Are intracranial bleeds caused by low platelets or prevented by platelet transfusion?

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Intracranial Bleeds

- Incidence 24 to 48 per 100,000
- 1 month mortality 25 to 35% (2000 to 2008)

Feigen et al, Lancet Neurol 2009; 8:355-69
Van Asch et al, Lancet Neurol 2010; 9:167-76

Are intracranial bleeds caused by low platelets?

General population-based studies of intracranial bleeds

Systematic review of risk factors for ICH 2003 (Ariesen 2003)

14 case-control (1,746 cases)

11 cohort studies (1,314 cases 628,060 participants)

No studies identified low platelet count as a risk factor

Risk factors were:

- Age
- Hypertension
- Alcohol intake
- Males

Ariesen 2003, Stroke 34(8): 2060-5

General population-based studies of intracranial bleeds

Sturgeon 2007 (15 792 participants)

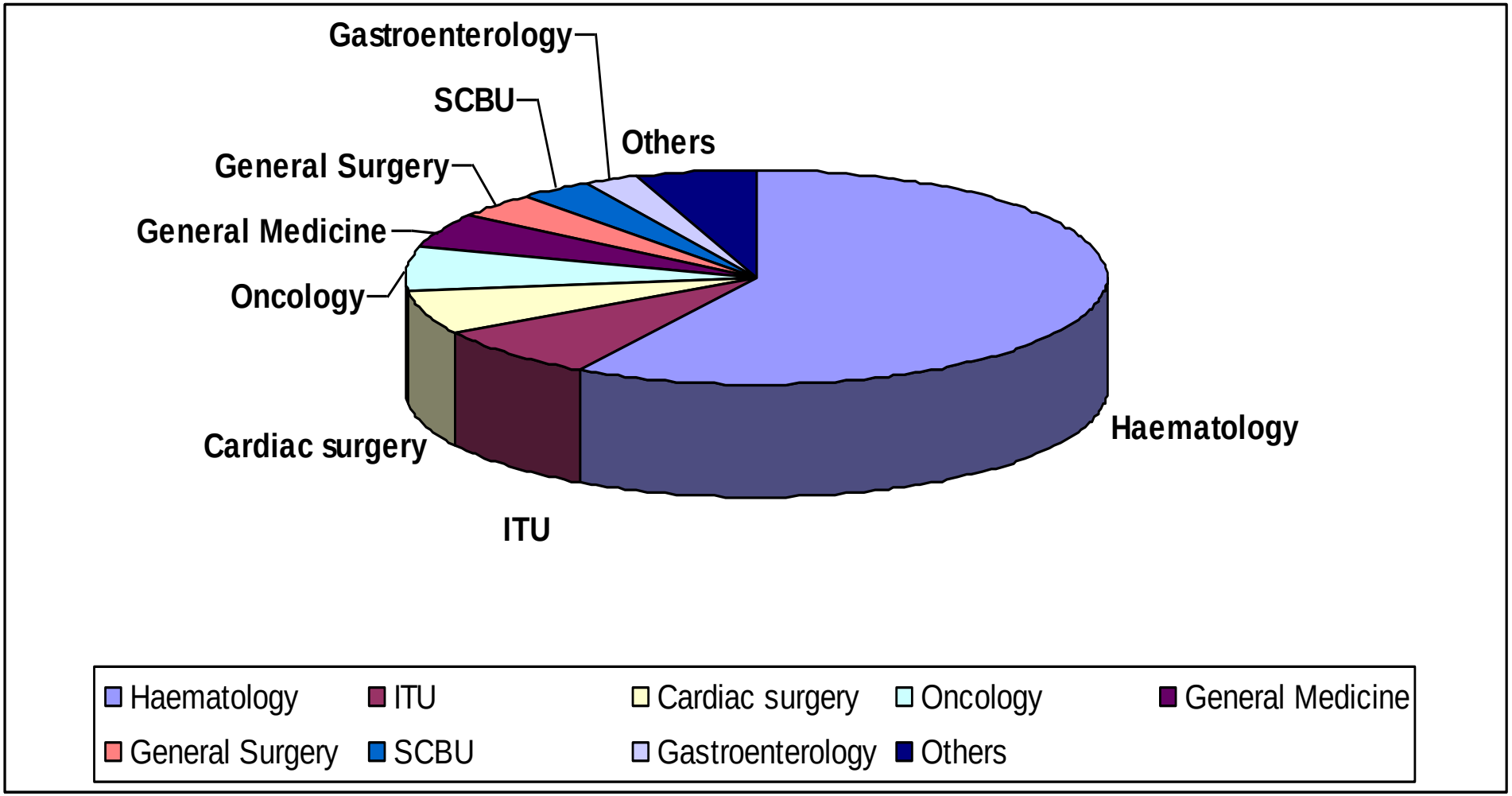
- Cohort study
- Platelet count not assessed as a variable

