CMV testing of blood donors: are there any unresolved issues?

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September 2017

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CMV and transfusion

- Background
- CMV transmissions in alloSCT patients
- UK survey of current practice
- CMV serology in transfused patients
- The future

Cytomegalovirus and transfusion

- Beta herpes virus (HHV5)
- Lies latent in monocytes
  - Potential for transmission
- Major cause of morbidity and mortality among SCT recipients
- Historically, CMV-negative components for CMV naïve SCT recipients
- Series of studies in late 1990s showing equivalence of use of CMV-negative donors versus leucocyte reduction
  - Leucocyte-reduction methods
  - CMV detection methods
- CMV-negative components are not completely “safe”
  - ?relevance of window period

Advantages of CMV-unselected components

“Leucocyte-reduction is considered equivalent in reducing risk of transfusion-transmitted CMV” (SaBTO, 2012)

- Additional cost of testing
- Reduced inventories
- Reduced *ad hoc* deliveries
- Emergency availability

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Transfusion in CMV seronegative T-depleted allogeneic stem cell transplant recipients with CMV-unselected blood components results in zero CMV transmissions in the era of universal leukocyte reduction: a UK dual centre experience

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- OUH + UHB from change in transfusion policy to CMV-unselected components
- 77 neg/neg transplants (59 T depleted) Day 0 to end of study
  - CMV PCR results
  - Transfusions given
- 1 patient excluded due to false negative CMV IgG result

Patient demographics

Demographics	n total = 76 patients	%
Centre		
OUH	54	71.1
UHB	22	28.9
Sex		
Male	46	60.5
Female	30	39.5
Mean age (range)	49.0 years (17-70 years)	
Follow-up		
Median follow-up (range)	22 months (3-46 months)	
Alive at follow-up	56	73.7
Alive at D+100	70	92.1
Diagnosis		
Acute myeloid leukaemia	20	26.3
Acute lymphoblastic leukaemia	7	9.2
Myelodysplasia	8	10.5
Chronic myeloid leukaemia	5	6.6
Myeloproliferative disorder	5	6.6
Chronic lymphoid leukaemia	3	3.9
Non-Hodgkin lymphoma	12	15.8
Hodgkin lymphoma	8	10.5
Waldenstrom's macroglobulinaemia	2	2.6
Multiple myeloma	2	2.6
Aplastic anaemia	3	3.9
Other	1	1.3

Demographics	n total = 76 patients	%
Donor type		
Sibling donor	23	30.3
Unrelated donor	53	69.7
Stem cell source		
Peripheral blood stem cells	73	96.1
Bone marrow	3	3.9
Conditioning regime		
Myeloablative conditioning	13	17.1
Reduced intensity conditioning	63	82.9
T cell depletion		
T deplete	59	76.6
Alemtuzumab	48	81.4
Anti-thymocyte globulin	11	18.6
T replete	17	22.3
CMV serostatus		
Recipient CMV seronegative	76	100.0
Donor CMV seronegative	76	100.0

Transfusions

	All patients (n=76) D0-D100			All patients (n=76) Total study period			T-deplete patients (n=59) Total study period		
	Total	**Median**	**Range**	**Total**	**Median**	**Range**	**Total**	**Median**	**Range**
Red cells	503	4	0-38	819	6	0-73	702	7	0-73
Platelets	423	3	0-54	623	3	0-54	535	3	0-54
Pooled	102	0	0-12	140	1	0-13	116	0	0-13
Apheresis	321	2	0-48	483	3	0-48	419	3	0-48
Total components	**926**	**7**	**0-92**	**1442**	**8**	**0-92**	**1237**	**8**	**0-92**
Total donor exposure	**1232**	**8**	**0-110**	**1862**	**10.5**	**0-122**	**1585**	**10**	**0-122**

