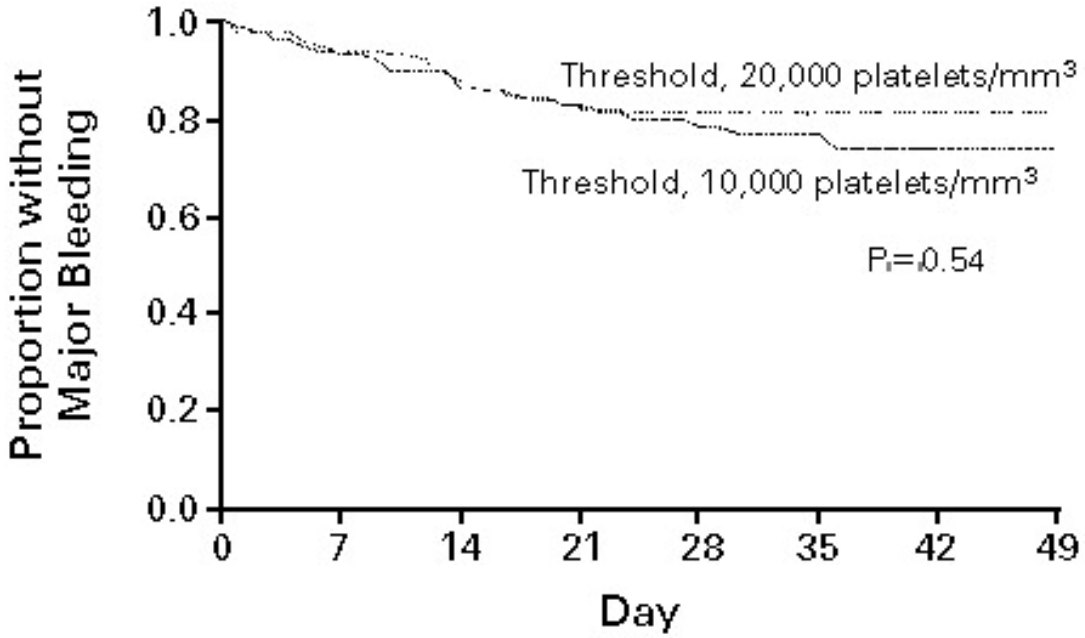
Platelet Thresholds: Survey of Practice in ALL 2014

What is your usual threshold for platelet transfusion in the following groups of children/adolescents with ALL ?

	10 x 10^9	20 x 10^9	30 x 10^9	50 x 10^9	70-80 x 10^9	100 x 10^9
Well patient	**88.9%**	11.1%	0.0%	0.0%	0.0%	0.0%
Febrile patient	15.8%	**84.2%**	0.0%	0.0%	0.0%	0.0%
Patient with bleeding	0.0%	0.0%	16.7%	**66.7%**	11.1%	5.6%
Prior to LP	5.3%	10.5%	26.3%	**52.6%**	5.3%	0.0%
Prior to CVL Insertion	0.0%	0.0%	0.0%	**52.6%**	36.8%	10.5%

Platelet Support: Evidence

- Well patient with no bleeding
- Rubella, N Engl J Med 1997Adults & adolescents with AML
- Threshold of 20 $x10^9$ vs 10 x 10^9



Supported by Cochrane Systematic Review 2015 – low quality evidence

Platelet Support: Evidence Prior to LPs

- Cochrane review 2016
  - No evidence from RCTs to determine the correct threshold
  - Would likely require a very large study
- Cohort study data support safety of lower thresholds
- van Veen BJH 2010 Review concluded platelet count of 40 $x10^9$ was safe for LPs
- Howard et al JAMA 2000
  - 941 LPs in Children with ALL
  - Variable platelet counts – majority: 21-50 $x10^9$/l
  - No serious bleeding events
  - CI calculated for different thresholds

Platelet Support: Evidence Prior to CVL Insertion

- Cochrane review 2010
  - No RCT evidence on platelet support or thresholds pre CVL insertion
- Most guidelines recommend a platelet count of $50x10^9/l$

- Zeidler et al 2011
  - Adult study n= 193
  - 604 CVL placements
  - Un-tunnelled CVL

