ANZSBT Position Statement on Prevention of Transfusion-Transmitted Cytomegalovirus (TT-CMV)

Summary

The collective evidence supports the use of pre-storage leucodepleted blood components as “CMV-safe” for immunosuppressed patients.

CMV-seronegative cellular blood components do not offer additional benefit over leucodepletion in any population including immunosuppressed patients.

Key findings and recommendations

The Clinical Transfusion Practice Committee (CTPC) undertook a systematic review of Cytomegalovirus (CMV) infection rates with and without selection for CMV seronegative units and performed a meta-analysis of comparative studies[1]. We have also reviewed haemovigilance data and correlated with preclinical studies. International guidelines were reviewed and evidence-based recommendations developed to prevent transmission of CMV through the blood supply and referenced broader CMV harm reduction strategies for at risk populations.

Key findings:

- CMV infection is common in the population, including blood donors
- Supply constraints may limit the availability of CMV-seronegative blood components to meet perceived clinical demand
- Detectable CMV (by either viral load/PCR) in clinically well, longstanding CMV seropositive donors is rare
- Detectable CMV in CMV seronegative donors may rarely be seen within a primary infection window period and poses a theoretical risk of transmission
- Modern leucocyte depletion processes routinely reduce CMV to levels below those shown to result in transmission in murine models
- Rates of failure of leucocyte depletion filters are low
- CMV infection rates are equivalent following transfusion of leucodepleted cellular blood components irrespective of whether it has been sourced from CMV seropositive or CMV seronegative donors
- No confirmed case of transmission of CMV with leucocyte depleted cellular blood components was found, including documented cases of transfusion of viral DNA positive units

- Pathogen reduction technologies, where available, are an effective alternative to leucodepletion to prevent CMV transmission
- International guidelines have gradually reduced the populations for which CMV seronegative cellular blood components should be given
- Effective strategies to limit consequences of CMV include primary prevention public health strategies, monitoring with pre-emptive therapy and provision of cellular blood components with a negligible risk of transmission (leucodepletion, pathogen inactivation or selection of CMV seronegative donors) to at-risk populations. These include immunocompromised, neonatal or intrauterine patients and all women who are or may become pregnant.

Recommendations:

- **Leucodepletion, pathogen inactivation or selection of CMV seronegative donors are each independently suitable methods to reduce transfusion transmitted CMV to negligible levels.**
- **Selection of blood from serologically negative donors is not recommended when transfusing leucodepleted cellular blood components.**
- **Seronegative donors must be used where possible for transfusion of cellular blood components that are not leucodepleted to at risk recipients. At risk recipients are people with conditions known to be associated with severe consequences of CMV including all women who are pregnant or likely to become pregnant within 12 months, people who are seronegative and have immunosuppression following stem cell or solid organ transplant, primary or secondary immunodeficiencies where CMV infection is a known risk.**
- **Where transfusion of non-leucodepleted cellular blood components from CMV seropositive donors occurs, clinical follow-up with consideration of pre-emptive therapy should be considered in recipients at risk of clinically serious CMV infection.**
- **Suspected cases of TT-CMV in immunocompromised, neonatal or intrauterine patients, and CMV-seronegative transplant recipients should be investigated using a standardised pathway. This should include assessment of reactivation, other common sources including maternal CMV serostatus and breast-milk exposure, prior to donor and component tracing and residual component testing where available.**

