



National Transfusion Advisory Group NTAG; Guidelines for use of CMV antibody screened negative (CMV negative) cellular blood components (red cells, platelets and granulocytes) in the Irish healthcare setting. Version 01/September 2020

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Rationale and intended audience

In the absence of a National guideline for the use of CMV antibody screened negative (CMV negative) cellular blood components (components) in Ireland, there is significant evidence of variation in practice within and between Hospital levels. This has resulted in an excessive economic burden and unnecessary blood supply/inventory management challenges.

As there is evidence of demand outside of clinical indications, NTAG has developed guidelines for clinicians ordering components, laboratory staff managing requests and inventory, and Haemovigilance staff, for all hospitals in Ireland.

Glossary of Terms

Allogeneic HSCT	Transplantation of stem cells derived from a donor
Apheresis platelets	Platelet components procured from a single donor by cell separator technology
Autologous HSCT	Transplantation of stem cells derived from the patient
CMV	Cytomegalovirus
CMV negative	Cytomegalovirus antibody screened negative
HSCT	Haemopoietic stem cell transplantation
Leucodepletion	Reduction in the white cell constituent of blood components
NTAG	National Transfusion Advisory Group
PAS	Platelet additive solution
Pooled platelets	Platelet components processed from whole blood donations from 4 donors
PR	Pathogen reduction
SaBTO	Advisory committee on the Safety of Blood, Tissues and Organs (UK)
Seronegative	no antibody detected
Seropositive	antibody detected
SHOT	Serious Hazards of Transfusion (UK Haemovigilance system)
TT-CMV	Transfusion transmitted cytomegalovirus infection

Key recommendations for patient cohorts

Allogeneic HSCT or autologous HSCT	CMV negative components are not required .Patients should receive leucodepleted components. There is no evidence that CMV negative components add beneficially to this. (Practice point : arrangements should be put in place to CMV screen patients at diagnosis)
Neonatal population.	CMV negative leucodepleted components should be transfused to neonates up to 40 weeks corrected (or postmenstrual) age + 28 days. There is insufficient evidence to support a change in the practice for this vulnerable cohort.
Pregnant women	CMV negative leucodepleted components should be selected for pregnant women. This is not required during labour, delivery or thereafter. In emergency, where it is not possible to supply CMV negative components, leucodepleted components of unknown CMV antibody status may be used.
Foetuses	CMV negative, leucodepleted components should be selected for intra-uterine transfusion.
Patients with HIV infection	CMV negative components are not required. Patients who have HIV infection should receive leucodepleted components. There is no evidence that CMV screening adds beneficially to this process.
Solid organ transplant patients	CMV negative components are not required. Patients should receive leucodepleted components. There is no evidence that CMV screening adds beneficially to this process.
Patients with immunodeficiency	CMV negative components are not required. Patients should receive leucodepleted components. There is no evidence that CMV screening adds beneficially to this process.
Patients undergoing management for oncological disorders	CMV negative components are not required. Patients should receive leucodepleted components. There is no evidence that CMV screening adds beneficially to this process.
Patients receiving granulocyte components	CMV negative Granulocyte components must be considered for CMV seronegative recipients.

Methodology

This is the first national guideline on the use of CMV negative components in Ireland. This guideline was compiled through a working group of the National Transfusion Advisory Group NTAG (see membership Appendix 1).

Literature Review details

A search of published literature was undertaken using PubMed for relevant publications over the last 50 years. Previous guidelines were critically reviewed, including those by SaBTO (2012), Mainou (2016) and Harmon (2017). Mainou's review of the Cochrane database (1980-2015) showed that 10 comparison group studies, out of 457 studies, were eligible for meta-analysis. High quality evidence, in particular clinical trials, is lacking and a large scale randomised prospective trial is unlikely to be undertaken. Information from other relevant international guidelines is also considered. International experience and expert opinion from clinicians and transfusion practitioners within the various relevant practice areas in Ireland and major centres abroad was sought. This included interrogation of the

Haemovigilance database 'Serious Hazards of Transfusion (SHOT)' UK. A position paper was then developed.