Platelet count ($x10^9$)	OR	95% CI	(p value)
< 20	2.88	1.23-6.75	(0.015) *
20-49	1.27	0.77-2.18	(0.38)
50-99	1.60	0.98-2.63	(0.062)
>100	1.0	-	

* Significant bleeding only in those with platelets < 20

Zeidler K, Transfusion 2011

BSH Paediatric Transfusion Guidelines :2016

Platelet count (x 10^9/l)	Clinical situation to trigger platelet transfusion
< 10	Irrespective of other issues (excluding ITP, TTP/HUS, HIT)
< 20	Severe mucositis Sepsis Laboratory evidence of DIC in the absence of bleeding* Anticoagulant therapy Risk of bleeding due to a local tumour infiltration Insertion of a non-tunnelled central venous line
< 40	Prior to lumbar puncture**
< 50	Moderate haemorrhage (e.g. gastrointestinal bleeding) including bleeding in association with DIC Surgery, unless minor (except at critical sites) -including tunnelled central venous line insertion
< 75 -100	Major haemorrhage or significant post-operative bleeding (e.g. post cardiac surgery) Surgery at critical sites: central nervous system including eyes

FFP use in neonates & children

- FFP use static or increasing
  - 4% increase in use documented in UK audit (*Stanworth 2011*)

- Evidence base for FFP currently inadequate
  - Lack of supporting evidence for many indications
  - Variations in clinical practice
    - Range of FFP use 0.99 – 5.84% (*Puetz, 2012*)
  - Data suggest some use likely ineffective/inappropriate

Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials

Lucy Yang, Simon Stanworth, Sally Hopewell, Carolyn Doree, and Mike Murphy

Transfusion 2012

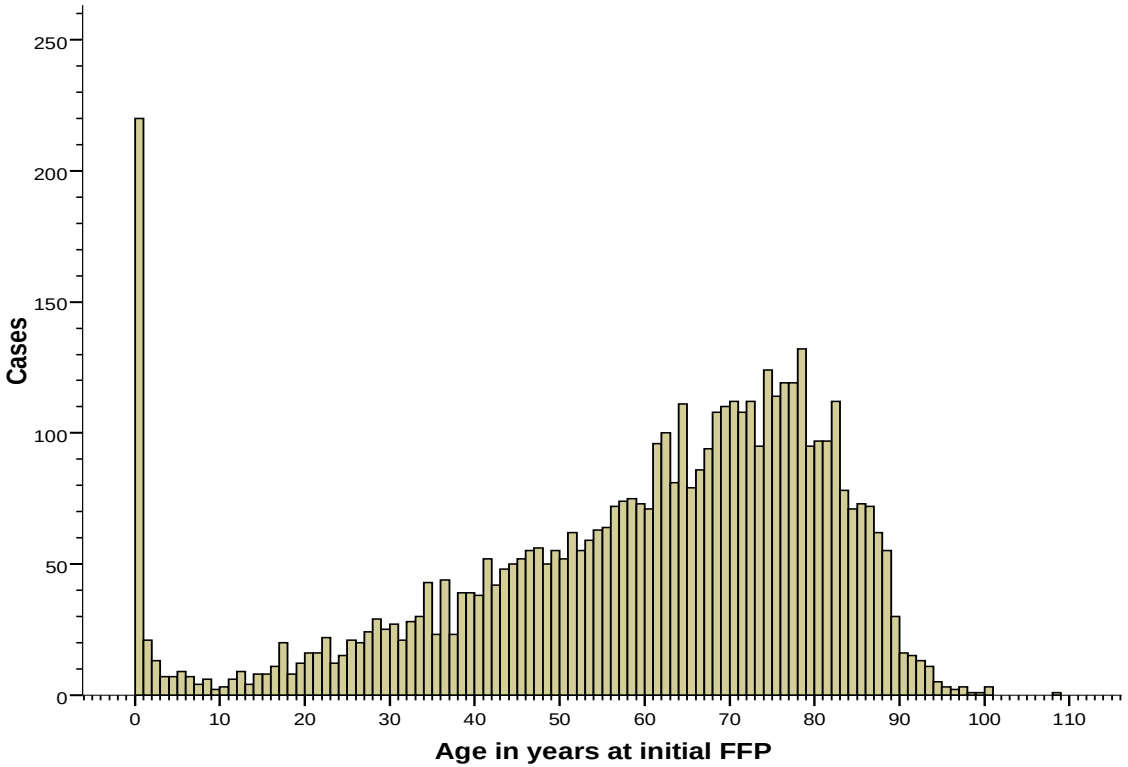
CONCLUSION: Combined with the 2004 review, 80 RCTs have investigated FP with no consistent evidence of significant benefit for prophylactic and therapeutic use across a range of indications evaluated.