INTERSTROKE study 2010 (663 cases)

- Case-control study 22 countries
- Platelet count not assessed as a variable

Sturgeon 2007, Stroke 38(10):2718-25
O'Donnell 2010, Lancet 2010: 376; 112–23

Platelet transfusion usage



Data from NW England & Wales Audit of platelet use and wastage. Pendry & Davies 2011. Blood and Transplant Matters.

Premature babies

2 case-control studies

- Infants < 1500g
- Platelet count had no effect on risk of ICH

Linder 2003 (36 ICH 69 controls matched for age and weight)

Risk factors

- Early sepsis — Odds Ratio 8.19 (95% CI 1.55 to 43.1)
- Fertility Rx — Odds Ratio 4.34 (95% CI 1.42 to 13.3)
- Antenatal steroids — Odds Ratio 0.52 (95% CI 0.30 to 0.90)
- Low $PaCO_2$ — Odds Ratio 0.91 (95% CI 0.83 to 0.98)

Linder et al 2003; Pediatrics; 111(5):e590-e595

Premature babies

Risk prediction model for severe intraventricular haemorrhage

- Infants 500g to 1250g
- Using data from 6538 neonates in 6 S. American countries
- Platelet count was not included within the model

Risk factors in model were:

- Male, respiratory distress syndrome, mechanical ventilation
- Lower gestational age, APGAR scores, birth weight
- Caesarean section and antenatal steroids decreased risk

Luque et al; Journal of Perinatology (2014) 34, 43–48

Neonatal ICU

Neonatal ICU 11 281 NICU admissions

Severe thrombocytopenia in 273 (2.4%)

Lowest Platelet Count X 10^9/L	Number of neonates	% with IVH grades 3 or 4
< 20	78	17
21 to 30	78	15
31 to 50	117	19

Baer et al Pediatrics 2009;124:e1095–e1100

Adult ICU

Single centre study (1992 to 1996)

- 74 adults (> 17 years) on ECMO for > 24 hours
- 14 developed ICH

Risk factors

• Female	Odds Ratio 4.1	(95% CI 1.2 to 14.0)
• Use of heparin	Odds Ratio 8.5	(95% CI 1.1 to 69.8)
• Dialysis	Odds Ratio 4.3	(95% CI 1.7 to 15.6)
• Thrombocytopenia	Odds Ratio 18.3	(95% CI 2.2 to 150.5)
• Creatinine > 230µmol/l	Odds Ratio 6.5	(95% CI 1.6 to 26.4)

Kasirajan 1999; European Journal of cardio-thoracic surgery 508-514

Intracranial bleeds in thrombocytopenic haematology patients

Systematic review of risk factors for ICH 2001 to 2010

255 studies 1159 cases

- Presence of thrombocytopenia unknown in 72.6% of cases.
- Only 3.5% known to have platelet count < 10 x 10^9/L

Risk factors that may be associated (univariate) were:

- Female Hazards Ratio 1.87 (95% CI 1.27 to 2.75)
- Acute leukaemia Hazards Ratio 2.29 (95% CI 1.21 to 4.33)
- Auto HSCT vs Allo Hazards Ratio 0.09 (95% CI 0.03 to 0.30)
- Auto HSCT vs Chemo Hazards Ratio 0.13 (95% CI 0.04 to 0.43)

Study	Platelet count threshold	Number of Cases	Number of Participants	Number (%) of cases with platelet count below threshold	Number (%) of cases with platelet count above threshold
Kim 2004	35	41	792	Relative risk 3.28 (95% CI 1.43 to 7.55)	
De la Serna 2008	40	37	732	32/563 (5.7)	5/168 (3.0)
Molgaard-Hansen 2010	20	12	525	2/108 (1.9)	10/417 (2.4)
Testi 2005	40	3	110	1/80 (1)	2/27 (7)

