Granulocytes

ProGrES and considerations

East of England RTC

May 2022

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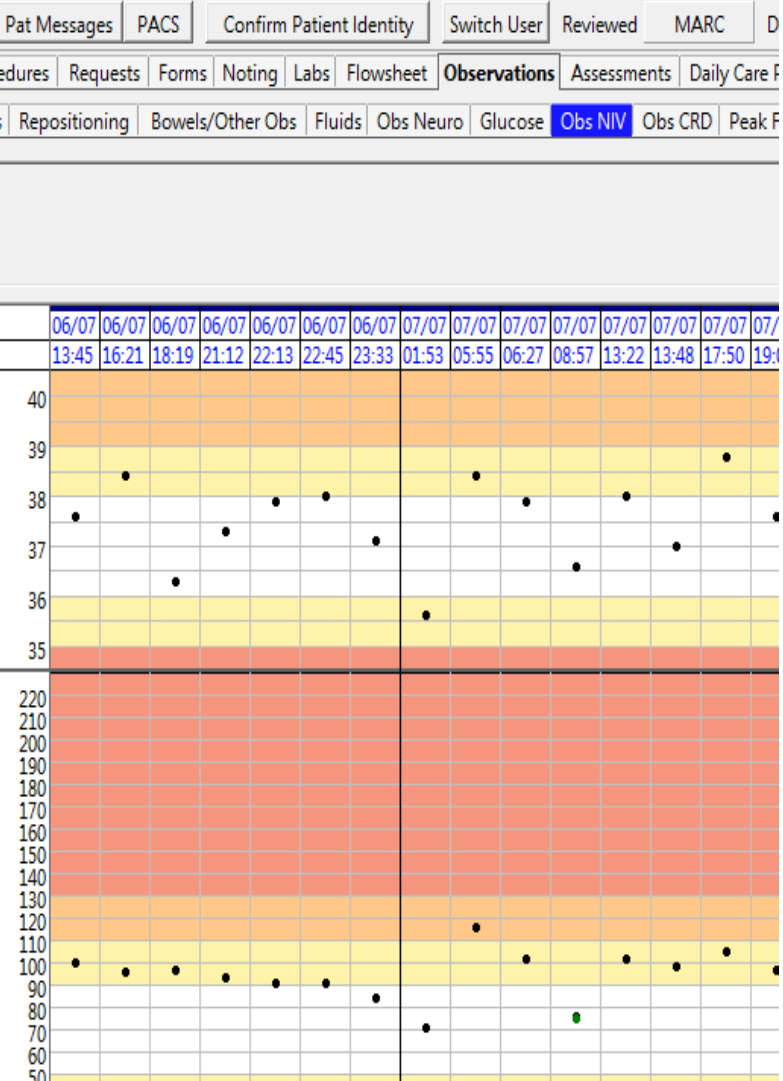
NHS
University Hospitals Birmingham
NHS Foundation Trust

NHS
Blood and Transplant

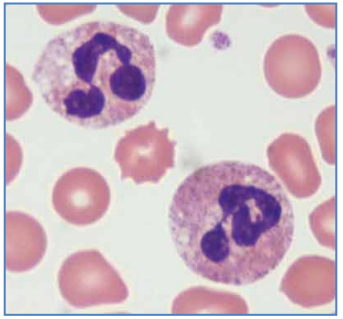


Case presentation

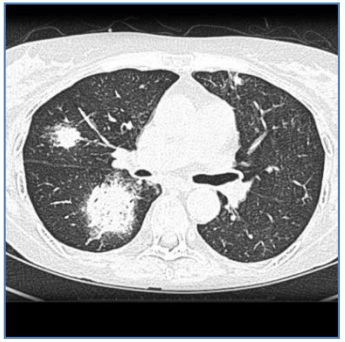
- 55yo with AML
- 2 x CPX then relapsed → FLAG-ida
- Failed to recover counts
- Recurrent positive blood cultures with *Enterococcus*
- Lesion suspicious for endocarditis on echo
- Fungal chest infection
- Embarking on unrelated bone marrow transplant…

Background

- Neutropenic sepsis is a major cause of morbidity and mortality for patients with bone marrow failure
- Supportive care improving but challenges e.g. antibiotic resistance



- Efficacy of granulocyte transfusion unclear (Estcourt, 2015 and 2016)
- Concerns over toxicity
- Previous RCTs failed to recruit (Price, 2015; Seidel, 2008)



Lack of evidence is a barrier to use but despite this NHSBT issue granulocytes to 8.6 new patients per month

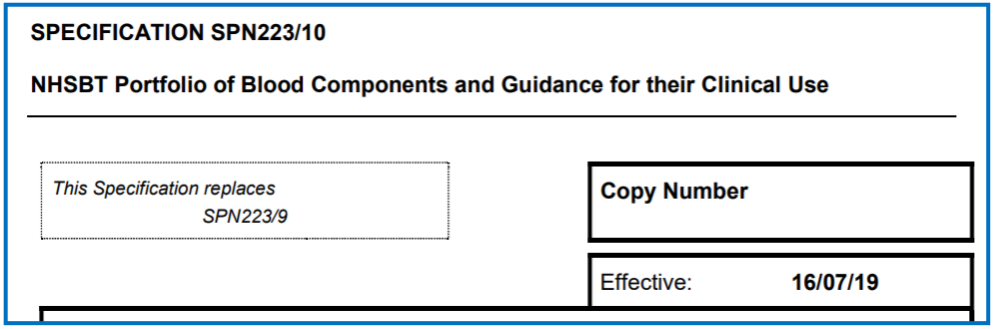
Granulocytes, Pooled, Buffy Coat derived, in Platelet Additive Solution and Plasma, Irradiated

