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BENEFITS OF LEUKOREDUCTION OF BLOOD COMPONENTS AND ITS MAIN INDICATIONS: INTEGRATIVE REVIEW

BENEFÍCIOS DA LEUCOREDUÇÃO DE HEMOCOMPONENTES E SUAS PRINCIPAIS INDICAÇÕES: REVISÃO INTEGRATIVA

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ABSTRACT: Blood transfusions are used to treat potentially life-threatening medical conditions and health problems in a short space of time. However, transfusions can produce adverse events, some of which may be related to immune system responses or the transmission of infectious agents (e.g., HCV, HTLV-I/II, HBV, and human immunodeficiency virus). Leukoreduction is a process in which white blood cells are intentionally removed from donated blood to minimize the risk of adverse reactions in individuals receiving a blood transfusion. This is an integrative review of the literature carried out in the electronic databases BVS, Scielo and Pubmed from 2003 to 2024. Using inclusion, exclusion and eligibility criteria, sixteen articles were selected for discussion. The review showed that although the benefits of leukocyte removal to reduce infectious and non-infectious complications in all types of transfused patients are evident, the adoption of universal leukocyte removal is not fully implemented in medical transfusion practice, especially due to the high cost of the filters.
KEYWORDS: Leukocyte reduction. Blood transfusion. Filtration.

RESUMO: As transfusões de sangue são utilizadas para tratar condições médicas potencialmente fatais e problemas de saúde em um curto espaço de tempo. No entanto, as transfusões podem produzir eventos adversos, alguns dos quais podem estar relacionados a respostas do sistema imunológico ou à transmissão de agentes infecciosos (por exemplo, HCV, HTLV-I/II, HBV e vírus da imunodeficiência humana). A leucorredução é um processo em que os leucócitos são intencionalmente removidos do sangue doado para minimizar o risco de reações adversas em indivíduos que recebem uma transfusão de sangue. Esta é uma revisão integrativa da literatura realizada nas bases de dados eletrônicas BVS, Scielo e Pubmed, de 2003 a 2024. Utilizando critérios de inclusão, exclusão e elegibilidade, dezesseis artigos foram selecionados para discussão. A revisão mostrou que, embora os benefícios da remoção de leucócitos para reduzir complicações infecciosas e não infecciosas em todos os tipos de pacientes transfundidos sejam evidentes, a adoção da remoção universal de leucócitos ainda não é totalmente implementada na prática médica de transfusão, especialmente devido ao alto custo dos filtros.
PALAVRAS-CHAVE: Redução de leucócitos. Transfusão de sangue. Filtração.

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INTRODUCTION

In recent years, the need for blood transfusions has increased due to the rise in chronic diseases, improvements in life-support services, and the treatment of surgical procedures. Blood transfusion is an acute intervention implemented to address short-term life and health conditions; generally, its long-term effects tend to be of secondary importance[1].

However, blood transfusion is associated with an increasing risk of adverse infectious[2,3] and non-infectious events[4]. The incidence of non-infectious transfusion reactions is higher than that of infectious complications. Mortality associated with non-infectious risks is significantly higher, accounting for 87% to 100% of fatal transfusion complications[5].

Recipient safety measures play a crucial role in the overall effectiveness of transfusion. The key advancements in safety over the first century of transfusion medicine include the development of techniques to prevent hemolytic transfusion reactions, hemolytic disease of the newborn, and the transmission of viral pathogens. Although these risks remain significant, they affect far fewer patients than in the past. Some of the most important current safety issues relate to toxicities broadly associated with the immunomodulatory effects of allogeneic transfusion. This includes universal leukoreduction (URL) to mitigate nosocomial infections, inflammation, and organ injury[6].

Various countries have adopted URL policies to leukoreduced all the blood components prepared[7,8]. While for resource-poor countries, selective leukoreduction of blood components using new generation leukofilters is a viable option to prevent leukocyte-associated adverse transfusion reactions in the recipients and improve the outcome, particularly of the multitransfused patient population[9].

Several countries, including the United Kingdom and Portugal, adopted ULR as a precautionary measure to address the theoretical risk of transfusion-associated variant Creutzfeldt-Jakob disease (TA-vCJD). This decision was based on evidence suggesting that the pathogenic prion responsible for vCJD is associated with B-lymphocytes. The precautionary principle advocates for mitigating potential serious public health risks, even when scientific evidence has not yet fully confirmed cause-and-effect relationships[10].