CMV Consensus Terminology

Acellular blood components	The non-cellular, liquid portion of blood, primarily consisting of plasma
Blood Components	The cellular and plasma portion of a whole blood donation that has been separated for targeted therapy. Blood components include red blood cells, platelets, fresh frozen plasma, cryoprecipitate and granulocytes
Cellular blood components	The cell proportion of whole blood following removal of the plasma. These include red blood cells, platelets and granulocytes
Cell free cytomegalovirus (cfCMV) viremia / cytomegalovirus DNAemia	CMV DNA that is molecules of DNA not enclosed within cells and may be detectable from a peripheral blood plasma or serum, and bodily fluids (saliva, breast milk and urine) from which cells have been removed. Qualitative polymerase chain reaction (qPCR) is generally utilised to assess for presence of CMV DNAemia and may be useful in detecting levels required for treatment and early exposure in immunocompromised patients or those who require treatment with antivirals. While cfDNA indicates active and / or recent CMV virus, the cfDNA is fragmented and may not indicate transmissibility through a cell free sample.
Cytomegalovirus seronegative / seronegativity	An absence of detectable CMV antibodies (IgG), indicating the person has not been exposed, or has recently been exposed but has not yet developed an immune response and development of IgG antibodies.
Cytomegalovirus seropositive / seropositivity	A presence of CMV IgG antibodies following exposure and an immune response (seroconversion) to the virus. The detection of IgM, IgG may be related to recent infection, reinfection or indicate previous (latent) infection. Once exposed and an immune response has resulted in the development of CMV IgG antibodies the person remains seropositive for life
Cytomegalovirus seroprevalence	The frequency of the population with detectable cytomegalovirus IgG antibodies (seropositive)
Iatrogenic CMV infection	Infection of CMV as a result of medical care or treatment, including transfusion transmission, organ/stem cell transplants and severe immunosuppression
Pathogen Inactivation	The use of physical or chemical methods such as ultraviolet (UV) light to damage DNA/RNA of pathogens such as CMV, to inactivate/eliminate a pathogen
Primary infection window	The period between initial exposure to cytomegalovirus where the person becomes infected until the

	development of reliably detectable CMV antibodies (IgG, IgM)
Serological conversion	The progress from undetectable to detectable CMV IgG antibodies following exposure to the virus
Universal leucocyte filtration / leucodepletion	Standardised approach to the removal of leucocytes from blood donations using filtration to minimise leucocyte mediated adverse events related to transfusion such as viral transmission and febrile reactions. In Australia and New Zealand this is completed prior to the storage of the blood components.

Abbreviations

CAR-T	Chimeric Antigen Receptor (CAR) T-cell
CMV	Cytomegalovirus
cCMV	Congenital cytomegalovirus
DNA	Deoxyribonucleic acid
FFP	Fresh frozen plasma
HSCT	Haematopoietic stem cell transplant
IUT	Intrauterine transfusion
NAT	Nucleic acid testing
SOT	Solid organ transplant
TT-CMV	Transfusion transmitted cytomegalovirus
VLBW	Very low birth weight
LB	Lifeblood
NZBS	NZBS

Background

CMV, a human herpes virus is prevalent in the Australian and New Zealand communities and once infection occurs, it remains latent within the host. For most people CMV infection is a mild, self-limiting infection, however serious illness and death can result in immunocompromised or susceptible individuals. CMV is clinically relevant in transfusion medicine due to its transmission in transfused cellular products. Donor to recipient transmission has been confirmed with molecular characterisation of virus[2]. Transmission is primarily through leucocytes in cellular blood components and leucodepletion was introduced with CMV transmission reduction specifically as one aim[3]. Selection of blood from CMV serologically negative donors remains common.

In both Australia and New Zealand leucodepletion is universal for all cellular blood components and is performed pre-storage as part of routine manufacturing. Current leucodepletion filters result in $< 10^6$ leucocytes in RBC or platelet components. Filter failures are rare. Enumeration of residual leucocytes in select components is performed as part of routine quality control (QC).

Cellular blood components that are leucodepleted:

- Red cell components (all variants)
- Platelet components (apheresis and pooled)

Cellular blood components that are NOT leucodepleted:

- Granulocyte infusions
- HSCT infusions (including CAR-T cells)

Acellular components that have low leucocyte numbers and do NOT require leucodepletion:

- Fresh frozen plasma (FFP / clinical plasma)
- Cryoprecipitate
- Cryodepleted plasma

The Australian Red Cross Lifeblood (LB) and New Zealand Blood Service (NZBS) currently screen selected new and previously CMV seronegative donors for CMV IgG antibodies using a commercially available immunoassay. Testing for IgM antibodies is not performed as these antibodies appear almost simultaneously to IgG antibodies in acute infections and nonspecific reactivity is seen with available assays.

CMV-seronegative blood components in Australia and New Zealand are defined by donor CMV IgG seronegativity, without routine nucleic acid testing (NAT). This approach does not exclude window-period infection or low-level viraemia, including potential cell-free CMV in plasma (cfCMV). Consequently, CMV-seronegative status functions as a surrogate marker of donor exposure rather than direct exclusion of transmissible virus. CMV risk mitigation relies primarily on universal pre-storage leucodepletion, with seronegative selection used as an adjunct in specific clinical settings.

