

Irradiation of Platelets: all, none or some

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Why do we irradiate?

- Transfusion associated Graft versus Host Disease
 - First recognised in 1960/70s
- Patient Risk factors
 - Immuno-deficiency, HLA compatibility
- Component risk factors
 - Cellular components
 - <15 days old
- Outcome
 - >90% fatal

Who should we give irradiated components to?

BCSH 2010 Treleaven *et al*

- Components
 - Directed donations
 - Granulocyte components
 - HLA selected components
- Patients
 - Severe T cell immunodeficiency
 - HSCT recipients
 - Hodgkins disease
 - Fludarabine rx patients
 - ATG rx patients
 - IUT/exchange transfusion

Which policy would you support?

1. Selective irradiation
2. Universal irradiation
3. No irradiation

How does irradiation work?

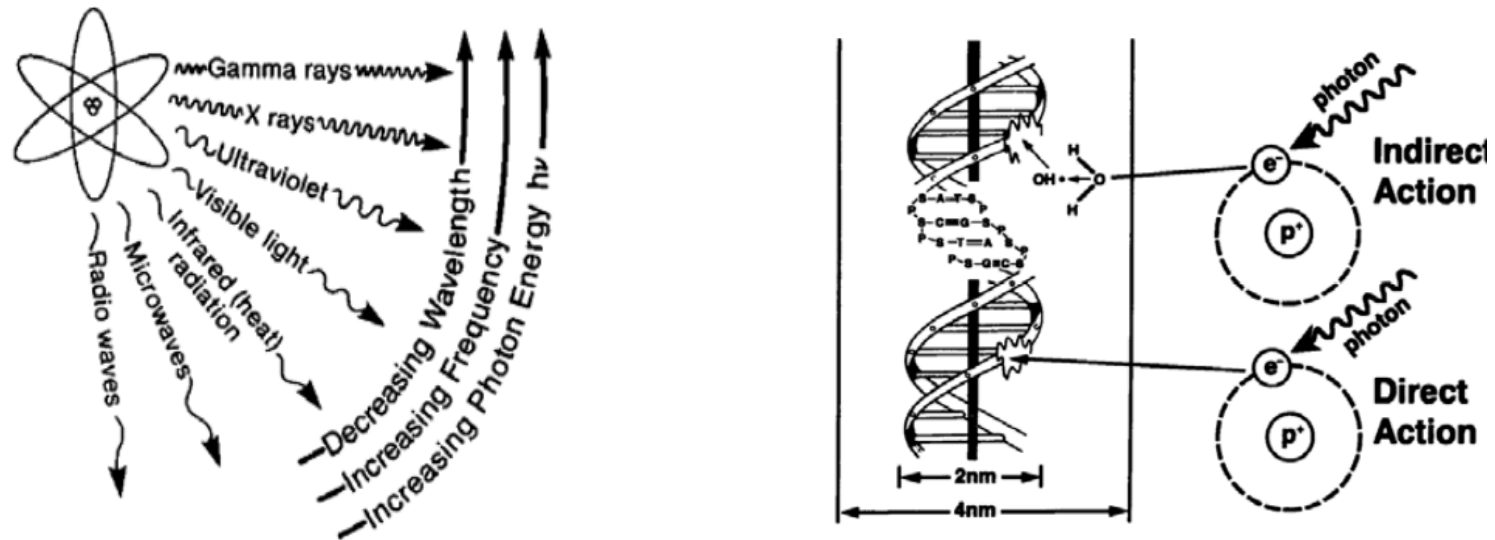


Fig. 2.2 Direct versus indirect action (Hall and Giaccia, 2006).

TABLE 2.5 TRIAGE CRITERIA USED AFTER THE CHERNOBYL ACCIDENT

Severity	Vomiting time	Lymphocytes day 3	Hair loss within 2 weeks	Cytogenetic Radiation Dose	Lethality including skin burns
Mild	no	>600	no	< 2 Gy	0/105
Intermediate	after 1-2 h	300-600	no	2 – 4 Gy	0/53
Severe	after 30-60 min.	100-300	yes	4 – 6 Gy	6/23
Very severe	immediate	<100	yes	6 – 16 Gy	19/22

Does irradiation damage platelets?