Canada, France, Germany, and England have implemented ULR[10]. Until the end of 2015, red blood cell (RBC) leukodepletion in Italy has been used in only few centers and for specific clinical cases. A recent decree of the Italian Ministry of Health, designated as mandatory RBC pre-storage leukodepletion starting January 2016[11]. However, in countries like Korea and the United States, economic concerns have delayed the adoption of ULR. As a result, these nations have opted for selective leukoreduction protocols, targeting patients at the highest risk of experiencing adverse effects related to leukocytes in blood components[12].

The highest parasite concentration was found in the buffy coat (BC), followed by RBC prior to leukoreduction. There is a significant risk of transfusion-transmitted Chagas disease associated with non-leukoreduced RBCs. Leukoreduction may serve as an effective preventive measure against transfusion-transmitted *Trypanosoma cruzi* infection, particularly in endemic regions and in non-endemic countries with high immigration rates from Latin America[13].

Whole blood contains approximately $2x10^9$ to $3x10^9$ leukocytes; Brazilian legislation requires that leucoreduced components must contain less than $5x10^6$, which means a reduction of more than 99% of leukocytes after the filtration process[9,14].

The main complications associated with the presence of leukocytes in blood are febrile non-hemolytic transfusion reactions (FNHTR) (Figure 1), alloimmunization to human leukocyte antigens

(HLA)[15], transfusion-related immunomodulation (TRIM), graft-versus-host disease (GVHD), and platelet refractoriness[16–19].

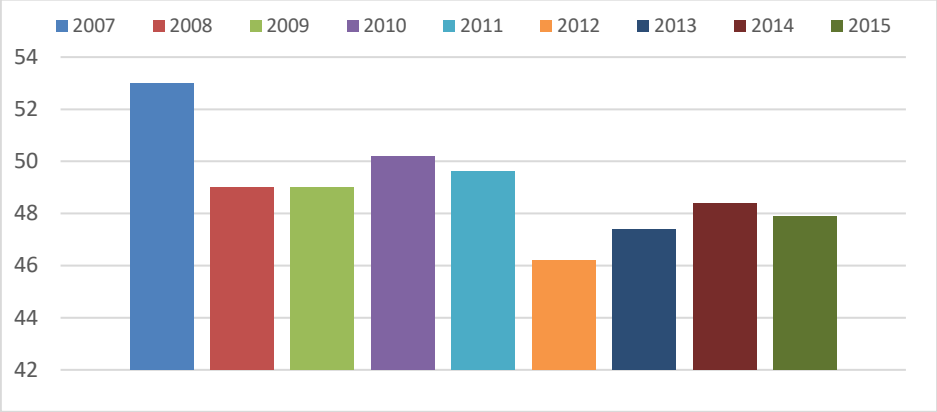

Figure 1 – Relative frequency (%) of febrile non-hemolytic transfusion reactions occurring in Brazil between 2007 and 2015, demonstrating a decrease over the years
Source: ANVISA,2016

Blood banks, together with industry, have sought to reduce transfusion risks. In Brazil, tests are conducted for Chagas disease, hepatitis B and C, human T-lymphotropic viruses (HTLV-I/II), human immunodeficiency virus (HIV), syphilis, Plasmodium falciparum in malaria-endemic areas, and cytomegalovirus (CMV) in specific situations. The introduction of nucleic acid testing for HIV and hepatitis B and C was crucial for reducing the window period[20,21].

LEUKOCYTE FILTERS AND THEIR EFFECTIVENESS

Allogeneic leukocytes can promote adverse reactions, which justifies leucoreduction. The 100-to-1.000-fold reduction (2 to 3 log) provided by leukocyte filters enables a decrease in the frequency of many adverse reactions[22]. Studies have shown that the necessary reduction level is less than 90%, transmission of some infectious agents is close to 99.9%, and platelet alloimmunization is around 99.9% to avoid FNHTR. However, this percentage still needs to be well established to preclude TRIM[1].

Leukocyte filtration is the most commonly used method to prepare leukocyte-poor blood. The process is simple, fast, effective, and does not require expensive equipment. Additionally, it preserves the product's shelf life[23].

ULR has been considered a transfusion safety policy in some countries. Several authors discussing the costs consider this analysis complex due to the difficulty in the dimensionality of long-term morbidity attributed to transfusion. However, they state that filter indications should be reserved for specific situations due to competition for resources for resources for other serious public health issues[22].