There is variation in clinical practice and guidelines[4-10]. Expert opinion-based guidelines have increasingly limited the target populations where CMV seronegative cellular blood components are recommended and some national guidelines no longer recommend CMV seronegative units in addition to leucodepletion, including the 2025 Canadian guidelines[9].

CMV seronegative cellular blood components add no additional benefit for recipients. However, some transfusion services continue to hold or preferentially transfuse CMV seronegative components, which may create unnecessary anxiety among recipients and clinicians when supply constraints require the use of CMV-untested leucodepleted products. In addition, maintaining CMV seronegative inventories adds complexity in blood banks and transfusion laboratories and may become increasingly difficult if donor seroprevalence rises [11].

Epidemiology of CMV

CMV is common in the community, including in blood donors[12] . The seroprevalence of CMV in Australians up to 60 years was 57% in 2006. Mother-to-child transmission (antepartum, intrapartum and postpartum including via breastmilk) is common with further substantial acquisition through community exposure across childhood and adolescence, such that 53% of individuals were seropositive by 20 years of age in the aforementioned dataset[13]. Age-weighted seroprevalence in Australian blood donors was 76.1% in 2012[11] and 60.1% in New Zealand blood donors in 2006.[14]. Both cohorts had a disproportionate number of seropositive females. It is posited women have higher rates of infection due to increased contact with small children with exposure to bodily excretions or contaminated objects[15, 16].

Relatively low levels of plasma CMV DNA are detectable from several days to weeks following primary infection. The window period between infection and serological conversion can last up to several weeks. CMV DNA rises during the window period with peak plasma levels seen shortly after the appearance of anti-CMV IgG. IgM antibodies are detected prior to IgG antibodies or shortly after. Peak IgM antibody titres occur during the first 3 months after infection then rapidly decline[17, 18] whereas IgG levels persist lifelong.

Lifelong latency is established within cells of the myeloid lineage, particularly monocytes, and these are considered the major source of CMV transmission in cellular blood components[19, 20]. cfCMV DNA may be seen in plasma, but there is at most a low possibility of transmission. Of 221 (39 CMV seronegative) immunocompetent recipients of cellular blood components with detectable CMV in the plasma, none developed a CMV-like illness or confirmed seroconversion[21]. Reactivation at times of immunocompromise due to medications, health conditions or pregnancy [22] can release cfCMV into the blood stream, breast milk, urine and saliva[23]. Reinfection with a new strain can also occur.

Transfusion-transmitted CMV infection (TT-CMV) has been reported since the 1960s[24] and was first reported after cardiac surgery. Clinically significant infections are particularly seen in immunocompromised populations including premature infants, haematology, including bone marrow transplant recipients, and solid organ transplant (SOT) patients. High rates of community transmission confound attribution of a post transfusion infection to cellular blood components. Secretion in saliva, urine and breast milk is common, may be prolonged after infection and may re-emerge during otherwise latent infection[25].

Clinical significance

CMV can lead to diverse clinical manifestations. Asymptomatic infection, respiratory symptoms or a mononucleosis-like illness are common in immunocompetent people. Seroconverting blood donors reported compatible symptoms in 85% of cases in one study, however 69% of persisting CMV seronegative controls experienced similar symptoms[18]. In immunocompromised patients, retinitis, pneumonitis, hepatitis,

enterocolitis and marrow suppression are common with fatal infections, particularly in the post-transplant setting, both from primary infection and reactivation.

Congenital CMV (cCMV) is acquired from the mother during pregnancy and is more likely in maternal primary infection during or leading up to pregnancy than with secondary infection or reactivation. While transmission rates appear lower during first trimester, the resulting disease is more severe, with few longer-term sequelae if acquired in second and third trimesters[26]. Deafness and neurodevelopmental delay can develop during childhood, even in children asymptomatic at birth. The incidence of cCMV in Australia is estimated to be at least 3.85 per 100 000 live births[16]. The case fatality rate is estimated at 20% from intrauterine or neonatal death. Additional morbidity includes sensorineural hearing loss (12%) and cerebral palsy (10%)[27].