- Platelets have no nucleus
- They have mitochondrial DNA + RNA
- They have sensitive membranes

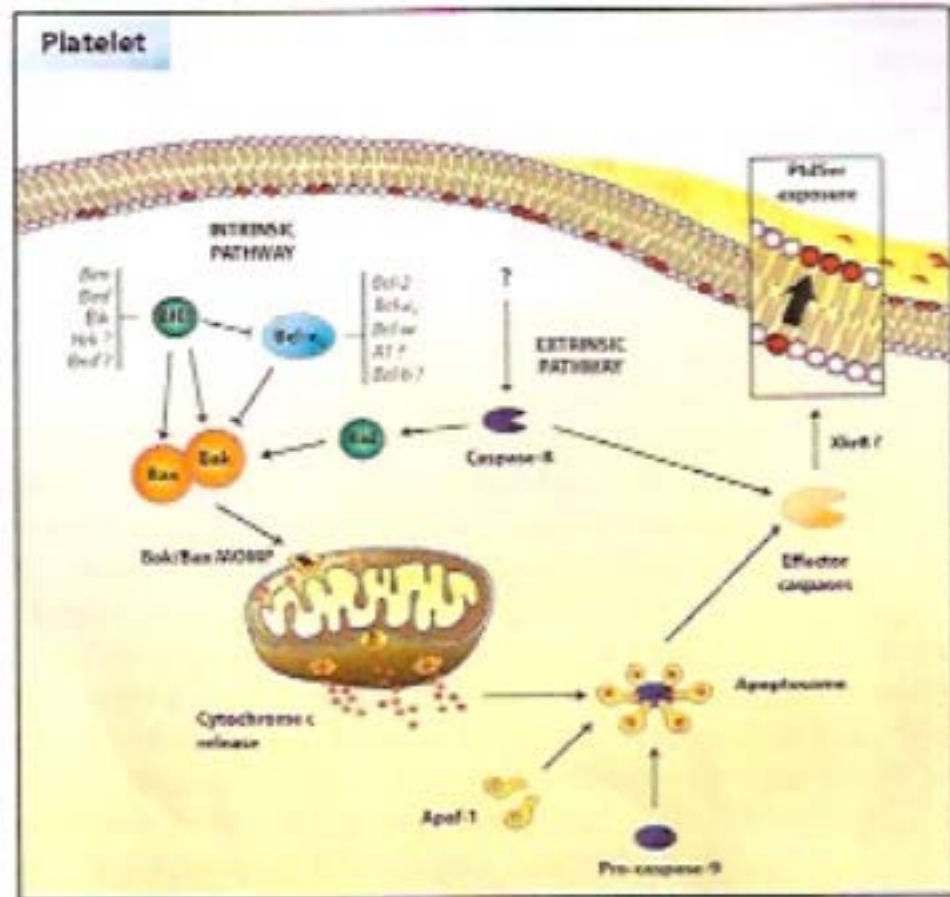
Standard irradiation dose 25-50 Gy

Why do Platelets die?