- No CMV transmissions
  - 2 single positive PCR results
- No CMV disease

Current data

Author	Population	Transmissions CMV-unselected	Transmissions CMV-negative
Wu et al., 2010	CMV seronegative multiply transfused patients; predominantly haemonc	6.5% (3/46)	NA
Thiele et al., 2011	Allogeneic SCT CMV neg/neg	0% (0/23)	NA
Kekre et al., 2013	Allogeneic SCT CMV neg/neg	1.3% (1/77)	3.4% (3/89)
Nash et al., 2012	Allogeneic SCT CMV neg/neg	0% (0/46)	NA
Hall et al., 2014	Allogeneic SCT CMV neg recipients with neg or pos donor	0% (0/24)§	0% (0/24)
Hall et al., 2015	Allogeneic SCT CMV neg/neg	0% (0/76)§	NA
Evans et al., 2016	Allogeneic SCT CMV neg/neg	14.0% (6/43)*	1.8% (1/56)
Evans et al., 2017	Allogeneic SCT CMV neg/neg	8% (4/50)**	NA
Gamlath et al., 2017	Allogeneic SCT CMV neg/neg	1.4% (1/72)***	NA

§18 patients represented in both studies
*5 of whom had single PCR positive
**1 patient had 1 single PCR positive, 2 had false negative CMV IgG
*** patient had received apheresis granulocytes from CMV pos donor

Survey of UK transplant centres

Transfusion Medicine | ORIGINAL ARTICLE

Provision of cellular blood components to CMV-seronegative patients undergoing allogeneic stem cell transplantation in the UK: survey of UK transplant centres

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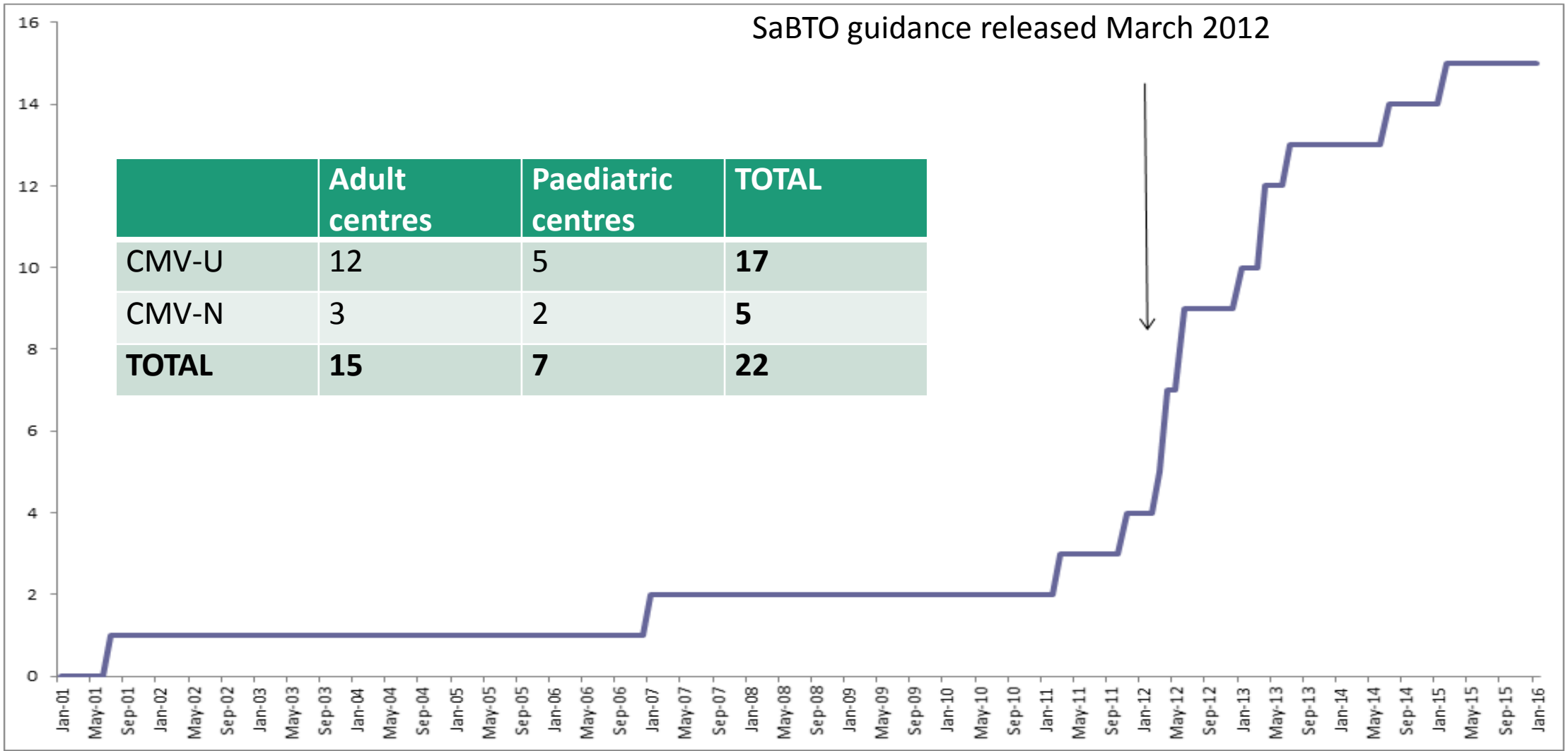
Received 16 May 2016; accepted for publication 16 August 2017