Infection rates following transfusion

Prior systematic reviews have not supported reliance on leucodepletion to prevent CMV transmission [28], largely because they were based on historical evidence that does not reflect modern practice. Most included studies pre-dated universal, validated pre-storage leucodepletion and relied on small, heterogeneous, and underpowered cohorts, often using bedside or post-storage filters with inconsistent leucocyte removal. CMV-seronegative cellular blood components were already entrenched as the "gold standard," setting a high evidentiary bar that leucodepletion studies could not meet, while theoretical concerns about cfCMV viraemia and the absence of mature haemovigilance systems encouraged conservative interpretation. Despite a low estimated residual risk,[29] recommendations continued to support use of CMV seronegative cellular blood components in selected recipients. We therefore undertook a systematic review to evaluate the risk of TT-CMV in the context of universal pre-storage leucodepletion.[1}

There were four comparative clinical studies (one randomised and three observational) that examined CMV infection rates following transfusion of leucodepleted cellular blood components with or without CMV serological donor selection. Meta-analysis demonstrated no difference in CMV infection rates between groups (relative risk 1.21, 95% CI 0.42–3.49).[1] Pooled analysis of 19 observational studies reporting CMV incidence following transfusion of leucodepleted cellular blood components found rates of 0.17% for leucodepletion alone and 0.22% for CMV-seronegative plus leucodepleted cellular blood components, reinforcing the absence of a clinically meaningful difference. Haemovigilance reports were also reviewed and found no confirmed cases of TT-CMV attributable to leucodepleted cellular blood components, despite inclusion of high-risk populations and decades of surveillance. Pre-clinical, translational, and modelling studies provided strong biological plausibility for the clinical findings.

Residual risk modelling has estimated the likelihood of TT-CMV with leucodepleted cellular blood components to be less than 1 in 13 million transfusions, a frequency below the detection threshold of population-based surveillance.[29] Collectively, these data indicate that CMV serological donor selection does not confer additional safety

benefit when effective leucodepletion is in place, supporting rationalisation of CMV-negative inventory requirements in modern blood systems.

Haemovigilance

Over the past decade, international haemovigilance systems have shown no evidence of TT-CMV in jurisdictions using universal pre-storage leucodepletion. In the United Kingdom, the Serious Hazards of Transfusion (SHOT) scheme applies stringent attribution criteria for transfusion-transmitted infections, including exclusion of non-transfusion sources and, where possible, donor or component testing. Within this framework, SHOT has continued to report only very small numbers of suspected CMV cases, with no confirmed cases to suggest ongoing TT-CMV risk (SHOT Annual Reports 2015–2024, available from https://www.shotuk.org/shot-reports).

Canadian haemovigilance and policy outputs similarly describe TT-CMV as an exceptionally rare event since the implementation of universal leucodepletion, with National Advisory Committee (NAC) guidance consistently framing leucodepleted cellular blood components as “CMV safe” and clinically equivalent to CMV-seronegative cellular blood components. The Canadian Blood Service moved to a single CMV prevention strategy in 2017 with the provision of leucodepleted cellular blood components for all indications except IUT. To date there have been no reported cases of TT CMV infection with this strategy, and very recently they have extended the single strategy of pre-storage leucodepletion to include IUT[30].

In the United States, haemovigilance data from AABB-aligned guidance, the CDC’s National Healthcare Safety Network (NHSN), and FDA surveillance demonstrate transfusion-transmitted infections are uncommon overall**,** and CMV is not a pathogen in reported cases. The lack of contemporary high-quality trials demonstrating superiority of CMV-seronegative over leucodepleted cellular blood components reflects the near-elimination of TT-CMV rather than ongoing uncertainty. Collectively, these haemovigilance data support the conclusion that residual TT-CMV risk in modern blood systems is extremely low and largely theoretical.