UK Paediatric and neonatal FFP transfusions

FFP National Comparative Audit 2009

Age ranges:

- 4635 - 16+;
- 114 - 1-15 yrs;
- 220 < 1 yr



http://hospital.blood.co.uk/media/26877/nca-audit_of_ffp_elsewheres2009.pdf

Stanworth et al, *Transfusion* 2011

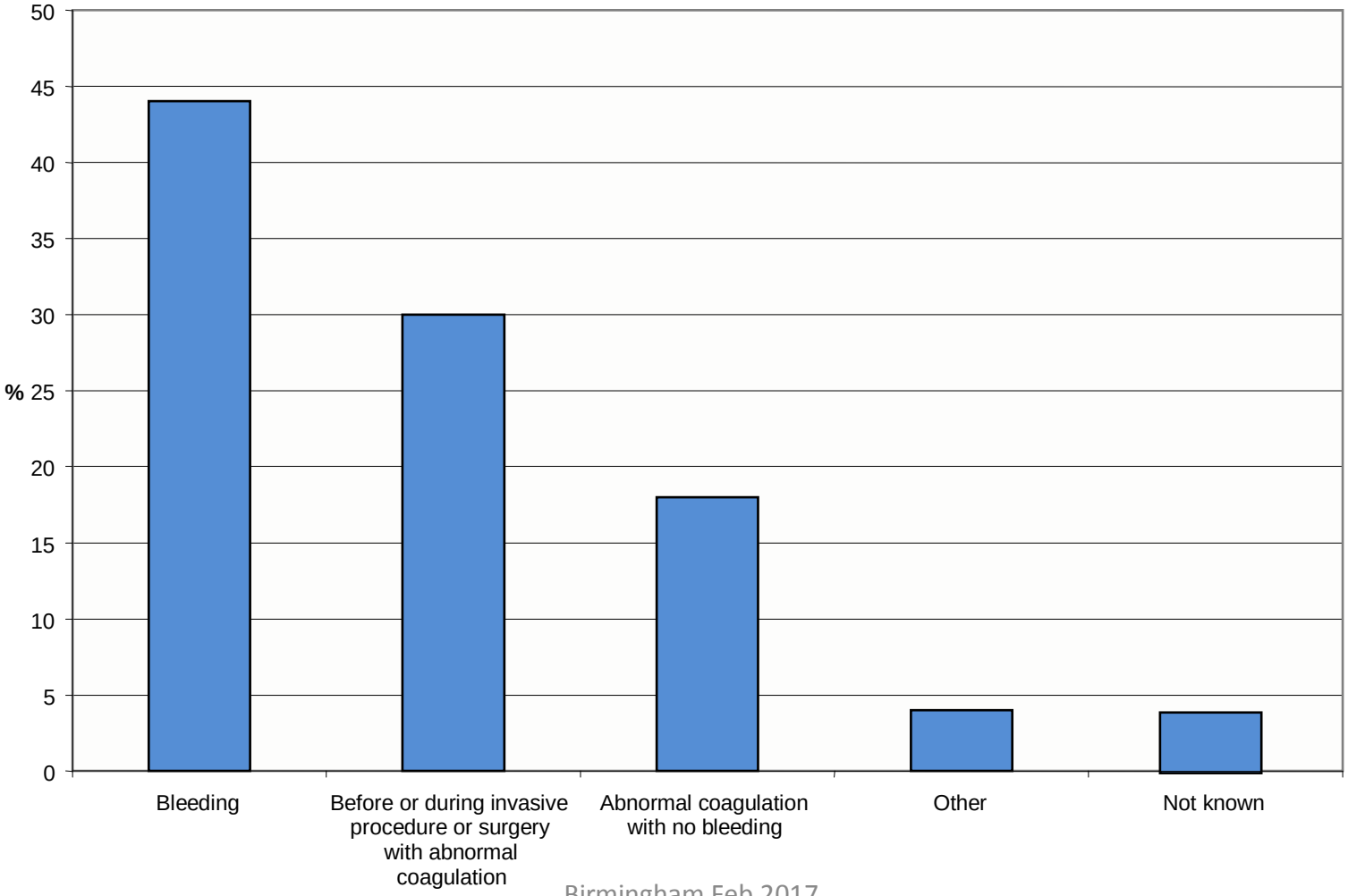
EASTR study, 2016

- 9% of FFP recipients paediatric (<16 yrs)
- 63% of paediatric FFP recipients < 1yr of age

FFP National Comparative Audit 2009

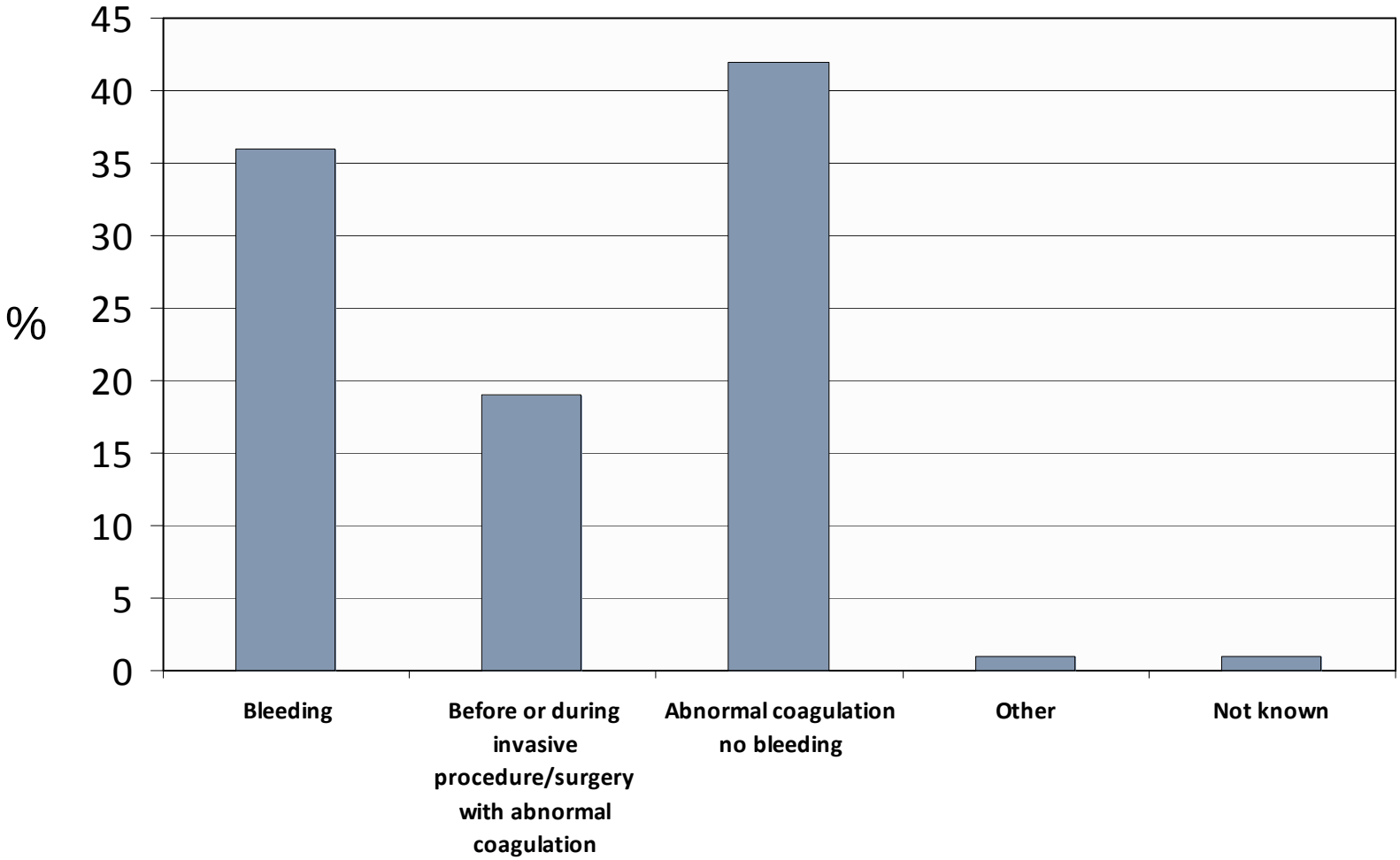
Age ranges: 16yrs+ (4635) 1-15 yrs (114) < 1 yr (220; 4%)