- 10 buffy coats, pooled in SSP+ and male plasma

- Hct 0.15
- 2.5 adult doses of platelets per pool

- Volume 207 mL
- Stored at 22°C without agitation
- Expire at midnight the day after donation

- ABO and D compatible, immediate spin “cross match compatible”
- CMV neg for CMV neg recipients if potential for SCT



SPECIFICATION SPN223/10

NHSBT Portfolio of Blood Components and Guidance for their Clinical Use

This Specification replaces SPN223/9

Copy Number

Effective: **16/07/19**

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology

Good Practice Papers | Free Access

Cytomegalovirus serological testing in potential allogeneic haematopoietic stem cell transplant recipients: A British Society for Haematology Good Practice Paper

Suzy Morton, Fiona Dignan, Husam Osman, Mike Potter, Tony Pagliuca, Karl S. Peggs, BSH Administrator

- Beta herpes virus (HHV5)
- Lies latent in monocytes; potential for TTI
- Major cause of morbidity and mortality among HSCT recipients
- Historically, “CMV-negative” components for CMV naïve HSCT recipients
- Series of studies in late 1990s showing equivalence of use of CMV-negative donors versus leucocyte reduction

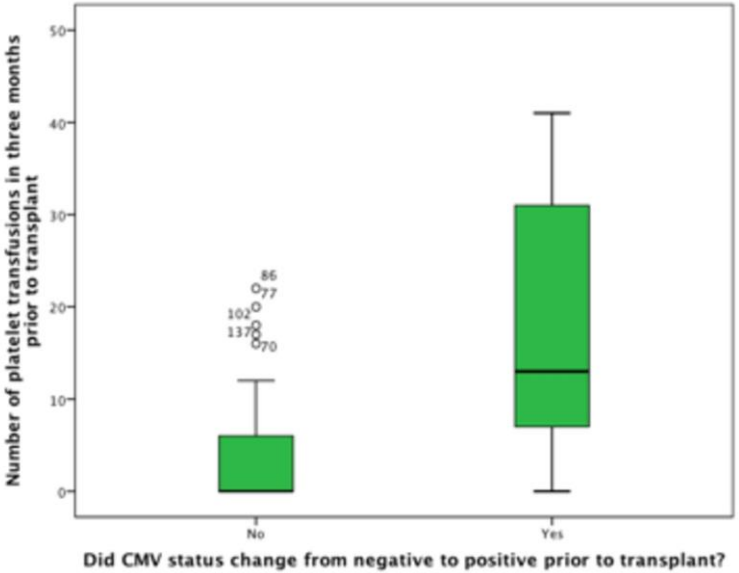
CMV “unintended” consequences

- We have “forgotten” about CMV risk with transfusion
  - CMV status no longer reliably ascertained at baseline for haematology patients who may later undergo HSCT
- Two important clinical scenarios
  - Identifying serostatus to allow donor matching at HSCT
    - Risk of inadvertent selection of donor with inappropriate CMV status
    - Risk of delay to transplant if patient appears to seroconvert
  - Granulocytes need to be CMV neg for CMV neg patients
    - Granulocytes are not leucocyte reduced!!

High Rates of Passive CMV Antibody Acquisition Pre–Allograft in Patients Receiving Plasma–Rich CMV Unselected and Leukodepleted Blood Components: A Caution for Donor Selection

Robert N Lown, Unell Riley, Mark Ethell, and Michael N Potter

Blood 2014 124:1140;