Beyond population-level haemovigilance reporting, evidence addressing whether CMV-untested but universally leucodepleted cellular blood components confer an acceptably low risk of transfusion-transmitted CMV (TT-CMV) is best drawn from prospective and observational studies in high-risk populations, in whom even rare transmission events would be most readily detected. CMV-seronegative allogeneic haematopoietic stem cell transplant (HSCT) recipients represent a particularly sensitive model, given their profound immunosuppression, frequent transfusion exposure, and routine post-transplant virological surveillance. In this setting, Bowden *et al.* demonstrated in a prospective randomised trial that leucocyte depleted cellular blood components were equivalent to CMV-seronegative cellular blood components in preventing CMV infection, despite the use of filtration techniques less effective than contemporary pre-storage leucodepletion[31, 32]. Subsequent observational and prospective studies using CMV-unscreened leucodepleted cellular blood components have shown similarly reassuring results. Narvios *et al.* reported no

cases of CMV disease or clinically significant TT-CMV in 72 CMV-seronegative HSCT recipients monitored for at least 100 days post-transplant [33]. Thiele *et al.*, using systematic CMV DNA NAT alongside serology, observed no CMV DNAemia or disease across 1,847 transfused cellular blood components from over 3,000 donors [34].

Parallel findings are observed in neonatal and very-low-birth-weight (VLBW) populations. Prospective studies consistently demonstrate that when leucodepleted (with or without CMV-seronegative selection) blood components are used, transfusion-transmitted CMV is effectively prevented, and postnatal CMV acquisition is instead dominated by non-transfusion sources**,** particularly breast-milk exposure and perinatal infection [15, 25, 35-39]. Importantly, even in studies employing intensive virological surveillance, TT-CMV has not emerged as a measurable contributor to CMV infection in modern neonatal practice.

Finally, we acknowledge the inherent limitations of passive haemovigilance in attributing CMV acquisition to transfusion. To address this, any future suspected TT-CMV cases in immunocompromised, neonatal or intrauterine patients and CMV-seronegative transplant recipients should trigger a standardised investigation pathway**,** including assessment of reactivation, other common sources including maternal CMV serostatus and breast-milk exposure, prior to donor and component trace-back and residual component testing where available.

Early notification of transfusion services and haemovigilance programs is essential to enable timely component tracing and maximise the feasibility of residual component testing and molecular analysis.

Recommendation:
Suspected cases of TT-CMV in immunocompromised, neonatal or intrauterine patients, and CMV-seronegative transplant recipients should be investigated using a standardised pathway. This should include assessment of reactivation, other common sources including maternal CMV serostatus and breast-milk exposure prior to donor and component tracing and residual component testing where available.

Risk of transmission from CMV-negative donors

Although CMV-seronegative blood components have traditionally been considered the safest option, there remains an inherent limitation due to the window period following acute infection. During this period, donors who have not yet seroconverted to have detectable IgG antibodies may have circulating CMV DNA in plasma or latently infected leucocytes. Several studies have documented the presence of CMV DNA in otherwise seronegative donors, albeit at low frequency[17, 40]. The infectivity of such low-level viraemia remains uncertain, but its existence highlights CMV-seronegative status does not provide absolute protection and challenges the perception of it as a gold standard.

Risk of transmission from cryopreserved and non-leucodepleted blood components

LB and the NZBS have limited stocks of long-term cryopreserved red cells (collected from donors with rare phenotypes generally), some which may have been collected prior to leucodepletion. Cryopreservation and deglycerolisation have a partial leucocyte-reducing effect, likely through washing and cell loss during processing, but the effect is variable and generally insufficient to guarantee compliance with current leucodepletion thresholds if applied to non-leucodepleted units [41, 42]. These cases should be individually reviewed in discussion with the treating haematologist and the blood service.

Granulocyte transfusions, or any other cellular blood component not able to be leucodepleted, should preferably be from CMV seronegative donors when the recipient is CMV seronegative. Clinical consideration of monitoring and pre-emptive therapy is likely to be required in most CMV seronegative recipients if CMV negative granulocytes cannot not be sourced.

Laboratory / preclinical evidence

Leucodepletion

Universal leucodepletion of cellular blood components was introduced by NZBS in 2001 and by LB in 2008. Current leucodepletion filters result in < 1 x 10^6 residual leucocytes in RBC or platelet components. Filter failures are rare. Enumeration of residual leucocytes in select products is performed as part of routine QC.

Prior to leucodepletion the estimated rate of TT-CMV ranged between 28-57%. Post leucodepletion the prevalence of primary CMV fell to 0.23-4% in stem cell transplant recipients with earlier generation filters[23].