Main reason for transfusion in Children (1 – 15 yrs old)



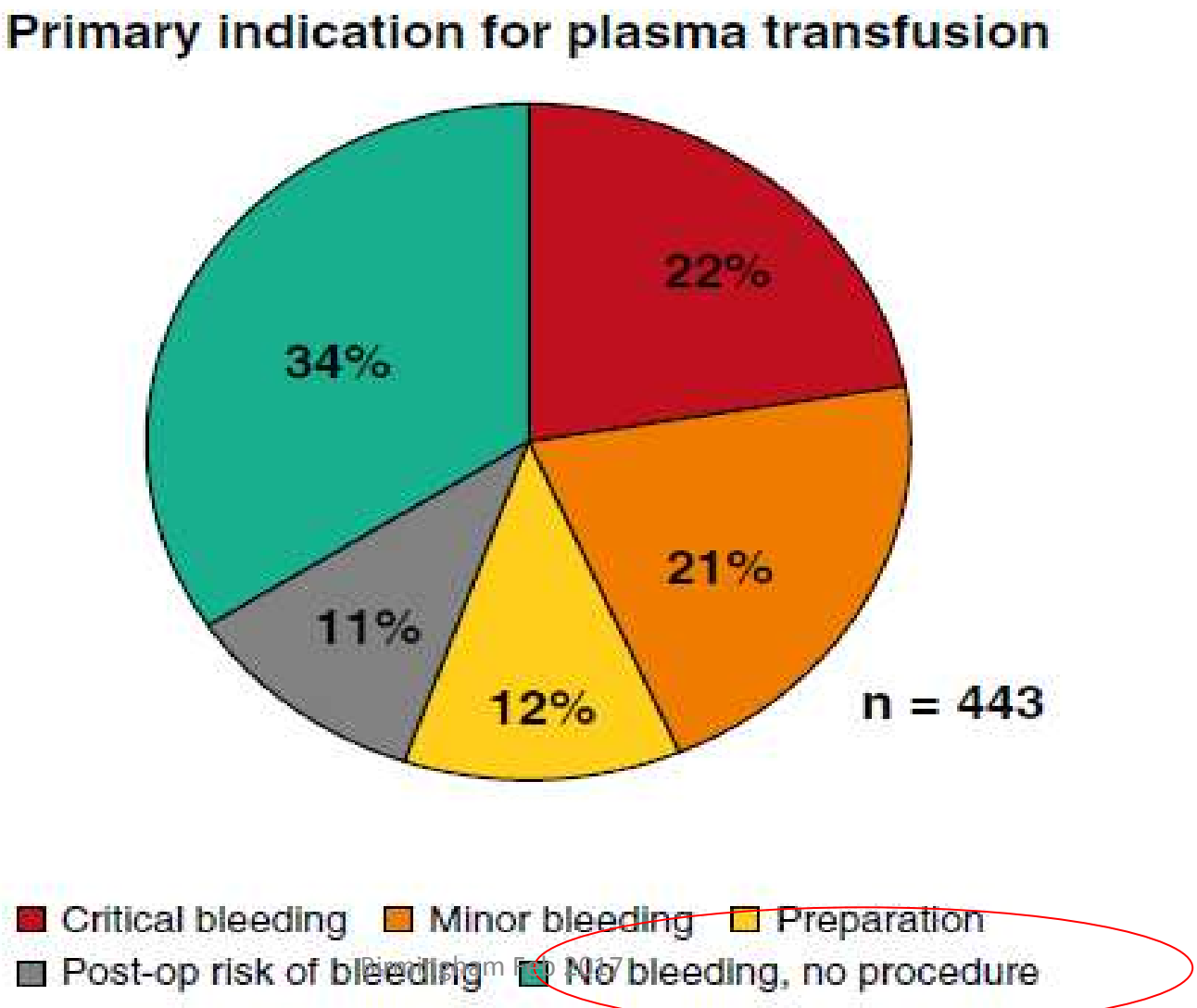
FFP National Comparative Audit 2009

Main reason for transfusion in Infants (< 1 yr old, n=220)