From Lebois and Josefsson 2016, Platelets 27;497-504

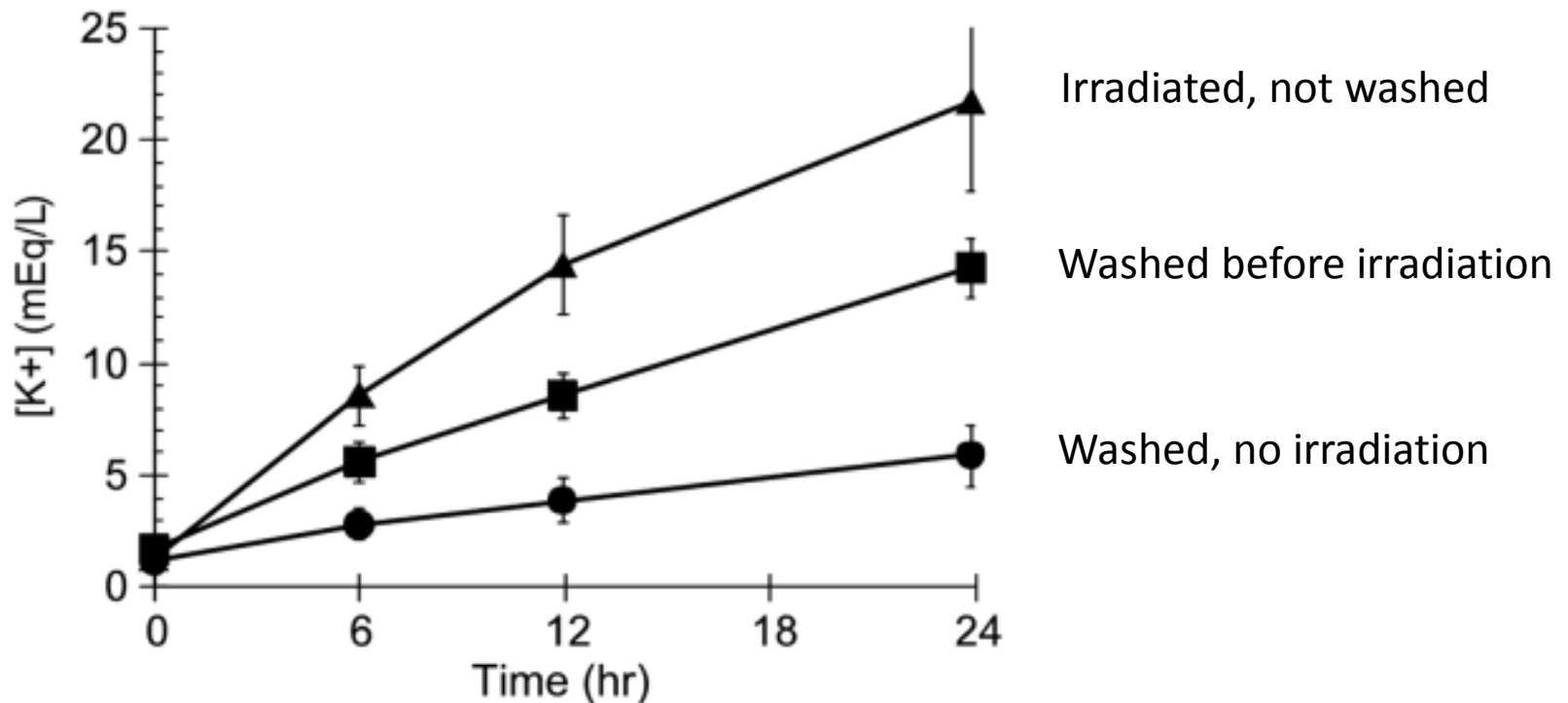
Platelet apoptosis occurs through mitochondrial signals as in nucleated cells

1. Do platelets undergo more apoptosis after irradiation?
2. Is there collateral damage affecting function?



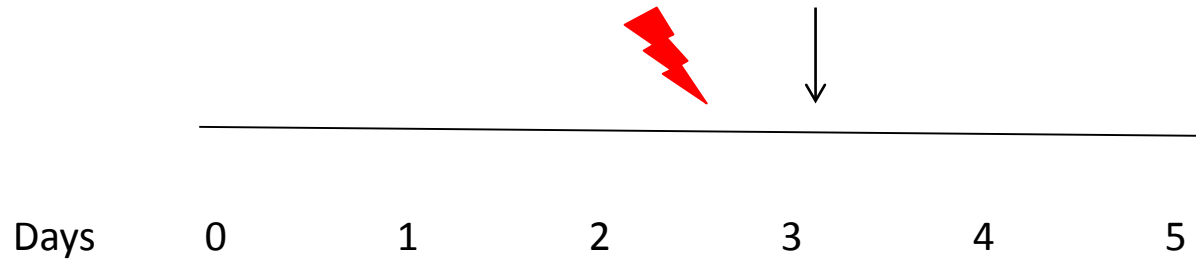
Does Irradiation damage cells?