The first filters (first generation) were developed to substantially reduce the number of leukocytes present in the blood to be transfused; however, they only had the capacity to retain about 1 log of white blood cells[24].

Second-generation filters emerged in the "centrifuge, cool, filter" technique, promoting the retention of about 3 logs with proven efficacy in preventing FNHTR[17]. Third- or fourth-generation filters currently remove more than 99.0 – 99.99% (>3 log) of the leukocytes initially present in donated blood. These filters have pores ranging from 5 to 50 micrometers and can meet current quality standards for blood components[24,25].

FILTRATION MECHANISMS

Filters have small pores that allow the retention of individual cells and increase adsorption capacity. Two main mechanisms are involved: mechanical entrapment, which depends on pore size and cell deformability, and physicochemical entrapment or adhesion[26,27].

Various factors can be responsible for leukocytes' adherence to filter surfaces, such as chemical characteristics, surface charge, and morphology (porosity and roughness). The filters have multiple layers with pores of different diameters, allowing depth filtration. The pore size of the filter determines the retention of particles larger than 30µm, while adhesion and depth filtration are responsible for retaining particles smaller than 1µm. Particles ranging from 1 to 30µm are retained by the simultaneous action of both processes[14,26,27].

The filter's surface charge can be adjusted by coating it with methacrylate polymers to create a strong positive charge, thus increasing the adhesion surface for leukocytes. Some properties of various cells, such as diameter, density, deformability, and adhesiveness, are essential for the success of the filtration process[28,29].

Leucoreduction can occur during processing, post-processing, or at transfusion time. However, leucoreduction before storage (within 48 hours after collection) offers several advantages[29–31]:

a) Reduced accumulation of leukocyte cytokines during storage, ensuring greater efficiency in preventing nonhemolytic transfusion reactions;
b) Minimizes the risk of HLA alloimmunization in patients with multiple transfusions by removing intact leukocytes during filtration. Filtration during transfusion (at the bedside) allows the passage of leukocyte fragments and may alloimmunized recipients;
c) It minimizes the risk of transmitting lymphotropic viruses, as the degradation of leukocytes and release of intracellular organisms after 72 hours of storage means they are no longer retained.

RECOMMENDATIONS FOR THE USE OF LEUKOCYTE REMOVAL FILTERS IN BRAZIL

The use of leukocyte filters, as recommended by the Ministry of Health's Guide for the Use of Blood Components (2015), is indicated for conditions such as hemoglobinopathies, hereditary hemolytic anemia, a history of two or more nonhemolytic febrile reactions, congenital immunodeficiency syndrome, candidates for bone marrow transplantation, aplastic anemia, acute myeloid leukemia, intrauterine transfusion, patients with platelet disorders requiring frequent transfusions, severe oncohematological disease until proper diagnosis, and patients with platelet disorders requiring frequent transfusions[32].

Filtration is recommended under the following conditions to prevent CMV: HIV-positive patients with negative CMV serology; candidates for organ and bone marrow transplants if both donor and recipient are CMV-negative; intrauterine transfusion, pregnant women with non-reactive or unknown CMV serology; premature newborns and low birth weight infants (1200 g); newborns whose mothers are CMV-negative or have unknown serology. The effectiveness of leukocyte filters is equivalent to performing serology for CMV prevention[14,21,32,33]. Donor blood allogeneic leukocytes are responsible for the transmission of viruses such as CMV, HTLV-I/II, and Epstein-Barr virus [26,34–36].

CMV and HTLV-I/II are transmitted only by transfusion of cellular products. If URL were adopted, filtration would remove these viruses, eliminating the need for blood tests for these potential contaminants[37].