Indications and Effects of Plasma Transfusions in Critically Ill Children

Oliver Karam[1,2], Pierre Demaret[3], Alison Shefler[4], Stéphane Leteurtre[2,5], Philip C. Spinella[6], Simon J. Stanworth[7], Marisa Tucci[8]; on behalf of the Canadian Critical Care Trials Group (CCCTG), Pediatric Acute Lung Injury and Sepsis Investigators (PALISI), BloodNet, and the PlasmaTV Investigators*



FFP Use in infants : UK National Comparative Audit 2011

- Median INR pre FFP
  - Children with bleeding 1.5 (1.2-1.9)
  - Children with no bleeding 1.6 (1.2-1.8)

- Is this predictive of bleeding ?

Coagulation Screening – PT & APTT

•Initially developed as tests for patients with a high pretest probability of coagulation factor deficiency

•PT/APTT became screening tool to predict bleeding risk in a variety of clinical situations

Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review

Volume 45, September 2005 **TRANSFUSION** 1413

Jodi B. Segal and Walter H. Dzik on behalf of the Transfusion Medicine/Hemostasis Clinical Trials Network

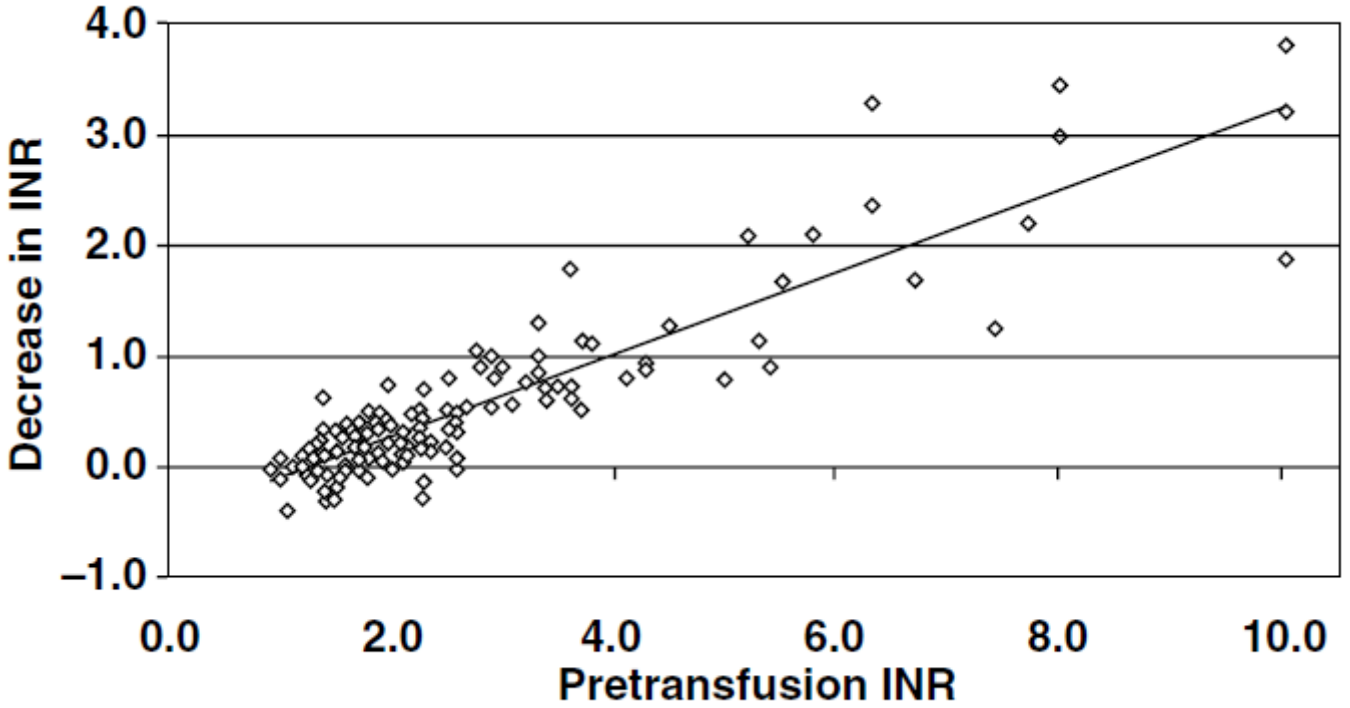
Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities

Volume 46, August 2006 **TRANSFUSION** 1279

Omar I. Abdel-Wahab, Brian Healy, and Walter H. Dzik

- Pre-transfusion INR 1.1 – 1.85
  - Normalisation of PT/INR: 0.8%
  - Reduction in INR (50%): 15%
  - Median decrease in INR: 0.2 sec

PT/INR



Puetz et al *J Pediatr Hematol Oncol* 2009; 31: 901-906.
Stanworth S et al. *Transfusion* 2011; 51: 62-70

Neonatal Haemostasis

Defining abnormal coagulation in neonates

AGE	I, V, VIII/vWF				Vitamin K-dependent factors (U/ml)				Contact factors (U/ml)		
	I	V	VIII	vWF	II	VII	IX	X	XI	XII	XIII
ADULT	3.40	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Term (37-41 WEEKS)	2.40	1.00	1.50	1.60	0.52	0.57	0.35	0.45	0.42	0.44	0.61

- Coagulation parameters are affected by gestational/postnatal age
- Physiological prolongation of PT and APTT in neonates
- Age adjusted normal ranges

- Problems of defining normal ranges and interpreting results

Andrew, 1988

Preterm normal ranges

		Post natal age	
Test	**Day 1**	**Day 5**	**Day 30**
PT (secs)	13.0 (10.6-16.2)	12.5 (10.0-15.3)	11.8 (10.0-13.6)
APTT (secs)	53.6 (27.5-79.4)	50.5 (26.9-74.1)	44.7 (26.9-62.5)
Fibrinogen (g/l)	2.43 (1.50-3.73)	2.80 (1.60-4.18)	2.54 (1.50-4.14)

Figures for healthy preterm infants (30-36 weeks gestation) during the first month of life.

Data from M. Andrews et al, 1988, 1990. All infants had had vitamin k

BSH recommendations - neonates

- FFP may be of benefit in neonates with clinically significant bleeding (including massive blood loss) or prior to invasive procedures with a risk of significant bleeding, and who have an abnormal coagulation profile
  - PT/APTT significantly above the normal gestational and postnatal age-related reference range (taking into account local reference ranges where available) (2C)

- There is no evidence to support the routine use of FFP to try to correct abnormalities of the coagulation screen alone in non-bleeding neonates (1C)
- FFP should not be used for simple volume replacement or routinely for prevention of IVH (1B).

BSH recommendations – Children

- FFP may be beneficial in children with DIC who have a significant coagulopathy (PT/APTT >1.5 times the mid-point of the normal range or fibrinogen <1g/l) associated with clinically significant bleeding or prior to invasive procedures.
- Early use of FFP is also recommended in the management of major haemorrhage

- FFP should not be administered to non-bleeding children with minor prolongation of the PT/APTT (including prior to surgery unless to critical sites)
- Other specific indications: TTP; coagulation deficiencies; vitamin K deficiency bleeding

Platelet & FFP transfusions in Children: Conclusions

- Optimal strategies for platelet use in children remain to be defined – thresholds recommended for treatment & prophylaxis
  - Thresholds largely unchanged from previous guideline

- Doubt exists on the efficacy of FFP in a range of settings & there is evidence to suggest inappropriate
  - Extensive use in non-bleeding children with abnormal coagulation
  - Poor predictive value of PT/APTT to predict bleeding
  - Problems defining abnormal coagulation in neonates
  - Limited correction of abnormal parameters by FFP
- Likely that more restrictive use would be appropriate

- Clear need for ongoing research