Breakthrough infections could occur due to failure of filtration mechanisms or due to the transfusion of cell free CMV. In a nationwide Swiss study of blood donors, Voruz et al found 0.009% (4 of the 42,240) of donations tested were positive for CMV DNA. However, viremia levels were low, and at levels where infectivity is unknown[23]. Whilst all donors were CMV IgG positive, others have reported similar prevalence of CMV DNA in CMV seronegative donors in the window period of primary infection[43].

Pathogen inactivation

Currently there are no pathogen-inactivation (PI) technologies used in Australia or New Zealand, but they are used in other jurisdictions with- amotosalen/UV-A (INTERCEPT) most commonly used for platelets. This process reliably inactivates CMV in vitro and in platelet concentrates, with studies demonstrating ≥5–6 log reductions in CMV infectivity and prevention of transfusion transmission in animal models[44].

Contemporary policy and guidance increasingly recognise PI platelets as an acceptable CMV-risk–mitigation strategy alongside universal leucodepletion, with AABB materials explicitly listing PI as a CMV-risk–reducing option and Canadian services moving toward broader PI adoption within their inventories.

Recommendations:

- **Leucodepletion, pathogen inactivation or selection of CMV seronegative donors are each suitable methods to reduce transfusion transmitted CMV to negligible levels.**
- **Selection of blood from serologically negative donors is not recommended when transfusing leucodepleted cellular blood components.**

Clinical contexts

While TT-CMV has been a significant concern in the past, and vigilance must remain when transfusing non-leucodepleted cellular blood components, the implementation of universal pre-storage leucodepletion has effectively reduced TT-CMV. A holistic approach to preventing harm due to CMV recognises that community acquisition is a far greater issue than iatrogenic infection through the blood supply.

Strategies need to consider prevention of community infection as well as managing both primary infection and reactivation in populations at risk. Sourcing cellular blood components from CMV seronegative donors in addition to universally applied leucodepletion, comes at additional cost, increases inventory management complexity and creates anxiety without additional benefit.

Pregnancy

Congenital CMV (cCMV) is transmitted from the mother and is more likely in the context of primary rather than secondary infection. The rates of primary CMV infection in pregnancy vary depending on the setting with estimates of between 0.3 – 7% in high income settings [45, 46]. In the Australian setting, the incidence of primary CMV infection is estimated to be 6 per 1,000 pregnancies (0.6%) [47].These figures are well below the theoretical risks associated with leucodepleted cellular blood components and public health recommendations with a strong focus on prevention of infection through contact with bodily fluids have a far greater impact on prevention of cCMV [48].

Current recommendations on the prevention of TT cCMV also fail to acknowledge the risk that exists in the periconceptual period, where maternal infection can remain active and be transferred to the fetus if conceived within a 12 month period.[29, 30, 49]

Intrauterine and neonatal/infant transfusion

Neonatal and intrauterine transfusion (IUT) are of particular concern due to possible catastrophic outcomes following intrauterine infection with CMV. Fetal/neonatal immunity immaturity and lack of effective treatments have resulted in significant apprehension when determining strategies to prevent TT-CMV in this vulnerable population.

Comparison of NAC (Canada), BSH (UK) CMV Recommendations for IUT

Aspect	NAC (Canada, 2025) [9]	BSH (UK, 2016)[50]
Position on CMV-safe vs CMV-	Pre-storage leucodepleted (CMV-safe) cellular blood	CMV-seronegative required; leucodepleted only acceptable if

seronegative cellular blood components	components are considered equivalent to CMV-seronegative, including for IUT.	CMV-seronegative cellular blood components not available.
Rationale	Residual CMV transmission risk with modern pre-storage leucodepletion is extremely low; operational priority is extended phenotype matching for IUT.	Traditional concern about CMV transmission risk; default to CMV-seronegative where possible.
Other requirements for IUT RBC	Extended phenotype matching prioritised; irradiated as per local practice (not specified in this statement).	Must be irradiated; transfused within 24 h of irradiation; within 5 days of collection.

Although CMV-seronegative, leucodepleted cellular blood components have historically been preferred for neonates—especially for very low birth weight (VLBW) infants—current evidence indicates transfusion is not a significant source of CMV infection, particularly since the widespread use of leucodepleted cellular blood components. The latest SHOT (UK) data show no confirmed TT-CMV, despite numerous process deviations where CMV-seronegative units were recommended and not provided[51]. In VLBW infants in particular postnatal CMV is overwhelmingly linked to maternal milk, not transfusion[37].