Dosing and provision

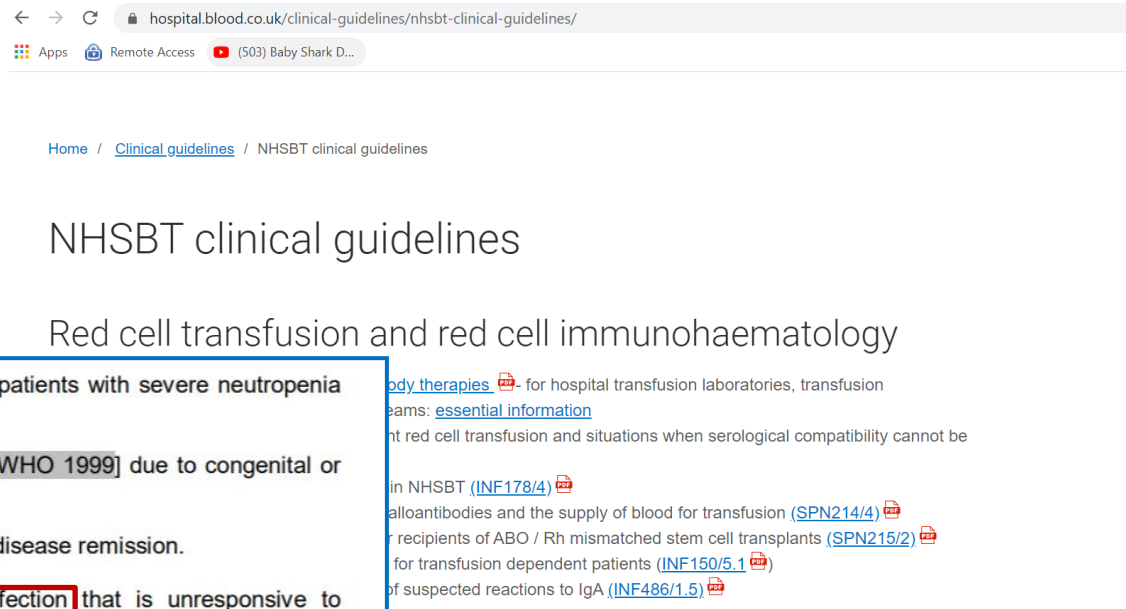
- 10 donations; 0.9-1 x 10^{10} neutrophils
- **Dose**
  - 1-3 bags (adults)
  - 10-20ml/kg (children)

- **Availability** Tues-Sat
  - 4x O pos, CMV-U on Mon, since Sept 2020

Buffy coats sometimes available over weekends
Apheresis granulocytes no longer available

Internationally, most countries use apheresis granulocytes, however some now moving to pooled because of (relative) ease of preparation

What are the indications?



2.1 Therapeutic granulocyte transfusions may be indicated for patients with severe neutropenia who fulfil **all** of the following criteria:

2.1.1 Severe neutropenia, defined as ANC <0.5 x 10^9/L [WHO 1999] due to congenital or acquired bone marrow failure syndromes.

2.1.2 Receiving active treatment in an attempt to achieve disease remission.

2.1.3 Proven or highly probable fungal or bacterial infection that is unresponsive to appropriate antimicrobial therapy as demonstrated by visible spreading lesions on skin, mucosa or radiological examination [Ascioglu et al 2002].

2.1.4 In whom neutrophil recovery is expected (ANC>0.5x10^9/l) in the near future and / or in whom definitive therapy of curative potential is planned.

2.2 Therapeutic granulocyte transfusions may also be indicated for patients with a known congenital disorder of neutrophil function [Kuijpers et al 1999] regardless of neutrophil count with proven or highly probable fungal or bacterial infection unresponsive to appropriate antimicrobial therapy, demonstrated by visible spreading lesions on skin, mucosa or radiological examination.

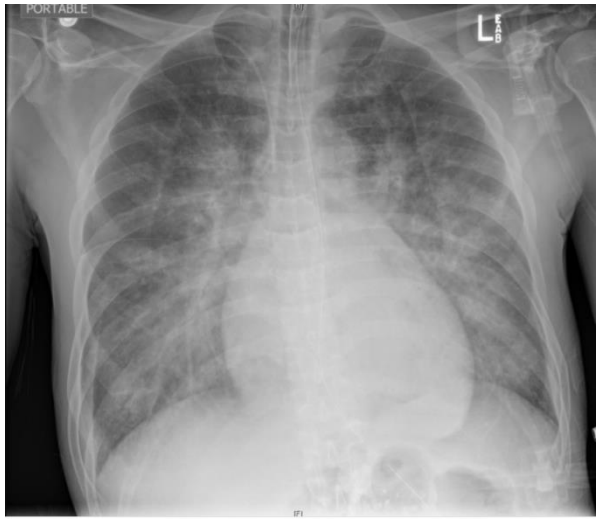
Guidelines don't address

- Acquired neutrophil dysfunction
- Patients with no definitive treatment planned
- Prophylaxis

What are the potential adverse effects?

- Fever (FNHTR)
- TRALI
- HLA sensitisation
- TACO

- CMV transmission
- Red cell incompatibility considerations



Cochrane Database of Systematic Reviews

Granulocyte transfusions for treating infections in people with neutropenia or neutrophil dysfunction

Cochrane Systematic Review - **Intervention** | Version published: 29 April 2016 see what's new

https://doi.org/10.1002/14651858.CD005339.pub2

Am score 7 **Used in 1 guideline** View article information

Lise J Estcourt | Simon J Stanworth | Sally Hopewell | Carolyn Doree | Marialena Trivella | Edwin Massey

- Cochrane review of therapeutic granulocyte transfusions 2016
- 10 trials, 587 participants, 1975 to 2015
- Quality of evidence low to very low
- No difference in 30 day mortality, no difference in resolution of infection
- Insufficient evidence to report on differences in adverse events