Health promotion related to blood transfusion involves various strategies and practices to ensure this procedure's safety and effectiveness. Some of the main characteristics include:

a) Ensuring transfusion safety: Implementing strict measures for donor screening and selection, including tests to detect blood-borne diseases such as HIV, hepatitis, and syphilis, to prevent the transmission of infections.
b) Leukoreduction: The removal of leukocytes from blood components before transfusion, which reduces the risk of febrile transfusion reactions, transmission of latent viruses (such as CMV), and alloimmunization in patients requiring frequent transfusions.
c) Rational use of blood: Encouraging the careful and judicious use of blood components, prioritizing transfusion only when clinically necessary, which helps prevent complications and preserves blood supplies.
d) Advanced filtration technologies: Utilizing leukocyte filters and blood irradiators helps prevent transfusion-associated graft-versus-host disease and pathogen transmission, promoting safer transfusions.
e) Education and training of healthcare professionals: Continuous training for doctors, nurses, and other professionals involved in the transfusion process to ensure the application of best practices, monitoring for adverse reactions, and proper transfusion indications.
f) Monitoring and reporting transfusion reactions: Active surveillance and reporting systems for adverse events related to transfusion, such as allergic reactions, circulatory overload, and infections, are used to promote patient safety and improve care protocols.

These characteristics are part of a healthcare system that addresses the needs of patients requiring transfusions, seeks to prevent risks, and promotes the safe and efficient use of blood.

Thus, this study aims to provide a narrative review of leukocyte filters' benefits and primary indications. This integrative literature review used electronic databases, following the methodological procedures outlined in the next section.

METHODOLOGY

Integrative review study[38,39], whose search was carried out in the electronic databases Biblioteca Virtual em Saúde (BVS), Pubmed, and Scielo, in the second half of 2023. The research question used for the bibliographic survey was: “What are the main indications and effectiveness of the leucoreduction procedure for blood components?” For this, the following descriptors and their combinations in Portuguese and English were used: “leucoreduction,” “blood transfusion,” and “filtration”.

The inclusion criteria for selecting articles were the following: articles that portray the theme in Brazil and other countries; articles published in Portuguese, Spanish and English; full articles that portray the theme of leucoreduction; articles published and indexed in the databases above in the last twenty-one years (2003-2024). Therefore, the exclusion criteria applied included dissertations, theses, books, book chapters, conference proceedings and duplicate articles.

After applying the search filter in the databases mentioned, 109 publications were identified based on the inclusion criteria. Duplicate records across portals (19 articles) were removed. A

preliminary review of titles and abstracts excluded 73 publications that did not meet the specified criteria, and one article did not clearly meet eligibility criteria, resulting in a final sample of sixteen articles (Figure 2).