Switch to CMV-U components

SaBTO guidance released March 2012

	Adult centres	Paediatric centres	TOTAL
CMV-U	12	5	**17**
CMV-N	3	2	**5**
TOTAL	**15**	**7**	**22**



5 adult and 2 paediatric centres continue to transfuse CMV-N

- The risk of CMV transmission by blood transfusion and its associated morbidity was considered to be too high despite SaBTO recommendation
- *"It was also noted that SaBTO continues to recommend the use of CMV NEG components for pregnant women and intrauterine transfusions suggesting acknowledgement of prevailing residual risk in unscreened leucodepleted components."*
- Concern regarding the risk of causing ambiguous CMV serostatus in seronegative potential transplant recipients due to passive antibody transfer from CMV seropositive blood donors, leading to erroneous donor/recipient CMV matching at transplant

Transfusion-transmitted CMV

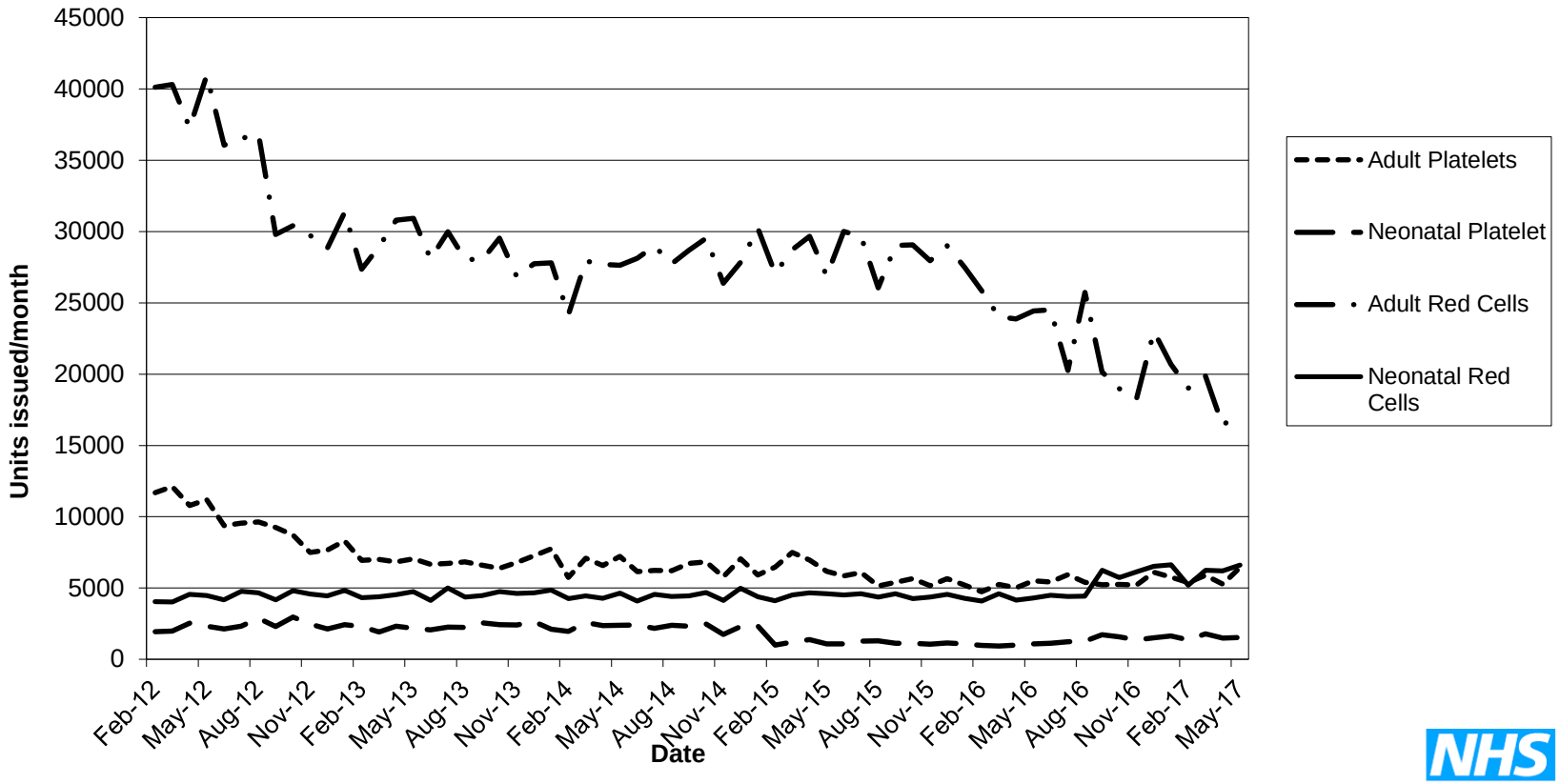
- 1 report among 17 centres
- Adult with AML in 1st CR
  - T depletion with Alemtuzumab
  - CMV PCR pos at D+5; nil historical
  - CMV IgG negative prior
    - Positive on repeat 16 months later
    - Multiply transfused
      - ***Including granulocytes from a CMV untested donor***
  - Treated with foscarnet
    - No CMV disease or treatment complication
  - Alive at 17 months FU
  - Not reported to SHOT

Other issues

- 4 centres failed to identify need to provide granulocytes from CMV-negative donors
- Requesting of CMV-negative blood has not decreased as much as would be expected

CMV-negative issues by NHS Blood and Transplant 2012-2017

Courtesy Michael Watson, NHSBT



Passive transfer of CMV IgG

- Recipient CMV status established on serology
- CMV-unselected products contain CMV IgG → false positive
- Is this a real problem in transplant units?

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Transfusion of CMV-unselected blood components may lead to inappropriate donor selection for patients subsequently undergoing allogeneic stem cell transplant

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Received 13 June 2015; accepted for publication 15 November 2015

Study design

- Retrospective analysis
- Acute leukaemia or myelodysplasia
- Diagnosed at OUH since change in transfusion policy and undergoing alloSCT prior to January 2015
  - Recipient/donor serostatus as recorded on transplant database
  - CMV IgG results
  - Transfusion details (products, no. CMV-negative units)
  - CMV reactivations/transmissions