- Similar in prophylaxis, with some suggestion of benefit for higher doses

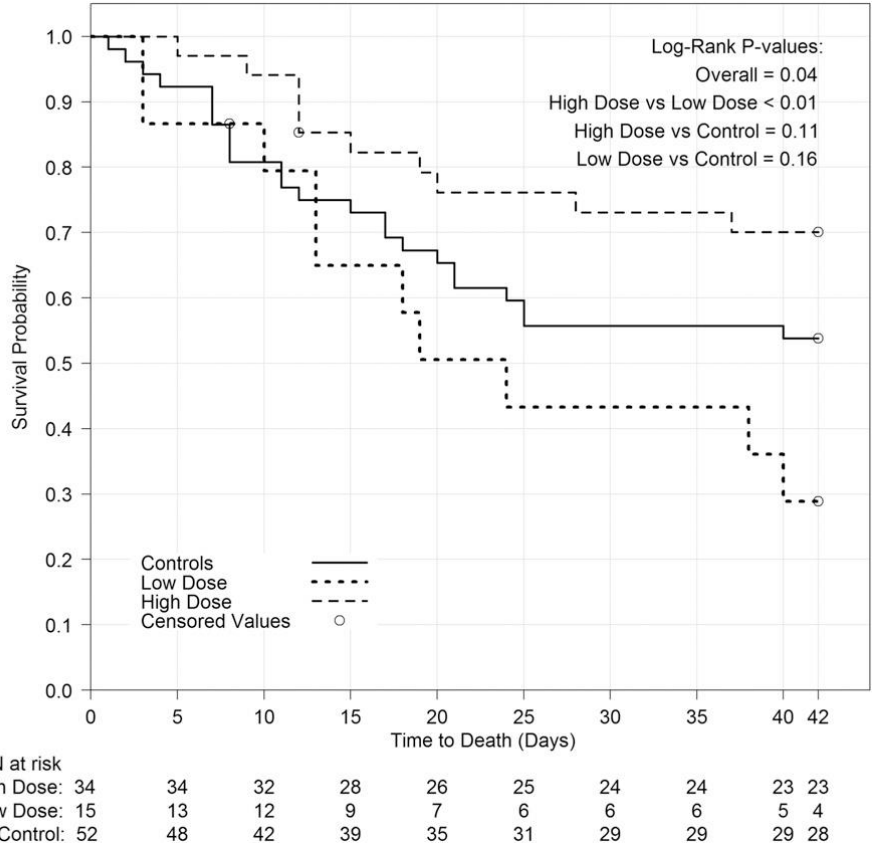
The RING trial

(Resolving Infections in Neutropenia with Granulocytes)

- Price et al., 2015 *Blood*
- RCT, open label, phase 3
- Standard antimicrobial therapy +/- apheresis granulocytes (G-CSF/Dex)
- Daily transfusions up to 42 days, neutrophil recovery, resolution of the infection or life threatening toxicity
- Primary endpoint: survival and resolution of infection at 42 days
- Calculated sample size: 236 patients

RING study: results

- 114 subjects randomised
- Success rates and mortality at 42 days similar in both groups
- No association between the average post-transfusion neutrophil count and the primary outcome
- Post hoc analysis to evaluate effect of dose: $\geq 0.6 \times 10^9$ vs. $< 0.6 \times 10^9$ granulocytes/kg
- ??higher doses associated with better outcomes



Challenges for randomised trials

- RING study challenges
  - Believers vs. non-believers
  - Difficult to recruit donors
  - Lower mortality than anticipated in control arm
  - Intervention ?too early

- Unlikely that future RCT will be funded

Despite this NHSBT issue granulocytes to 8.6 new patients per month

Why registries?

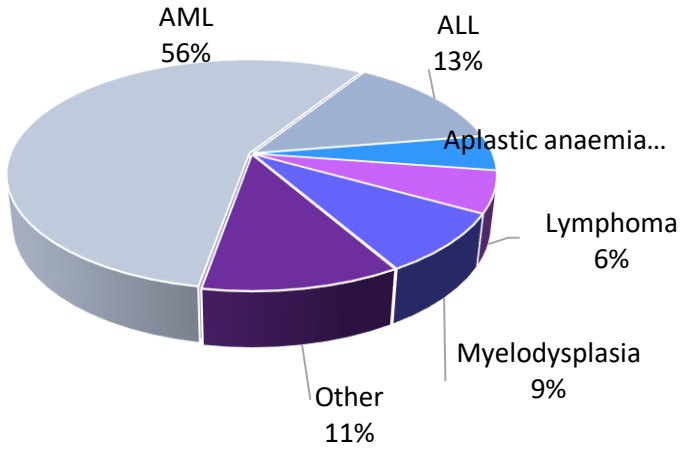
- "An organised system for the collection, storage, retrieval, analysis, and dissemination of information"
- *Detailed information* at patient, disease, and therapeutic intervention levels
- *"Real-world"* information, patients are not selected or excluded based on pre-stipulated protocols
- *Low frequency diseases* for which clinical trials would not be a feasible