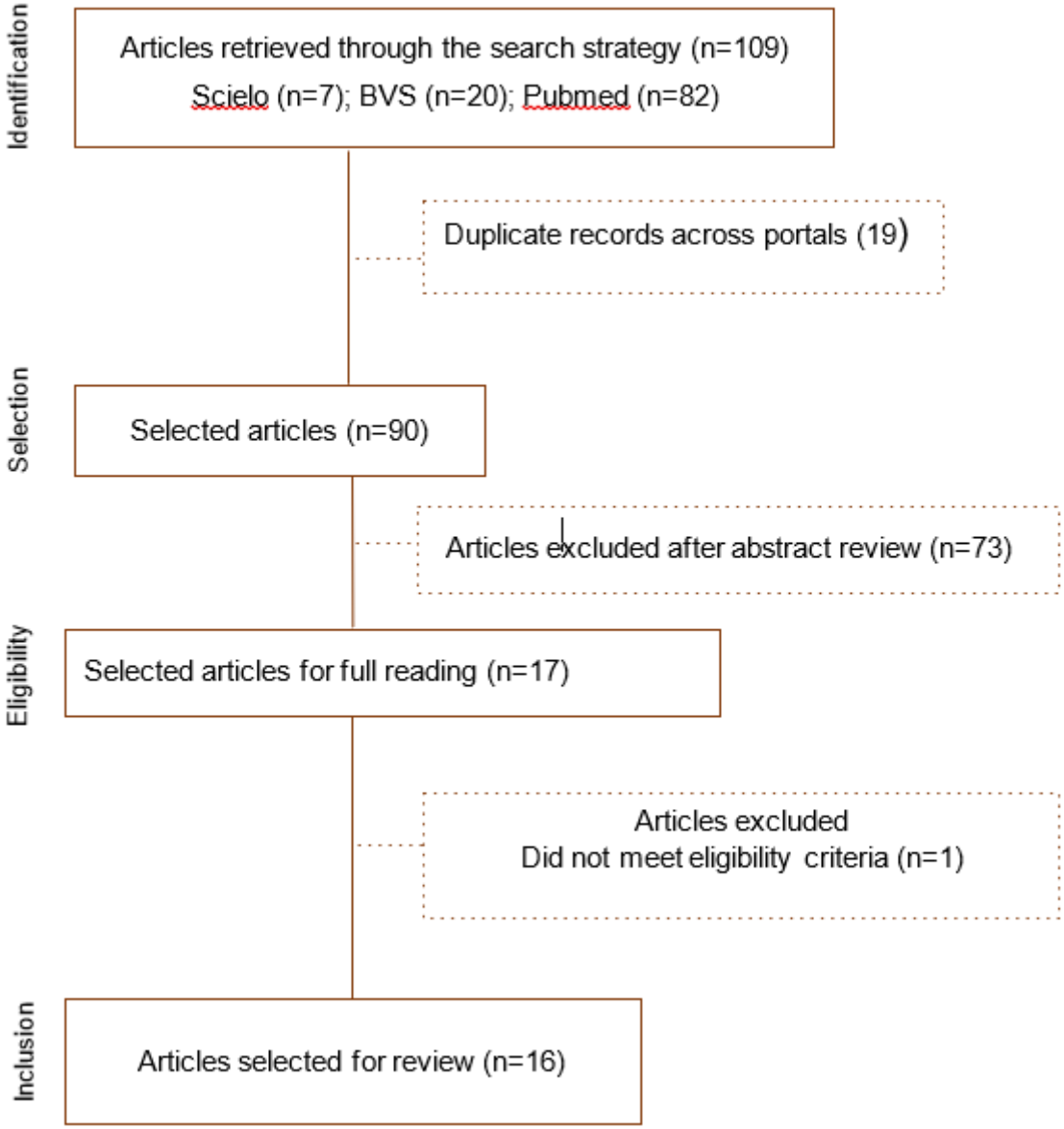

Figure 2 – Flowchart used for the integrative review according to pre-established criteria.
Source: Authors of the study.

RESULTS

Eighty-two articles were found in the Pubmed database, 7 in Scielo, and 20 in the BVS, totaling 109 initial articles. When the exclusion and duplication criteria were analyzed, 90 references remained and were studied. However, only sixteen articles were eligible for the discussion.

Based on the established methodology, the sixteen selected articles (Chart 1) report studies carried out predominantly outside Brazil and published in English. The years of publication ranged from 2003 to 2024. Regarding the types of studies, 68.7% comprised multicenter, retrospective, or review studies.

Chart 1 - Articles selected for the Integrative review.

Article title	Periodical	Authors/Year	Methodology	Summary of Results
Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions	JAMA	Hébert et al.,2003	Multicenter Study	Unadjusted in-hospital mortality rates were significantly lower following the introduction of leukoreduction compared with the control period (6.19% vs 7.03%, respectively; P =.04). Compared with the control period, the adjusted odds of death following leukoreduction were reduced (odds ratio [OR], 0.87; 95% confidence interval [CI], 0.75-0.99). For each major disease subgroup, we observed nonsignificant decreases in the adjusted odds of death following critical care and trauma (adjusted OR, 0.94; 95% CI, 0.76-1.17; *P* = .57); following cardiac surgery (adjusted OR, 0.88; 95% CI, 0.72-1.07; *P* = .20); and following hip fracture repair (adjusted OR, 0.74; 95% CI, 0.49-1.09; *P* = .13).
Alloimmunization to red blood cell antigens after universal leucodepletion. A regional multicentre retrospective study	Br J Haematol	Schonewille & Brand,2005	Multicenter Study	In conclusion, compared with BC leucoreduction, universal prestorage filter leucodepletion did not alter the development of clinically significant RBC alloimmunization.
Leucodepletion and Blood Products	MJAFI	Kumar et al.,2006	Qualitative and Descriptive	Universal leucodepletion is the best method in transfusion practice, but it is not cost-effective in developing countries like ours. To conclude, the aim should be to constantly prepare WBC-reduced blood products with less than 5 x 10^6 residual WBC so that primary alloimmunization to HLA antigens is prevented and transfusion is made safer.
Clinical effects of leucoreduction of blood transfusions	Neth J Med	Bilgin et al.,2011	Literature Review	Leucoreduction of platelet transfusions is significantly associated with a significant reduction of HLA-antibody formation and refractoriness to random donor platelet transfusions.
Cost-effectiveness of leucoreduction for prevention of febrile non-haemolytic transfusion reactions	Blood Transfus	Tsantes et al.,2014	Multicenter study	Leucoreduction does not have a favorable cost-effectiveness ratio in relation to the occurrence of FNHTR. However, many factors that cannot be efficiently and accurately assessed influence the long-term costs of transfusion.
Leucoreduction of blood components: an effective way to increase blood safety?	Blood Transfus	Bianchi et al.,2016	Literature Review	The current available literature data provides robust evidence supporting an equivalent role of CMV-seronegative and leucodepleted blood components in preventing the risk of CMV transfusion transmission.
Leucoreduction for preventing parasite transfusion-	Vox Sang	Jimenez-Marco &	Letter to the Editor	Although leucoreduction by filtration cannot completely eliminate parasitic transmission risk, it can represent a