Extracellular potassium concentrations in red blood cell suspensions

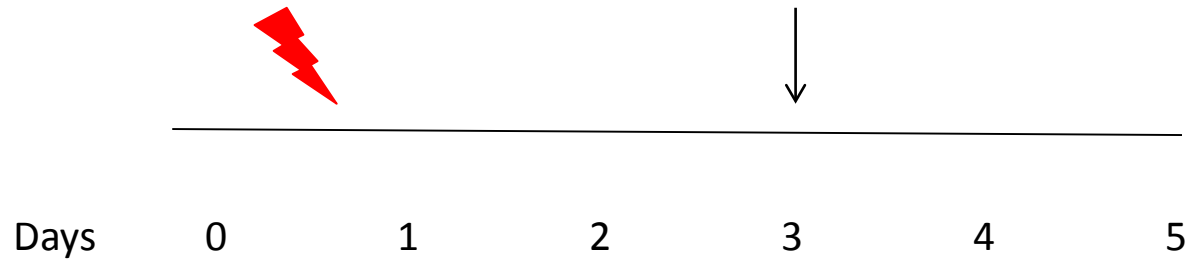


Timing of irradiation and transfusion

Collection



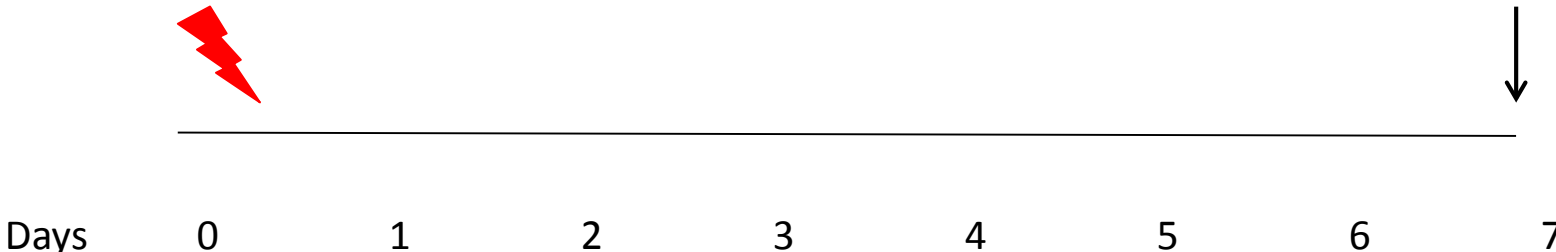
Collection



Collection



Collection



In vitro studies of irradiated platelets

- Conventional Platelet assays: Eg. CD62, aggregation, pH, etc
- Most studies of Rx day 0/1, tested up to 5 days
- Two studies on RT stored PCs for 7 days after Rx day1
 - Van der Meer 2005 Vox Sang 89; 97-9
 - Tynngard et al 2008 Transfusion 48; 1669-75
- Cytokine changes: Eg. Sandgren et al 2016
- MicroRNAs : Osman et al 2015 Platelets 26; 154
- No major/reproducible changes due to Gamma irradiation
- Metabolomics: eg Marrocco et al 2013
- Significant but not major alterations in proteins during storage

In vivo studies of irradiated platelets

1. Platelet function tests ex vivo
2. Bleeding symptoms post transfusion
3. Platelet recovery and survival

Various studies in 80's and 90's

- Duguid et al 1991 26 transfusions. 15Gy immediately before Tx. 1 Hour and 24 Hour increment. No difference
- Sweeney et al 1994. 10 patients. 25Gy Rx Day 1 or 3. Tx day 5. No difference in recovery (52%) or survival (6.1days)
- No clinical studies looking at 7day stored platelets irradiated either at manufacture or issue.