Patient characteristics

	n	Range or %
Age (mean)	49 years	18-65
Sex		
Male	16	51.6
Female	15	48.3
Diagnosis		
Acute myeloid leukaemia	20	64.5
Acute lymphoblastic leukaemia	6	19.4
Myelodysplasia	5	16.1
Donor type		
Sibling	12	38.7
Unrelated donor	18	58.1
Cord blood	1	2.3
CMV recipient/donor status recorded		
Neg/Neg	9/30	30.0
Pos/Neg	8/30	26.7
Neg/Pos	3/30	10.0
Pos/Pos	10/30	33.3
Cord recipient	1 (recipient seropositive)	n/a
CMV IgG checked prior the administration of any transfusion	20	64.5
Concordant serostatus throughout	21/29	72.4

CMV testing - definitions

Time point	Definition
Historical	>6/12 prior to diagnosis
Baseline	1st CMV IgG done, unless >6/12 prior to diagnosis
Intervening	Any result between baseline and pretransplant
Pre-transplant	Done at pre-transplant assessment (usually 4-6/52 prior to D0)
Subsequent	Any tests done after D0

Discordant CMV IgG results:
CMV tests undertaken

Case #	BMT record		Historical CMV IgG	Transfusion	Baseline CMV IgG	Transfusion	Intervening CMV IgG	Transfusion	Pre transplant CMV IgG	Transfusion	Subsequent CMV IgG
	R	D									
2	-	-	n/a		Neg	24 (0)	Equiv		Neg		n/a
12	+	-	n/a		Neg		n/a	29 (0)	Pos		Neg
13	+	-	n/a		Neg	3* (0)	Equiv	61 (6)	Pos		n/a
14	+	-	n/a		Neg		n/a	21 (2)	Pos		n/a
15	-	-	n/a	3* (0)	Equiv		Neg		Neg	13* (5)	Pos
20	+	-	n/a		Neg		Neg	110* (27)	Pos		Neg
21	+	+	Neg		Neg	25 (4)	Pos	0 (0)	Equiv		n/a
27	+	-	n/a		Neg		Neg	15 (1)	Pos		Neg

* = transfused within preceding 24 hours of the test

() = known CMV-negative exposures

Discordant CMV IgG results:
Donor exposures between tests

Case #	BMT record		Historical CMV IgG	Transfusion	Baseline CMV IgG	Transfusion	Intervening CMV IgG	Transfusion	Pre transplant CMV IgG	Transfusion	Subsequent CMV IgG
	R	D									
2	-	-	n/a		Neg	24 (0)	Equiv		Neg		n/a
12	+	-	n/a		Neg		n/a	29 (0)	Pos		Neg
13	+	-	n/a		Neg	3* (0)	Equiv	61 (6)	Pos		n/a
14	+	-	n/a		Neg		n/a	21 (2)	Pos		n/a
15	-	-	n/a	3* (0)	Equiv		Neg		Neg	13* (5)	Pos
20	+	-	n/a		Neg		Neg	110* (27)	Pos		Neg
21	+	+	Neg		Neg	25 (4)	Pos	0 (0)	Equiv		n/a
27	+	-	n/a		Neg		Neg	15 (1)	Pos		Neg

* = transfused within preceding 24 hours of the test

() = known CMV-negative exposures

Causes of discordant results

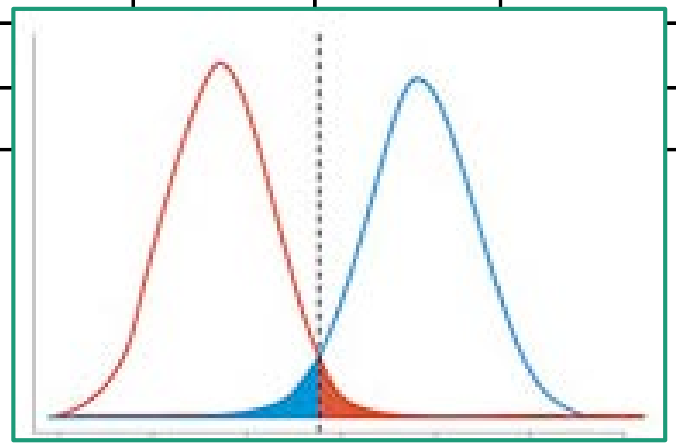
- **Primary infection** (via direct contact with an infected individual or from blood transfusion) in a previously seronegative patient
- **False positive** (due to transfusion/passive transfer of antibody or failure of testing) in a seronegative patient
- **False negative** (due to hypogammaglobulinaemia or failure of testing) in a previously infected patient