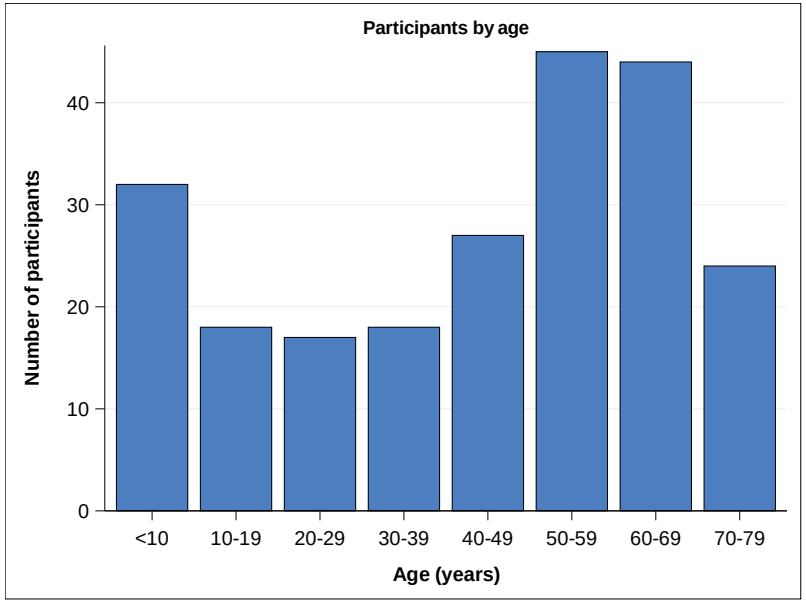
Pr GrES

859 transfusions to 246 patients over 2.5 years

Who needs granulocyte transfusions? Emerging findings from a national registry

Disease

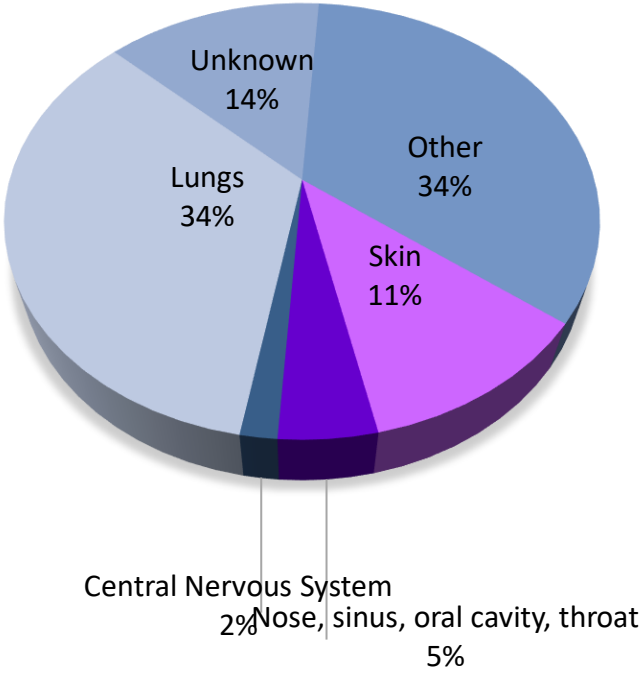




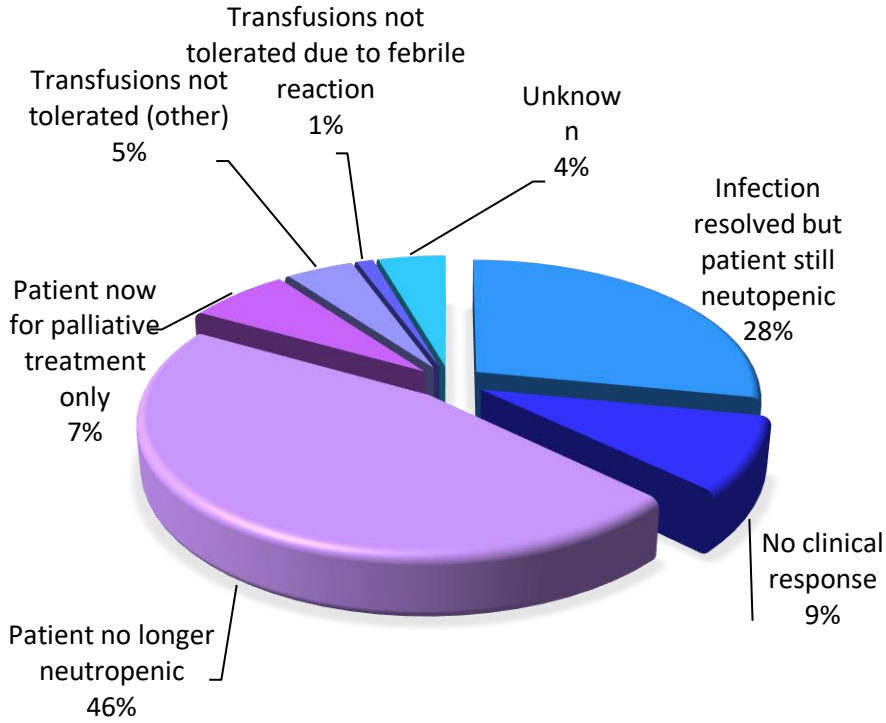
30% undergoing bone marrow transplant