Collection

Duguid et al

Days

0

1

2

3

4

5



Collection

Sweeney et al

Days

0

1

2

3

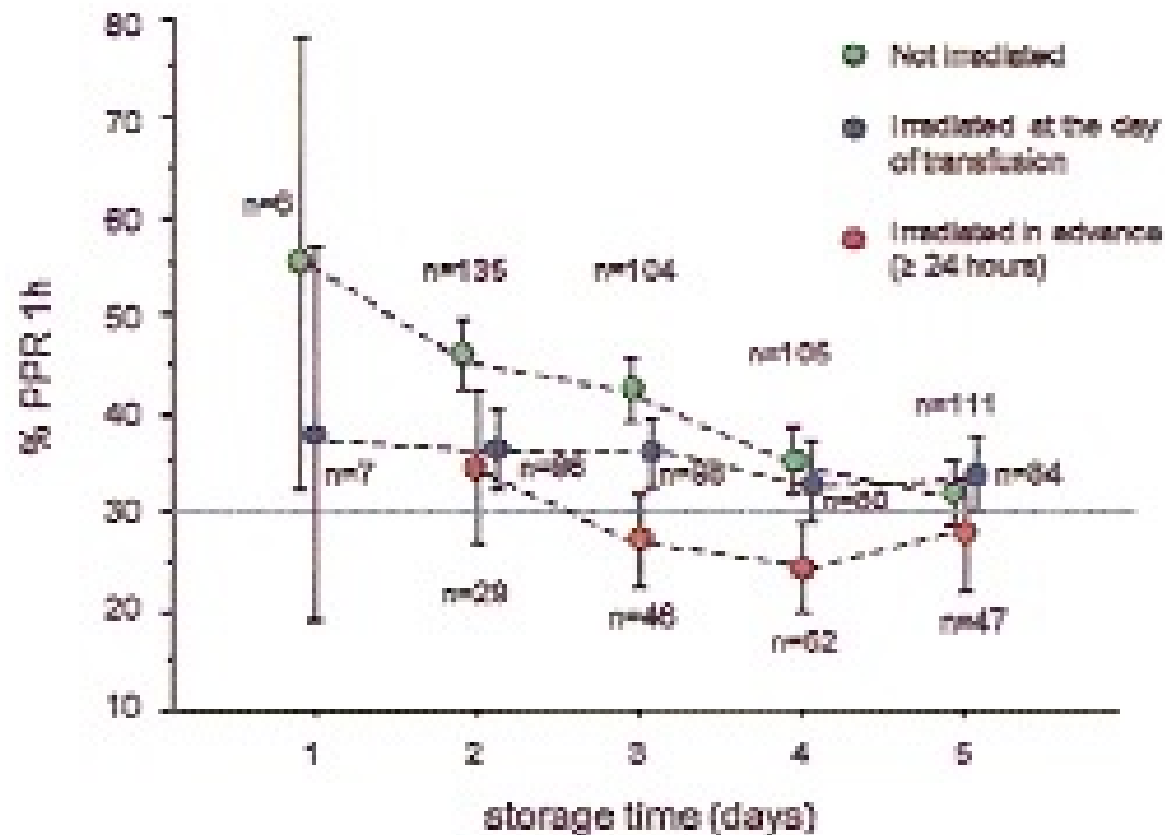
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Retrospective studies

- Slichter et al Blood 2005; 105: 4106-14.
533 pts, 6254 platelet transfusions from TRAP study. 10% decrease in 1 hr corrected count increment for irradiated BC pools, but not for apheresis platelets.
- Julmy *et al* Trans Med & Haemother 2014; 41:176-81.
 - 144 children. 1000 Plt Tx. Platelets transfused >24 hours post irradiation gave poorer CCI at 1 hour



Julmy *et al*

Fig. 1. Transfusion efficacy of 1000 APCs according to gamma irradiation, timing of irradiation, and storage time (error bars = 95% CI). Dotted blue line: According to the British Committee for Standards in Haematology an unsuccessful PLT transfusion is defined as one with a PPR_{1h} of 30% or less [4].

Bashir *et al* Transfusion 2013; 53: 990-1000

PI of platelets with UV light

- UV C light is generally regarded as non-ionising
- Causes pyrimidine dimers to crosslink DNA
- Similar effects to irradiation

In vitro testing

Recovery and survival after 5 days

TABLE 3. Recovery and survival of UVC-treated PLTs*

	Recovery (%)			Survival (days)		
	Fresh	Stored	Stored as % of fresh	Fresh	Stored	Stored as % of fresh
Control	56.8 ± 11.2	37.6 ± 6.5	64 ± 11	9.2 ± 1.3	7.3 ± 0.9	81 ± 6
Treated	52.4 ± 8.6	28.0 ± 8.2	51 ± 11	4.6 ± 1.3	5.2 ± 1.3	65 ± 15
% Reduction		26	17		29	20
p value	0.172	0.026	0.088	0.401	0.004	0.005