Discordant CMV IgG results:
All had negative baseline results except one

Case #	BMT record		Historical CMV IgG	Transfusion	Baseline CMV IgG	Transfusion	Intervening CMV IgG	Transfusion	Pre transplant CMV IgG	Transfusion	Subsequent CMV IgG
	R	D									
2	-	-	n/a		Neg	24 (0)	Equiv		Neg		n/a
12	+	-	n/a		Neg		n/a	29 (0)	Pos		Neg
13	+	-	n/a		Neg	3* (0)	Equiv	61 (6)	Pos		n/a
14	+	-	n/a		Neg		n/a	21 (2)	Pos		n/a
15	-	-	n/a	3* (0)	Equiv		Neg		Neg	13* (5)	Pos
20	+	-	n/a		Neg		Neg	110* (27)	Pos		Neg
21	+	+	Neg		Neg	25 (4)	Pos	0 (0)	Equiv		n/a
27	+	-	n/a		Neg		Neg	15 (1)	Pos		Neg

Discordant CMV IgG results:
Equivocal results

Case #	BMT record R	BMT record D	Historical CMV IgG	Transfusion	Baseline CMV IgG	Transfusion	Intervening CMV IgG	Transfusion	Pre transplant CMV IgG	Transfusion	Subsequent CMV IgG
2	-	-	n/a		Neg	24 (0)	Equiv		Neg		n/a
12	+	-	n/a		Neg		n/a	29 (0)	Pos		Neg
13	+	-	n/a		Neg	3* (0)	Equiv	61 (6)	Pos		n/a
14	+	-	n/a		Neg		n/a	21 (2)	Pos		n/a
15	-	-	n/a	3* (0)	Equiv		Neg		Neg	13* (5)	Pos
20	+	-	n/a		Neg		Neg	110* (27)	Pos		Neg
21	+	+	Neg					0 (0)	Equiv		n/a
27	+	-	n/a					15 (1)	Pos		Neg



Discordant CMV IgG results:
Possible incorrect designation on BMT database

Case #	BMT record		Historical CMV IgG	Transfusion	Baseline CMV IgG	Transfusion	Intervening CMV IgG	Transfusion	Pre transplant CMV IgG	Transfusion	Subsequent CMV IgG
	R	D									
2	-	-	n/a		Neg	24 (0)	Equiv		Neg		n/a
12	+	-	n/a		Neg		n/a	29 (0)	Pos		Neg
13	+	-	n/a		Neg	3* (0)	Equiv	61 (6)	Pos		n/a
14	+	-	n/a		Neg		n/a	21 (2)	Pos		n/a
15	-	-	n/a	3* (0)	Equiv		Neg		Neg	13* (5)	Pos
20	+	-	n/a		Neg		Neg	110* (27)	Pos		Neg
21	+	+	Neg		Neg	25 (4)	Pos	0 (0)	Equiv		n/a
27	+	-	n/a		Neg		Neg	15 (1)	Pos		Neg

Discordant CMV IgG results:

An apparently positive recipient is matched with a positive donor

Case #	BMT record		Historical CMV IgG	Transfusion	Baseline CMV IgG	Transfusion	Intervening CMV IgG	Transfusion	Pre transplant CMV IgG	Transfusion	Subsequent CMV IgG
	R	D									
2	-	-	n/a		Neg	24 (0)	Equiv		Neg		n/a
12	+	-	n/a		Neg		n/a	29 (0)	Pos		Neg
13	+	-	n/a		Neg	3* (0)	Equiv	61 (6)	Pos		n/a
14	+	-	n/a		Neg		n/a	21 (2)	Pos		n/a
15	-	-	n/a	3* (0)	Equiv		Neg		Neg	13* (5)	Pos
20	+	-	n/a		Neg		Neg	110* (27)	Pos		Neg
21	+	+	Neg		Neg	25 (4)	Pos	0 (0)	Equiv		n/a
27	+	-	n/a		Neg		Neg	15 (1)	Pos		Neg

Summary of findings

- 8 cases of likely passive acquisition of CMV IgG via transfusion
- 75% recorded as seropositive on transplant database although no clear instances of donor selection based on these results
- More than a third transfused prior to baseline CMV IgG
- Many examples of samples being sent in close proximity to transfusion

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;

- 137 patients
- Of 78 seronegative patients, 17.9% later tested positive
- Significantly more platelet transfusions
  - Median 13 vs 0; $p<0.001$
- Trend towards more red cell transfusions
  - Median 8 vs 0; $p=0.087$
- None subsequently showed viraemia

bjh guideline

Management of cytomegalovirus infection in haemopoietic stem cell transplantation

Vincent Emery,[1] Mark Zuckerman,[2] Graham Jackson,[3] Celia Aitken,[4] Husam Osman,[5] Anthony Pagliuca,[6] Mike Potter,[7] Karl Peggs,[8] and Andrew Clark[9] on behalf of the British Committee for Standards in Haematology, the British Society of Blood and Marrow Transplantation and the UK Virology Network

- All Potential HSCT recipients should be tested for the presence of CMV IgG antibody at diagnosis (Grade 1C)
- Donors or recipients who are initially found to be CMV IgG-negative should be retested pre-transplant to exclude primary CMV infection (Grade 1C)
- Apparent CMV seroconversion in potential allograft recipients who have received unscreened blood products should be actively investigated to exclude passively acquired antibody (Grade 1C)

Planned BSH guideline update, 2017

- All potential HSCT recipients should
  - be tested for the presence of CMV IgG antibody at diagnosis, before transfusion has occurred
  - have CMV IgG tested at least twice prior to transplantation
- Any change in serostatus should be confirmed with repeat testing in the first instance.
  - Pre-analytical, analytical and post analytic errors (particularly transcription errors) must be considered.
- Where CMV IgG testing cannot be undertaken prior to transfusion
  - testing of stored, pretransfusion samples must be undertaken where possible. This may include testing samples taken into plain tubes, EDTA or SST where assays have been validated and on the advice of local virologists.
  - positive results should be confirmed with repeat testing undertaken with as long a time from transfusion as practicably possible
- Where there is doubt as to whether CMV IgG is due to infection or passive acquisition, the following tests should be performed:
  - Repeat CMV IgG
  - CMV IgM
  - CMV PCR
  - CMV IgG avidity testing and serial monitoring of semi-quantitative CMV IgG may provide additional information but such results must be interpreted under the guidance of virologists.
- Equivocal or borderline CMV IgG values in patients transfused with CMV-U components may indicate passive rather than immune acquisition of IgG and should prompt a repeat confirmatory test.
- Patients referred to another hospital for transplant should have details of all CMV tests included in the referral and subsequent handover documentation.
- All CMV IgG results should be interpreted in the context of transfusion of any CMV-U components, particularly following transfusion of plasma products, intravenous immunoglobulin, large volume transfusion, or where there has been a short time between transfusion and sampling for serology.
- CMV IgG status informing a donor search for allogeneic stem cell transplantation must take into account all CMV IgG results available for each patient, in the context of the transfusion history and any clinical features of infection.

Thank you