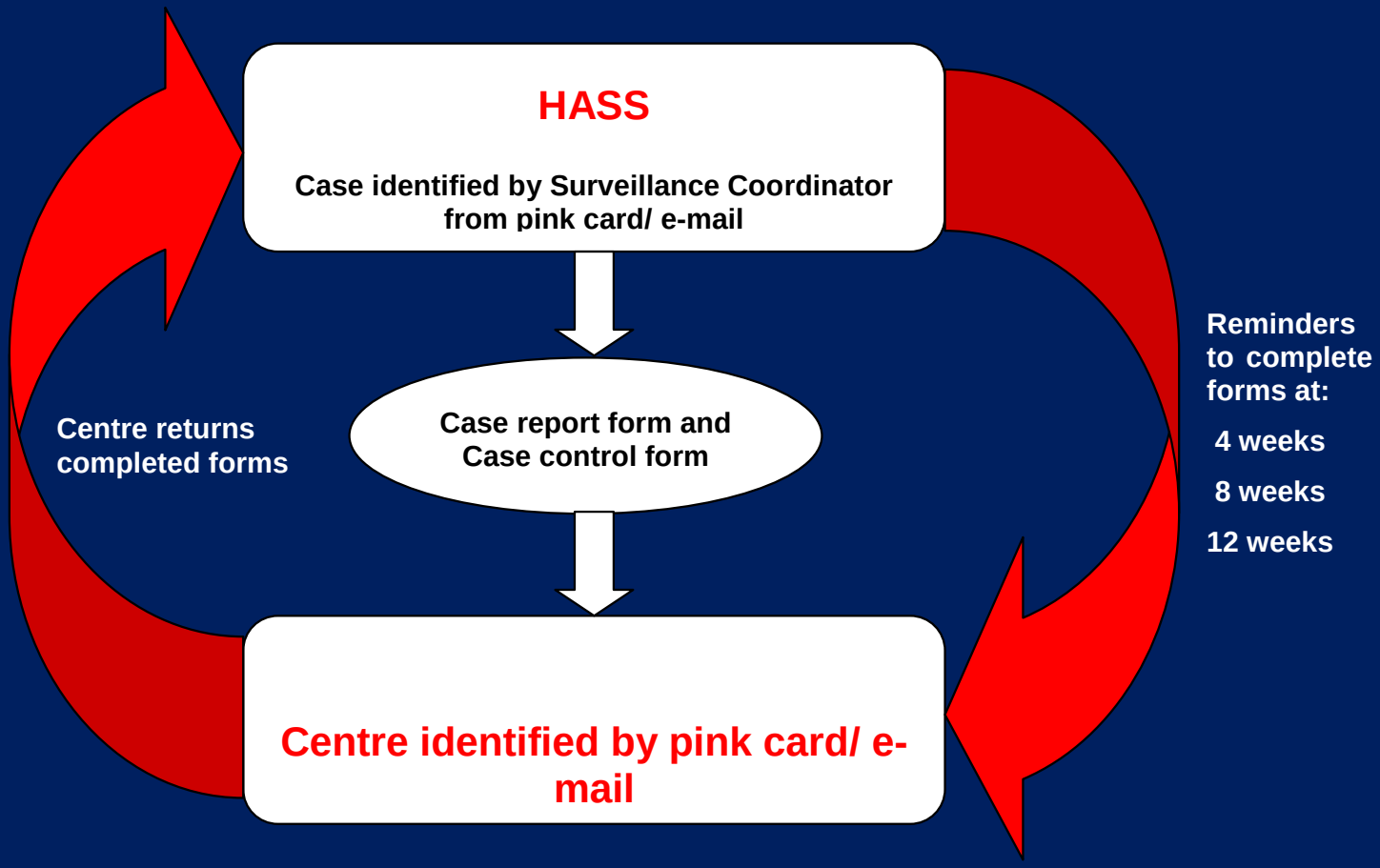
Case-control study of ICH in thrombocytopenic patients with haematological malignancies

What factors (e.g. age, haematological disease, treatment, infection) predispose patients to ICH?

What is frequency of ICH in these patients?