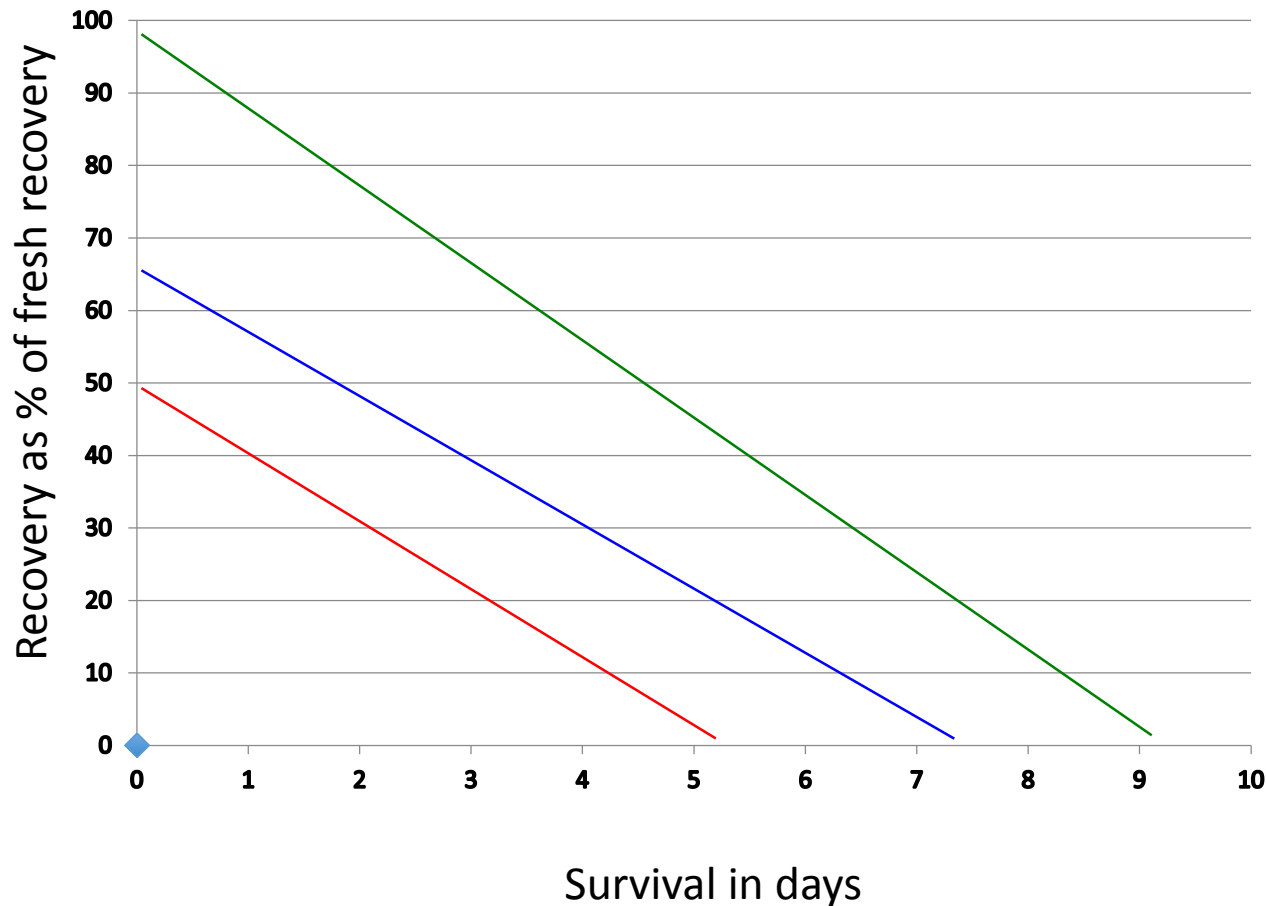
* Data are mean ± SD; n = 6 control and n = 6 treated.