CMV reactivation in mammary epithelial cells leads to viral shedding into milk in approximately 70–90% of seropositive mothers[52]. Systematic reviews and cohort studies demonstrate that among very preterm and VLBW (<32 weeks or <1500 g), infection rates reach 16–26% with fresh milk versus 8–13% with frozen or mixed milk[52-54]. The literature converges on a clear message: breast milk is both indispensable for neonatal health and the dominant vehicle for postnatal CMV transmission in high-risk preterm populations. [30, 51, 55-57].

<u>Haematological malignancies and HSCT recipients (both malignant and non-malignant)</u>
CMV is a concerning infection in immunocompromised haematology patients. Before leucodepletion, transfusion was a recognised pathway for TT-CMV. However, the introduction of universal pre-storage leucodepletion for cellular blood components has drastically reduced this risk to undetectable levels[28, 51] as supported by outcomes in a randomized trial, multiple comparative studies and subsequent systematic reviews and meta-analyses [28, 31, 32]. Community transmission remains possible in immunocompromised groups, with monitoring of CMV and pre-emptive treatment for rising quantitative DNA levels now standard practice.

Important to note, stem cells (and granulocyte transfusions) cannot be leucodepleted. Donor selection for allogeneic transplantation is complex, with CMV being a major but not sole factor in donor suitability. Cellular blood component components not able to be leucodepleted, should preferably be from CMV seronegative donors when the recipient is CMV seronegative. Clinical consideration of monitoring and pre-emptive

therapy is likely to be required in most CMV seronegative recipients if CMV positive non-leucodepleted products are required.

Solid organ transplant (SOT) recipients

SOT recipients, particularly CMV-seronegative recipients, are at high risk of CMV infection. Observational studies suggest CMV infections in SOT are more commonly attributable to reactivation or community acquisition than to transfusion. Accordingly, CMV prevention in SOT is centred on antiviral prophylaxis or pre-emptive therapy, not transfusion strategy[58, 59].

Contemporary guidelines from the UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), the Canadian National Advisory Committee (NAC), and the Australian National Blood Authority (NBA) all endorse leucodepletion as sufficient for SOT patients[30, 57, 60].

HIV-positive patients

In the anti-retroviral era, reports of TT-CMV in HIV are absent from the literature**.** The Viral Activation Transfusion Study[61], a randomized trial of leucodepleted versus standard red cells in HIV-infected patients, found no evidence of CMV reactivation or transfusion-attributable CMV DNA. Most participants were already seropositive and thus not at risk of primary TT-CMV.

Patients with primary immunodeficiency conditions including congenital T-lymphocyte immunodeficiency

Evidence specific to inherited immunodeficiency syndromes, including severe T-cell immunodeficiency, is extremely limited. Additionally, there is no high-quality evidence to indicate patients with inherited or T-cell immunodeficiency are uniquely susceptible to TT-CMV in the era of universal leucodepletion. There are no studies which have demonstrated a clear incremental benefit of CMV-seronegative components over leucodepleted components alone in this population. Previous recommendations for CMV-seronegative components in this population are based largely on extrapolation from broader immunocompromised cohorts and on expert consensus, rather than direct comparative outcome studies in primary immunodeficiency.

Recommendations

- **Seronegative donors must be used where possible for transfusion of cellular blood components that are not leucodepleted to at risk recipients. At risk recipients are people with conditions known to be associated with severe consequences of CMV, including all women who are pregnant or likely to become pregnant within 12 months, people who are seronegative and have immunosuppression following stem cell or solid organ transplant, primary or secondary immunodeficiencies where CMV infection is a known risk.**
- **Where transfusion of non-leucodepleted cellular blood components from CMV positive donors occurs, clinical follow up with consideration of pre-emptive therapy should be considered in recipients at risk of clinically serious CMV infection.**

Conclusion

The collective evidence supports the use of pre-storage leucodepleted blood components as “CMV-safe” for immunosuppressed patients.

CMV-seronegative cellular blood components do not offer additional benefit over leucodepletion in any population including immunosuppressed patients.

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