Review Process

This guideline, together with the supporting position paper, was considered by the Irish Haematology Society (IHS) Transfusion Special Interest Group (SIG), the Academy of Clinical Science and Laboratory Medicine (ACSLM) NATG Scientific Committee, the National Haemovigilance SIG. The Guideline was submitted for review to NTAG with its specialist relevant constituent members, including Patient Representatives (see membership Appendix 2). The revised document was made available to the IHS and ACSLM. The final draft was agreed by the NTAG working group prior to submission for authorisation to the Chair of the Working Group, Clinical Lead Advisor for Transfusion, Medical & Scientific Director Irish Blood Transfusion service (IBTS) and Chair NTAG, before submission to the HSE. The IBTS and the National Haemovigilance Office (NHO) have been part of the review process. The NHO will undertake any necessary changes in relation to transfusion- associated serious adverse event (SAE) reporting to the national Haemovigilance system.

Background

Cytomegalovirus (CMV) is a ubiquitous herpes virus which gives rise to chronic, persistent but usually asymptomatic infection in the majority of adults worldwide. It occasionally presents as a mononucleosis-like syndrome in the normal immunocompetent host. Following primary infection, seroconversion occurs and CMV specific IgG persists lifelong along with cellular immune responses. The length of the 'window period' when a person with primary infection may be viraemic and before they develop antibodies is said to last up to 6-8 weeks. However the course of the viraemia and its infectivity has not been extensively studied. In developed countries, congenital CMV infection occurs in 0.3% to 2.4% of all live births (Lazzarotto 2008).

Transfusion transmitted infections have been well chronicled over the past century. Transfusion transmitted CMV (TT-CMV) infection was first described in 1966 by Kääriäinen and confirmed using molecular evidence by Tolpin and colleagues in 1985. It was recognised that this can give rise to primary infection in CMV naïve recipients or to reinfection in previously infected individuals. These studies prompted the American Association of Blood Banks (AABB) to produce guidelines to address TT-CMV risk reduction.

Donors who have been seropositive for a year rarely have detectable CMV DNA - a study of 7,303 long term seropositive donors detected only one person with plasma DNA at low concentration (<30 IU/ml) (Ziemann 2014). DNA was detected in whole blood at low concentrations (800 IU/ml or less) in about 0.2% of long term seropositive donors leading to consideration of use of leucodepleted blood components from donors seropositive more than one year, for vulnerable patient groups. However, there is little further evidence of implementation. Studies in Ireland have shown an unusually low seroprevalence from 16.4% in first time donors born in Ireland, to 22% in donors overall, a seroconversion rate of 0.77% per annum, 30% of whom had seroconverted within the previous 12 months (Personal communication O'Flaherty 2020). This contrasts with seroprevalence rates varying

from 50% to 80% of reproductive-age women in the United States (Carlson 2010), up to 80% in Europe and up to 100% in Africa and Asia (Cannon MJ 2010)

Testing for total antibody (IgG and M) has reported sensitivities of >99.5% and specificity varying from 98.1-99.3% (2012 SaBTO Report). <https://www.gov.uk/government/publications/sabto-annual-report-2012-to-2013>

Leucodepletion

Universal component leucodepletion was implemented in the UK and Ireland in 1999 (primarily as a vCJD risk reduction measure). Currently up to 70% of IBTS platelet components are procured by apheresis and the balance from pooling whole blood derived buffy coats with 90 ml male donor plasma, suspended in platelet additive solution, PAS. In process leucodepletion steps are included in the apheresis procurement process whereas pooled platelet and red cell components have pre-storage leucodepletion applied.

The European specification for leucodepletion is $< 5 \times 10^6$ white cells per platelet or red cell component in 99% of components with 95% statistical confidence, and $< 1 \times 10^6$ white cells per unit in 90% of components (EU EDQM 2020). The former (3 log depletion) is accepted as “CMV safe” (Vamvakas 2005). Removal of CMV viral load has been demonstrated following 3-4 log white cell reduction of whole blood by filtration (Lipson 2001). Equivalent CMV viral genome load reduction was demonstrated following leucodepletion of platelets by apheresis, and filtration of platelet and red cell components, as these filters are particularly efficient at removal of monocytes from whole blood (CMV latent in monocytes in carriers).

Fourth generation filters applied pre storage reliably and consistently achieve 4 log reduction and the QC data with statistical process control is available to prove this- residual leukocytes in red cell components $< 5 \times 10^6$ (>99%); 1×10^6 (>95%) and also in pooled platelet components.