Mean age 43 years
20% under 16 years

Source of infection



Reason for stopping infusions



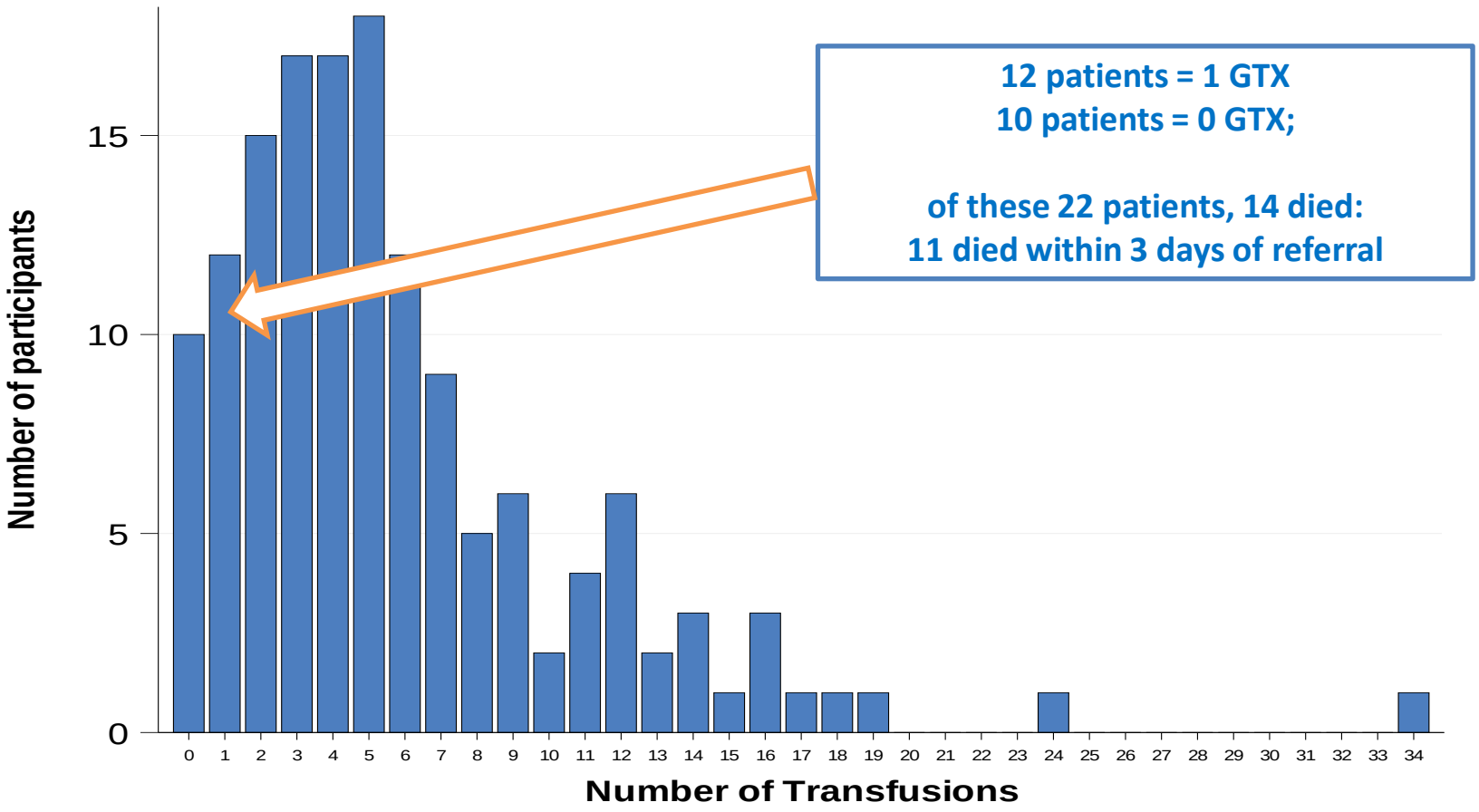
Dose of transfusions

Median 5.0 transfusions per episode

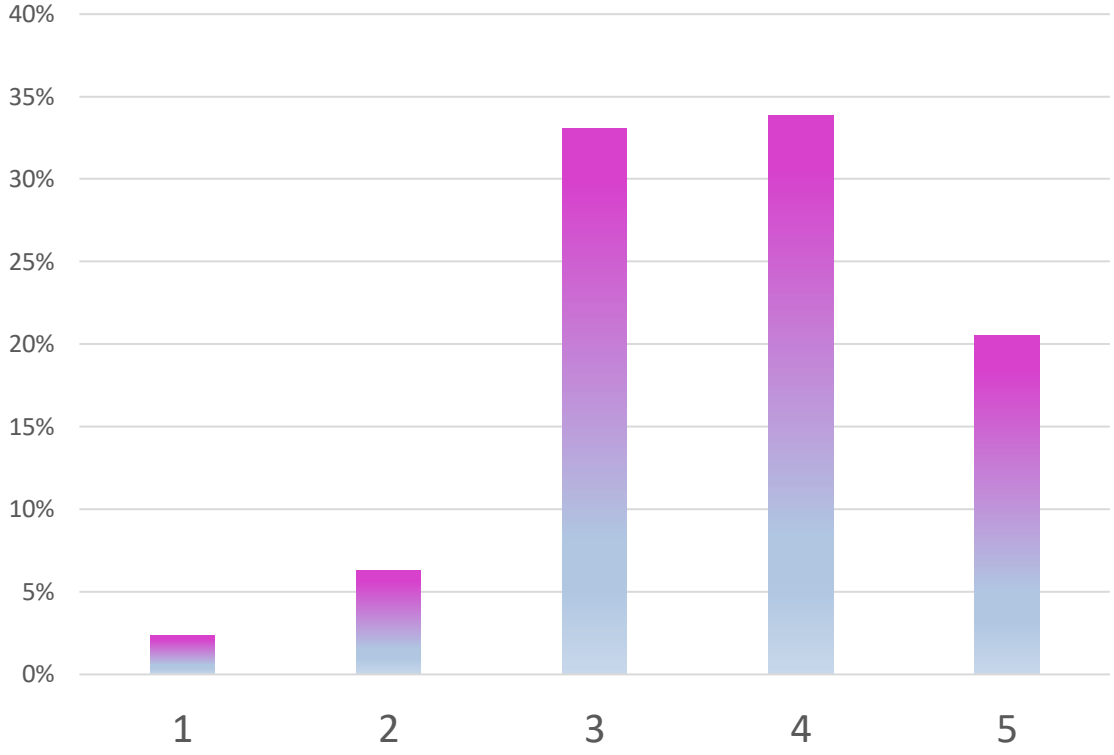
- one per 2.3 days
- median dose
  - 0.24 $x10^9$/kg overall
  - 0.98 $x10^9$/kg in children

