Welcome

- Mute your microphone To ensure no disruptions
- Turn off your video This could affect your connection to the meeting
- If you have a question, when prompted please "Raise your hand" or write in the conversation
- This event will be recorded and can be used as an educational resource

The RTC Is Delighted to Present our "First West Midlands Virtual Conference"



DR SUZY MORTON CONSULTANT IN HAEMATOLOGY & TRANSFUSION MEDICINE (NHSBT/UHB) 12.00-12.30 - GRANULOCYTES

DR LORNA CAIN HAEMATOLOGY REGISTRAR (UHBFT) 12.30-13.00 - MSBOS REGIONAL SURVEY

TUE 03 NOV 2020



Dr Suzy Morton Consultant Haematologist



Suzy Morton Consultant haematologist NHSBT and University Hospitals Birmingham





Case presentation

- 55yo with AML
 - 2 x CPX then relapsed \rightarrow 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

ISBT Portfolio of Blood Components	and Guidance for their Clinical Use
This Specification replaces SPN223/9	Copy Number

Dosing and provision

- 10 donations; 0.9-1 x 10¹⁰ neutrophils
- Dose
 - 1-2 bags or 10-20ml/kg for children
 - Therapeutic dose unknown but considered to be in the region of
 - 0.5-1.0 x10⁹/kg
 - i.e. for a 70kg patient, 3.5-7 x10¹⁰
- Availability Tues-Sat
 - 4x O pos on Mondays, since Sept 2020

Buffy coats also sometimes available over weekends

Apheresis granulocytes no longer available



What are the indications?

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ightarrow {f C}$ (f hospital.blood.co.uk/clinical-guidelines/nhsbt-clinical-guidelines/

Apps 🔞 Remote Access 🕒 (503) Baby Shark D...

Home / Clinical guidelines / NHSBT clinical guidelines

NHSBT clinical guidelines

Red cell transfusion and red cell immunohaematology

- 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 10⁹/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>0.5x10⁹/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.

ody therapies - for hospital transfusion laboratories, transfusion sams: <u>essential information</u> nt red cell transfusion and situations when serological compatibility cannot be

in NHSBT <u>(INF178/4)</u> 🖶

alloantibodies and the supply of blood for transfusion <u>(SPN214/4)</u> and recipients of ABO / Rh mismatched stem cell transplants <u>(SPN215/2)</u> for transfusion dependent patients (<u>INF150/5.1</u> and) of suspected reactions to IgA <u>(INF486/1.5)</u> and

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 🗗



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: ≥ 0.6x10⁹ vs. < 0.6x10⁹ 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



859 transfusions to 246 patients over 2.5 years

Who needs granulocyte transfusions? Emerging findings from a national registry



30% undergoing bone marrow transplant



Mean age 43 years 20% under 16 years

Reason for stopping infusions

Source of infection





Number of transfusions given



Source and dose of transfusions

Median 5.0 transfusions per episode

- one per 2.3 days
- median dose
 - 0.24 x10⁹/kg overall
 - 0.98 x10⁹/kg in children

12% GTX from buffy coats (provided on Sundays and Mondays)

Therapeutic dose unknown but considered to be in the region of 0.5-1.0 x10⁹/kg i.e. for a 70kg patient, 3.5-7 x10¹⁰

Clinician-reported outcomes

40%



ProGrES – day of first transfusion



(First 100 patients)

2020 Clinician Survey

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



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





- Continue to collect national data THANK YOU
- Regular discussion with NHSBT re provision
 - Now 6 day granulocytes
- International collaboration through
- 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 x10⁹/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

Trials team UK

Simon Stanworth

Charlotte Brierley

Emma Laing

Ana Mora

Chloe Fitzpatrick-Creamer

Pr- GrES

Eleanor Curnow

Joseph Parsons

Siobhan Martin

Suzy Morton (CI)







<u>Components</u> Rebecca Cardigan Edwin Massey Kay Harding

Registry team BEST Suzy Morton Monica Pagano Alan Tinmouth Simon Stanworth

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

All the hospital teams who have contributed data