Compliance with European specifications requires efficacy of leucodepletion to be monitored for each individual apheresis- procured platelet component and by a statistical process control of other components. Therefore, apheresis platelet components are universally tested in IBTS for residual leukocytes and only released when the components are within the EU EDQM specification. Filter failures are of low frequency, and when a donor's donations fail repeatedly, possibly due to cold agglutination, they are removed from this service. Pooled platelet and red cell component leucodepletion compliance has been demonstrated by the IBTS. The IBTS 2018 and 2019 QC data for component leucodepletion was considered by the working group and made available to the reviewers.

The chance of an issued component having a leucocyte count above the specification (corrected residual risk, CRR) can be calculated. This is a balance between the robustness and reliability of the leucodepletion process and the proportion of components tested.

Residual Risk of TT-CMV

A very small residual risk of CMV transmission by either CMV screened or leucodepleted blood components is noted. However, addition of CMV serology screening to leucodepletion does not appear to have added any significant advantage in the past quarter century. Risk estimates of an infectious component for the Australian population were published by Seed (2015) suggesting a residual risk of approximately 1 in 17,790,000 (95% C I 771,000,000 – 1 in 990,000) for red cell components. With leucodepleted platelet components there was a zero risk estimate (95% C I zero-1 in 1,074,000).

No reports of TT-CMV have been made to the UK Haemovigilance system 'Serious Hazards of Transfusion' – SHOT. This is notwithstanding 83 cases over a decade where seronegative components had not been provided that would have been considered clinically appropriate. A further review of 14 years of data identified 62 CMV seronegative patients transfused CMV DNA positive blood that had been leucodepleted. No case of TT-CMV was identified (Personal communication Bolton-Maggs, 2020). Goldfinger (2018) reported UT Southwestern Blood Service provided only leucodepleted products for all patient groups since 2006 without a single case report of TT-CMV.

CMV Disease Management

The guidelines of the British Transplantation Society (2015) set out recommendations for prevention and treatment of CMV diseases in the transplant setting. https://bts.org.uk/wp-content/uploads/2016/09/14_BTS_CMV_3RDE-1.pdf

SPECIFIC PATIENT GROUPS

1. Haemopoietic Stem Cell Transplant (HSCT)

Allogeneic HSCT is probably the most contentious area reviewed with major variation in practice occurring globally. Major centres in the UK and Ireland deviate from the SaBTO guideline or follow it rigidly, with no clear evidence that the patients of the latter have suffered as a consequence. Primary infection is now rare, reactivating strains are generally of recipient origin, and control is mediated by the donor immune response. It has usually been accepted that T cells from the donor are the sole source of CMV control as recipient immune effectors are ablated by the transplant process. However, patients receiving reduced intensity protocols may have CMV specific T cells contributing to immunity.

There are three issues that drive this divergence in practice:-

1. The impression that there will never be a supply issue in Ireland because of the low seropositivity rate in donors.
2. Belief that the early 1995 Bowden study which compared leucodepletion with CMV screening elicited a problem with leucodepletion.
3. Difficulty in ruling out passively acquired CMV antibody in allograft recipients transfused pre HSCT with seropositive products.

The Bowden study (1995) showed no difference between the two methodologies. However, there is an often quoted secondary analysis which showed 5 cases of CMV disease (2.4%) in the filtered arm versus none in the CMV antibody screened negative arm $p=0.03$. All five with pneumonitis died. This has been the basis for practice consideration over the last quarter of a century. However, in the two papers by Raleigh Bowden (1986 and 1995) bedside leucodepletion is applied (and often to stored blood) and equivalence with CMV antibody screened blood is inferred. Micro aggregate blood filters (20-40 micron mesh) as applied by Bowden, achieved 1-2 log reduction in leucocytes, whereas fourth generation filters applied pre storage reliably and consistently achieve 4 log reduction, and the QC data with statistical process control is available to prove compliance to this EU EDQM specification ($<5 \times 10^6$).

There is considerable concern over the issue of false positive serology results due to passively acquired antibody in allogeneic HSCT patients. Inability to await the waning of the antibody may have the detrimental effect of the donor search concentrating on positive donors. This has the consequence that one may then end up with a CMV mismatch which is believed to negatively affect transplant outcome. Specific practice issues may need to be addressed.

NTAG Recommendation: Patients undergoing allogeneic HSCT or autologous HSCT should receive leucodepleted components. There is no evidence that CMV negative components add beneficially to this and CMV negative components are not required.