Therapeutic dose unknown but considered to be in the region of
0.5-1.0 $x10^9$/kg
i.e. for a 70kg patient, 3.5-7 $x10^{10}$

Number of transfusions given



Clinician-reported outcomes



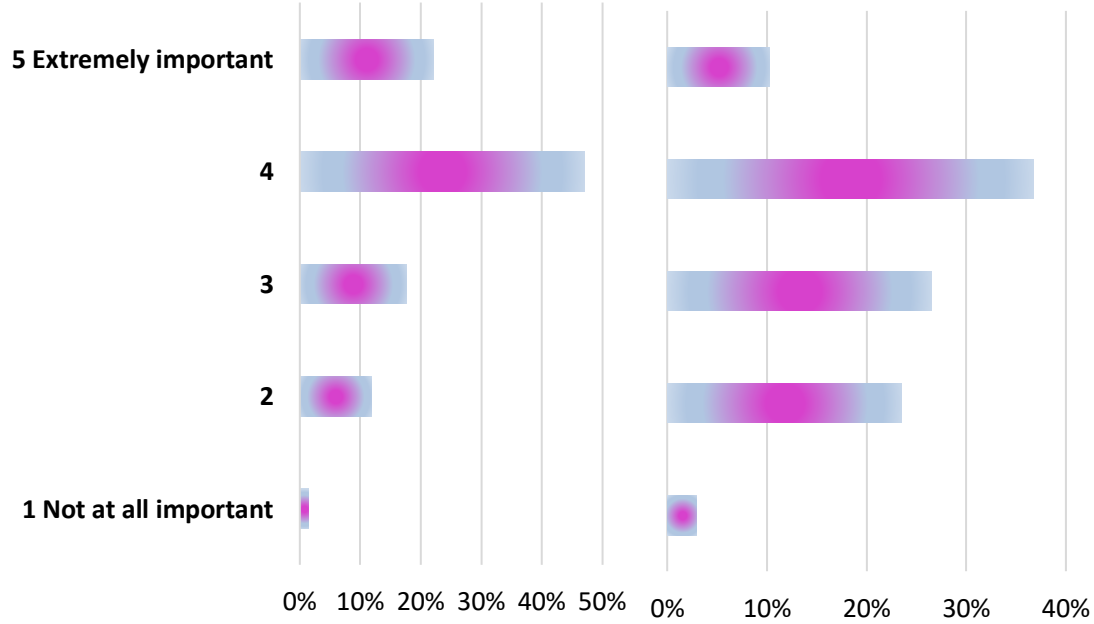
worsened outcome

improved outcome

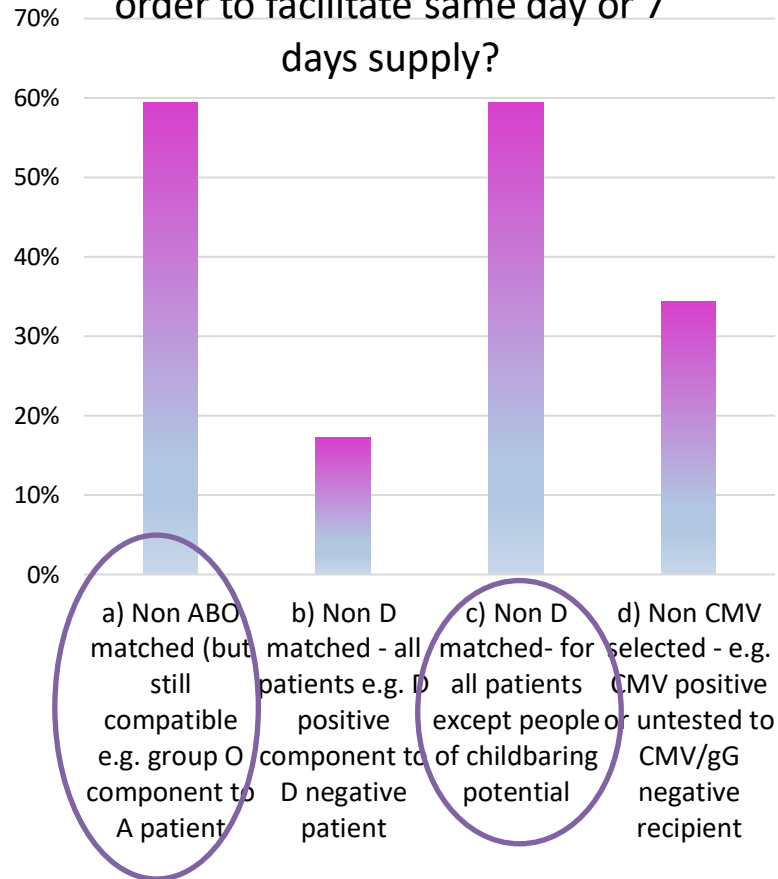
2020 Clinician Survey

On a scale of 1 to 5, how important for your patients is it for granulocytes to be available 7 days a week?

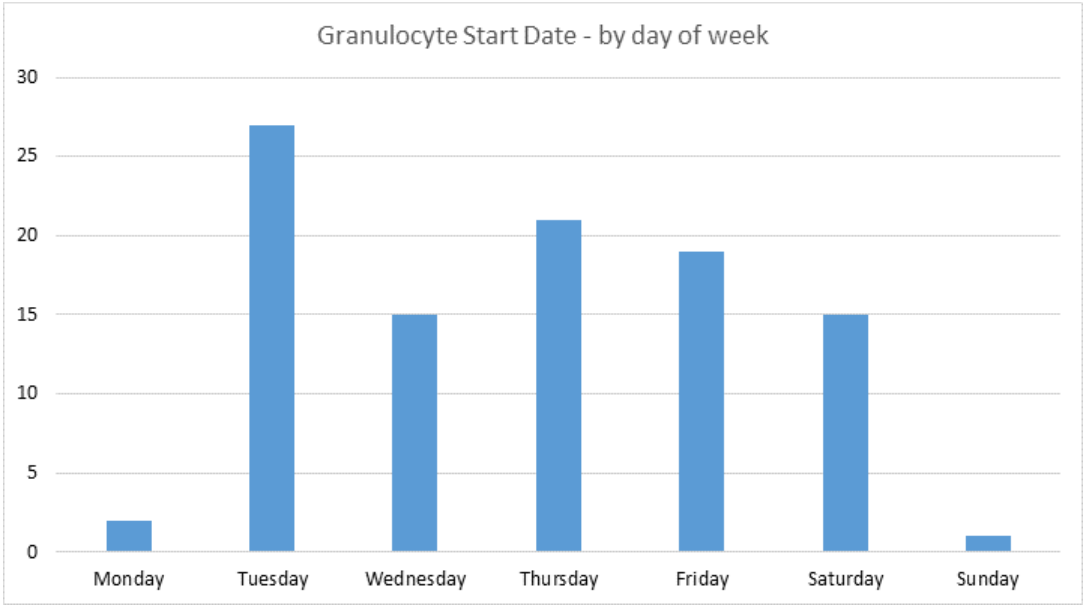
On a scale of 1 to 5, how important for your patient is it for granulocytes to be available on the same day you request them?



Which of the following concessions would you accept in order to facilitate same day or 7 days supply?



ProGrES – day of first transfusion



(First 100 patients)

PrOGrES

- Continue to collect national data – THANK YOU
- Regular discussion with NHSBT re provision
  - Now 6 day granulocytes
- International collaboration through BEST Collaborative
- Collaboration with statisticians at London School of Hygiene and Tropical Medicine re novel techniques
- ??randomisation within the registry

Back to the case

- Granulocytes given for secondary prophylaxis throughout transplant Tues-Sat
- Increments ~0.1 $x10^9/L$
- Many complications relating to transplant but nil additional infections
- Recovered counts after 3 weeks
- Ongoing complications from transplant

Summary

- Granulocytes are available
- Pooled component, short expiry
- Data are limited but studies ongoing with a goal of demonstrating whether there is benefit, or not
- Discuss if you have a patient you think may benefit
  - or if there are technical questions!
- Thank you for contributing data
- **Ask for what you want, not what you think we can provide**

Thank you

Trials team UK

Simon Stanworth

Charlotte Brierley

Emma Laing

Ana Mora

Chloe Fitzpatrick-Creamer

Eleanor Curnow

Joseph Parsons

Siobhan Martin

Suzy Morton (CI)

Components

Rebecca Cardigan

Edwin Massey

Kay Harding

Registry team BEST

Suzy Morton

Monica Pagano

Alan Tinmouth

Simon Stanworth

cureleukaemia
the blood cancer charity

Queen Elizabeth Hospital Birmingham Charity

NHS Blood and Transplant

Patient facing NHSBT consultants - without whom we would have no patients

All the hospital teams who have contributed data

PrGrES