BASHIR *et al*: CHANGES IN RECOVERY AND SURVIVAL WITH STORAGE (5 DAYS) AND UV LIGHT

RECOVERY (%)				SURVIVAL (DAYS)			
	fresh	stored	%		Fresh	Stored	%
Control	56.8	37.6	64		9.2d	7.3d	81
Treated	52.4	28.0	51		8.6d	5.2d	65

Bashir et al

Recovery and Survival



Plt days = recovery x survival

Fresh = $100 \times 9.2 / 2 = 460$ ■

Stored = $66 \times 7.3 / 2 = 240$ ■

Treated = $50 \times 5.2 / 2 = 130$ ■

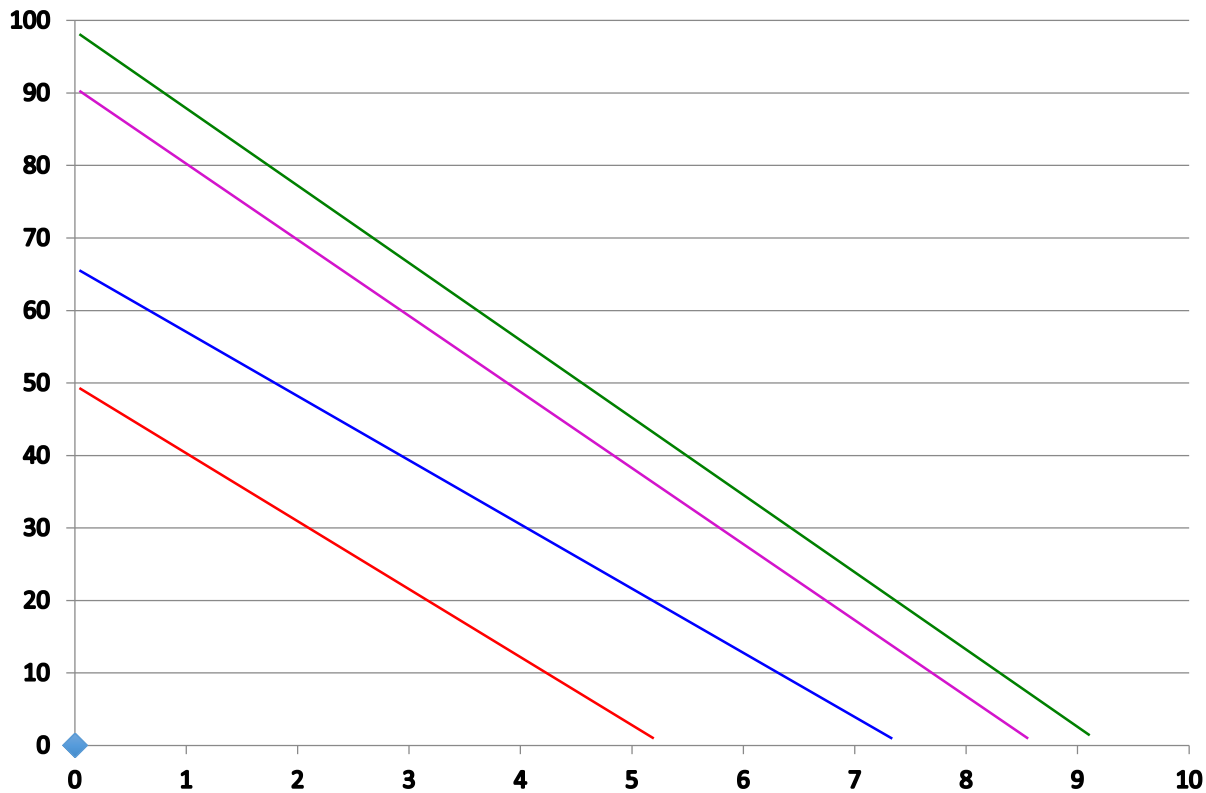
If Fresh = 100%

Stored = 52%

Treated = 28%

Bashir et al

Recovery and Survival



Treated and immediately transfused platelets seem to do better



Collection



Bashir et al

Days

0

1

2

3

4

5

6

7

Collection



No data



Days

0

1

2

3

4

5

6

7

Platelets and irradiation

- Impact of irradiation on in vitro function is negligible but there are metabolic changes
- Impact of irradiation on in vivo function has not been tested rigorously
- No Impact of irradiation on survival and recovery in 2 studies but has not been tested with early irradiation and day 7 transfusion