Practice point

The occurrence of passively acquired antibody causing false positivity in the recipient is an issue for some transplant physicians, although the situation is usually clarified if time allows, reducing the risk of CMV 'mis-match'. **Arrangements should be put in place to CMV screen patients at diagnosis.**

2. Neonates

Within Ireland, it is likely that all neonatologists are following the SaBTO guideline, although it would be necessary to carry out a survey to confirm this fact. This will be addressed by the NTAG working group - 'Transfusion support for Fetuses, Neonates and Paediatric patients'.

As fully elaborated in the SaBTO review, CMV is the commonest cause of congenital infection in the developed world (UK = 0.3-0.4% incidence) and up to 20% of infected babies die. It causes 12% of hearing loss and 10% of cerebral palsy, along with chorioretinitis, cataract, blindness, pneumonia, necrotising enterocolitis, bile duct destruction and haemochromatosis. Congenital acquisition occurs because of both recurrent and of primary infection, and mothers are often asymptomatic during the latter. Primary infection is more likely to cause symptomatic disease in the baby and also carries a higher risk of hydrops, abortion and still-birth. Transplacental transmission during reactivated infection is much less likely than with primary infection being 1% as opposed to 40% However, the high seropositivity prevalence in Mothers in many countries means that transplacental transmission accounts for 30-50% of congenital infections and the episodes of more than one infant affected.

NTAG Recommendation: There is insufficient evidence to support a change in the practice of administering CMV negative and leucodepleted components in the neonatal vulnerable population. Neonates up to 40 weeks corrected (or postmenstrual) age + 28 days should be transfused with CMV negative components.

Practice point

Due to potential difficulties in communicating corrected gestational age with current infrastructure, CMV negative components may be selected for infants up to 6 months of age.

Rare designated components may only be available from a CMV seropositive donor, in such cases risk management should be agreed with the IBTS Haematologist.

3. Pregnancy

Within Ireland, the SaBTO guidelines are probably followed although it would be necessary to carry out a survey to confirm this.

NTAG Recommendation: Pregnant women should be transfused with CMV negative leucodepleted components during pregnancy. This is not required during labour, delivery or thereafter. In emergency, where it is not possible to supply CMV negative components, leucodepleted components of unknown CMV antibody status may be used.

Practice point

There is no requirement to select CMV negative components for standby for clinical conditions e.g. placenta previa, which are associated with risk of emergency delivery.

4. Intrauterine Transfusions (IUT)

Within Ireland, the two centres follow SaBTO guideline and require CMV negative blood components, as explained in the pregnancy section.

NTAG Recommendation: CMV negative, leucodepleted components should be selected for intra-uterine transfusion in this very vulnerable cohort.

5. HIV

Within Ireland, the SaBTO guideline is followed at St James's Hospital and they do not request CMV negative blood components. The situation elsewhere would require a survey to monitor compliance however there is no evidence that CMV serology screening is of value in this situation.

NTAG Recommendation: Patients who have HIV infection should receive leucodepleted components. There is no evidence that CMV screening adds beneficially to this process and CMV negative components are not required.

6. Solid	Organ	Transplant	Recipients
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-immunosuppressants-solid-organ-transplantation_en.pdf			

The situation with regard to solid organ transplantation is clear, both from the SaBTO guidelines (2012) and the British Transplantation Society guidelines (2015). Within Ireland, the routine practice for several years is not to request CMV screened components and thus to rely on leucodepleted components for cardiac, heart-lung and lung transplants with no reported TT-CMV. This complies with the guidelines and is to be applauded. In the same manner, there is acceptance that renal transplant patients do not require CMV screened blood components. The guidelines are followed in this respect and in the other therapeutic recommendations.

CMV negative components are still requested for liver transplant patients in Ireland (personal communication Dr J Fitzgerald 2020), if the recipient is seronegative pre transplant and then after transplant if the donor organ is also seronegative. This does not follow the SaBTO guideline. This is not the case in the large transplant centres at King's College Hospital and Addenbrooke's Hospital in the UK (personal communication Prof Antonio Pagliuca, Dr Michael Gattens 2020).

NTAG Recommendation: Solid organ transplant patients should receive leucodepleted components. There is no evidence that CMV screening adds beneficially to this process and CMV negative components are not required.

7. Other Patient Groups

7.1 Immunodeficient patients

SaBTO (2012) agreed that there was no evidence to support the use of CMV screened negative blood for immunodeficient patients; they should receive leucodepleted blood and blood components.

NTAG Recommendation: Patients with immunodeficiency should receive leucodepleted components. There is no evidence that CMV screening adds beneficially to this process and CMV negative components are not required.