What are short-term outcomes? (e.g. death or persistent neurological deficit)

InCiTe Study



InCiTe Case Control Study (85 cases & controls) Univariable

Potential risk factor	Total	Odds Ratio	95% CI	P value
Female vs. Male	65/170	2.25	1.14 to 4.44	0.015*
Refractory to platelet Tx	16/170	5.00	1.10 to 22.82	0.016*
Complete remission	37/169	0.29	0.12 to 0.71	0.003**
Relapsed/refractory	37/168	3.20	1.17 to 8.73	0.014*
WCC ≥ 50 x 10^9/l	13/170	12.00	1.56 to 92.29	0.001**
CRP ≥100 mg/l	39/144	3.14	1.34 to 7.36	0.004**
Platelet count > 20 x 10^9/l	81/170	0.71	0.51 to 0.99	0.041*

Multivariable analysis

Potential risk factor	Odds Ratio	95% CI	P value
Female vs Male	3.34	1.18 to 15.86	0.027*
Complete remission	0.19	0.04 to 0.84	0.028*
Platelet count ≤ 20 x 10^9/l	2.50	0.82 to 7.60	0.106
WCC > 50 x 10^9/l	19.75	1.90 to 204.87	0.012*
CRP > 100 mg/l	4.33	1.18 to 15.86	0.027*

Are intracranial bleeds caused by low platelets?

- General population – not identified as a risk factor
- Premature neonates - not identified as a risk factor
- Neonatal ICU - unclear
- ECMO – increased risk with decreasing platelet count
- Haematological malignancy – may increase risk

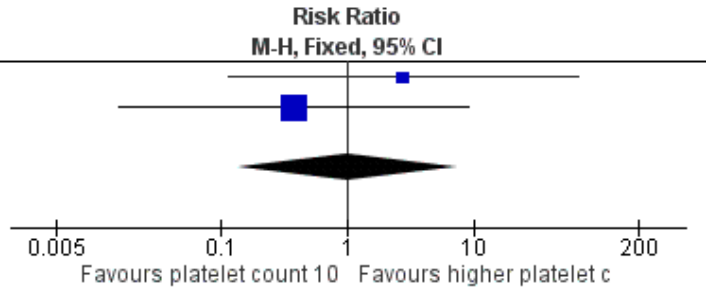
Many other factors increase risk of intracranial bleeds

Are intracranial bleeds prevented by platelet transfusion?

Lower versus higher platelet count threshold

Study or Subgroup	Platelet count 20 or 30 x 10^9/l Events	Total	Platelet count 10 x 10^9/l Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Diedrich 2005	1	87	0	79	27.1%	2.73 [0.11, 65.99]
Rebulla 1997	0	120	1	135	72.9%	0.37 [0.02, 9.11]
Total (95% CI)		**207**		**214**	**100.0%**	**1.01 [0.14, 7.49]**
Total events	1		1			

Heterogeneity: Chi² = 0.74, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)

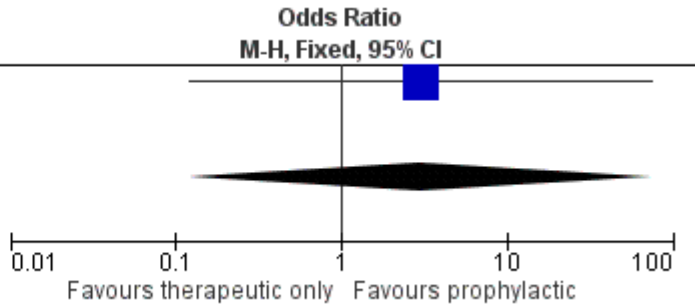


12,508 participants are required to have a 90% chance of detecting, as significant at the 5% level, a decrease in intracranial haemorrhage from 1% in the control group to 0.5% in the experimental group.

Therapeutic versus prophylactic

Study or Subgroup	Therapeutic only Events	Total	Prophylactic Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Stanworth 2013	1	300	0	298	100.0%	2.99 [0.12, 73.69]
Wandt 2012	0	103	0	98		Not estimable
Total (95% CI)		**403**		**396**	**100.0%**	**2.99 [0.12, 73.69]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)



41,938 participants are required to have a 90% chance of detecting, as significant at the 5% level, a decrease in intracranial haemorrhage from 0.3% in the control group to 0.15% in the experimental group.

Are intracranial bleeds prevented by platelet transfusion?

- RCT data - too few participants

Any questions?

NHS Blood and Transplant

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