Do platelets cause TaGvHD

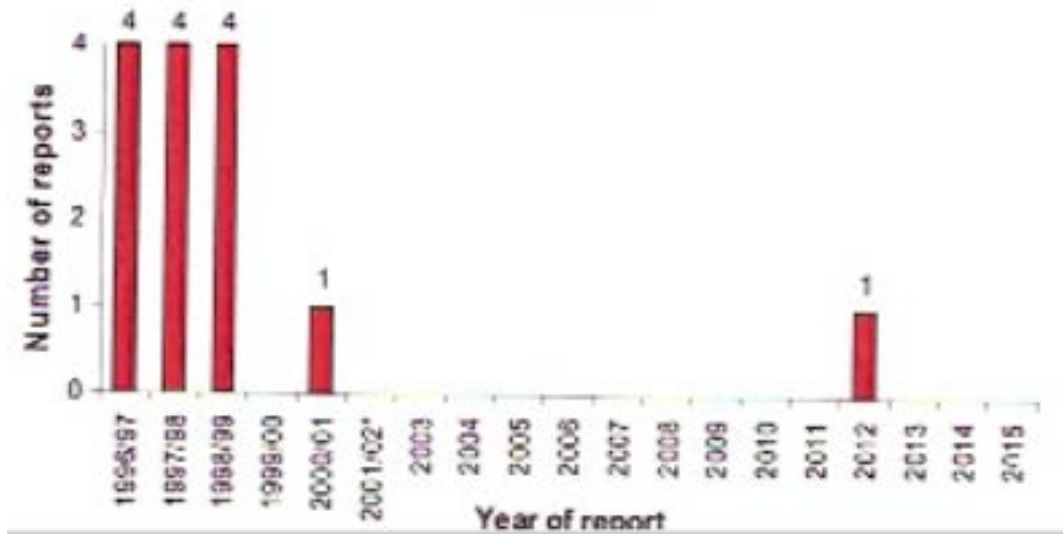
Benson et al Transfusion 1994; 34:432-7

Platelets from unrelated HLA homozygous donor

SHOT data on TaGvHD

Williamson et al Transfusion 2007, 47;1455-67
updated Jayne Addison et al ISBT poster 2017

**Figure 1. Number of reported cases of TA-GvHD
1996-2015**



- One case in recognised risk category
- All received red cells, two with platelets
- 2 received Leucodepleted components

1215 patients reported to have received non irradiated components in error

UK Conclusion

- TaGvHD in the immuno-competent has been 'eliminated' by high quality Leuco-depletion
- Risk Of TaGvHD in immuno-incompetent is less than 1 In 1000 patients with LD components
- 1 in 3000 units is a LD failure (<99.9% LD)
 - Figure courtesy of Dr Sheila McLennan

A systematic review of TaGvHD: 348 cases

Kopolovic ...Callum *et al.* Blood 2015; 126: 406-14

- 50% of cases occurred in the immunocompetent
- Incidence by indication was similar to incidence of transfusion by indication
- HLA epitope sharing was very common
- Implicated components:
 - RBC 38.2%
 - Whole blood 26.4%
 - Platelets 5.7%
 - Fresh plasma 1 case
 - Uncertain 29.3%
- LD in 23 cases: 10 bedside, 2 pre-storage, 11 not specified
- Irradiation used in 5 cases, 1x15Gy, 2x25Gy, 1 not specified

Summary

- Platelets are a rare cause of TaGvHD, 1 in 20 cases
- LD has 'eliminated' TaGVD from immunocompetent recipients
- Immuno-incompetent risk is $\ll 1000$ patients /components
- LD failure is rare
- TaGvHD is $>90\%$ fatal
- Irradiation has limited effects on platelet function
- Evidence for recovery and survival based on 2 small studies
- Possible combined effect of irradiation and storage
- No clinical studies on irradiation and storage for 7 days

Factors to consider

- Stock management, centre and hospital
 - Safety to blood service personnel
 - Safety to patient
 - TaGvHD
 - Efficacy in patient,
 - donor exposures, clinical benefit
 - Cost
-
- If we adopt universal irradiation can we ever go back?

Which policy would you support?

1. Selective irradiation
2. Universal irradiation
3. No irradiation