7.2 Oncology patients

SaBTO (2012) does not address this group of patients who may be very significantly immunocompromised, particularly due to therapy with medications such as the purine analogues and alemtuzumab. CMV negative blood components do not appear to be requested for these patients within Ireland.

NTAG Recommendation: Patients undergoing management for oncological disorders should receive leucodepleted components. There is no evidence that CMV screening adds beneficially to this process and CMV negative components are not required.

Specific components – Granulocytes

Granulocytes are issued as a component of granulocytes suspended in plasma and cannot be subject to leucodepletion. CMV negative components should be provided for CMV seronegative recipients of granulocytes.

NTAG Recommendation: CMV negative Granulocyte components should be provided for CMV seronegative recipients of granulocytes.

Conclusions and Recommendations

There is international consensus that large-scale randomised prospective studies should be performed but that they will not, because of what Goldfinger (2018) calls the ‘dread’ factor of putting a patient in harm’s way. The best example of the philosophy that drives this area is the extremely low risk of TT-CMV in pregnant women but that risk is not non-existent and the potential seriousness of the complication is too scary to contemplate. The other phenomenon is the way that some practices and beliefs, whether valid or not, become medical dogma and cannot be challenged.

The consequence of all of this is that the recommendations are conservative in nature.

Of particular note, pathogen reduction (PR) has the ability of rendering all discussions and complex technical issues moot. The IBTS has committed to undertake an evaluation of this risk reduction measure. Both adverse effects on supply and finances may be an issue with implementation. NTAG actively supports vigorous investigation of PR, linked with an analysis of the ability to discontinue CMV screening, as implemented in other jurisdictions.

Should PR be implemented in Ireland, information on the use of CMV negative components in pregnancy and neonates will be updated in NTAG guidelines.

Local protocols should be developed to empower blood transfusion laboratory staff to query appropriateness of requests for CMV negative components outside of these Guidelines.

Comprehensive audit and compliance outcomes are essential and should be carried out on a planned national audit programme. NTAG is seeking to address this.

All transfusion associated serious adverse reactions (SAR) and serious adverse events (SAE) as categorised by the National Haemovigilance Office (NHO) are required under statutory instrument (SI 547 of 2006) to be reported to the NHO.

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Mr Joe Flannagan PHE, Dr Michael Gattens, Dr Eibhlin Conneally, Prof Anna Curley and our excellent colleagues in the Irish Blood Transfusion Service and National Transfusion Advisory Group, NTAG.

Statement on Declaration of Interest

All working group members have made a declaration to NTAG.

Review Process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the recommendations made in this document. The document will be reviewed bi-annually by the working group, or earlier should the IBTS introduce component pathogen reduction (PR). A literature search will be re-run on a periodic basis to search systematically for any new evidence that may emerge.

Education and Audit Tool

The education and training to support implementation of these guidelines will be considered by the National Transfusion Advisory Group NTAG working group WG: Education and Training (Chair Dr Andrew Hodgson).

An Audit tool is being developed and NTAG will schedule a national practice Audit in 2021.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at this time, neither authors or NTAG accept any legal responsibility for the content of these guidelines.

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Appendix 1

National Transfusion Advisory Group NTAG, Guidance development working group membership

Member	Discipline
Prof Ian Hann Chairperson	Consultant Haematologist
Ms Carol Cantwell	Chief medical scientist
Dr Andrew Hodgson	Consultant Haematologist
Ms Anne Marie McCann	Chief medical scientist
Dr Kieran Morris	Consultant Haematologist
Dr SORCHA Ní Loingsigh	Consultant Haematologist
Ms Martina Williams	Chief medical scientist
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Appendix 2

National Transfusion Advisory group membership and disciplines

Dr Michael Dockery Chairperson	Consultant Anaesthesiologist, Director Perioperative Care University Hospital Waterford
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Ms Róisín Brady/Ms Joanne Scanlon	National Haemovigilance office
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Ms Fionnuala King	Chief Hospital Pharmacist
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Ms Angela Petraska	Phlebotomist Blackrock Clinic, Irish Phlebotomists' Association representative
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Prof Paul Ridgway	Consultant Surgeon Tallaght University Hospital, National Clinical Advisor for General Surgery
Mr Stephen Roe	Donor representative
Mr Barry Doyle/ Mr Kevin Sheehan	Irish Blood Transfusion Service medical science representative
Mr Keith Synnott	Consultant Orthopaedic Surgeon, Lead National Clinical Programme for Trauma Services
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