Article title	Periodical	Authors/Year	Methodology	Summary of Results
transmission: an overlooked strategy		Girona Llobera,2019		suitable and inexpensive alternative for reducing leishmaniasis, malaria, and Chagas transfusion-transmission risk not only where they are endemic but also in non-endemic countries with a high rate of immigration from Latin America and Africa.
Effect of leukoreduction on transfusion-related immunomodulation in patients undergoing cardiac surgery	Transf Med	Khan et al.,2020	Clinical Trial	Leukocyte depletion decreased TRIM effects in patients undergoing cardiac surgery, but this also depends on the degree of leukoreduction. As our study found, hemofiltration is more effective than buffy-coat depletion alone.
Infectious complications in neonatal transfusion: Narrative review and personal contribution	Transf Apher Sci	Bianchi et al.,2020	Systematic review	Our data clearly show that transfusion-transmitted CMV infection in premature neonates is still a concern in neonatal care units. In this context, an evidence-based clear equivalence of leukoreduced to seronegative-donor cellular products is still lacking, even for fetal and neonatal transfusions.
Effect of post-storage filters vs. pre-storage filters for leukoreduction of blood components on clinical outcomes: a systematic review and meta-analysis	Syst Rev	Silva et a.,2021	Systematic review	This systematic review revealed that although the meta-analysis indicated that using a pre-storage filter is a protective factor against FNHTR after RBC and Platelet Concentrate transfusions, there was great statistical heterogeneity among the studies. The results for infection were inconclusive.
Can transfusion-associated graft-versus-host disease (TA-GvHD) be prevented with leukoreduction alone?	Transf Apher Sci	Rodriguez et al.,2022	Review	Newer technologies beyond leukocyte reduction/depletion or filtration offer much promise. Since the late 1990s, pathogen reduction techniques have been successful in causing irreversible damage to nucleic acids and impairing the replication and repair processes of enveloped and non-enveloped viruses, bacteria, protozoa, and even white blood cells.
Leukoreduction as a control measure in transfusion transmission of visceral leishmaniasis	Transfusion	Pereira et al.,2023	Retrospective, case-control	Higher prevalence in the group with non-leukoreduced blood components and low prevalence in those who received leukoreduced blood components, similar to non-transfused patients, highlight the risk of transfusional visceral leishmaniasis transmission and reinforce the role of leukoreduction in its prevention.
Leukoreduced red cell concentrates: Are they meeting the quality standards?	Asian J Tran Sci	Chand et al.,2023	Retrospective	The current generation of leukofilters could achieve 4 log reductions in leukocyte content. Various countries have adopted ULR policies to leukoreduced all the blood components prepared.
A retrospective observational study to estimate the risk of HLA alloimmunization	Immunbiology	Pandey et al.,2023	Observational	Patients who received leucodepleted RBC units had a significantly lower transfusion-associated alloimmunization rate than those who

Article title	Periodical	Authors/Year	Methodology	Summary of Results
with blood transfusion: Can the risk be reduced by leucodepletion?				received non-leucodepleted RBC units. Multiparous women had a high risk for transfusion-related alloimmunization compared to nulliparous women and male patients. Furthermore, class I-anti-HLA antibodies (HLA-B and HLA-A + B) were significantly associated with pregnancy sensitization and/or blood transfusion as a single sensitization.
Comparing transfusion reactions between pre-storage and post-storage leukoreduced apheresis platelets: an analysis using propensity score matching	Ann Hematol	Chien et al.,2024	Retrospective	This study suggests that pre-storage leukoreduction apheresis platelets significantly decrease the transfusion reaction compared with those in post-storage leukoreduction, especially in FNHTR. The crude rate of transfusion reactions for pre-storage and post-storage leukoreduction groups was 0.53% and 0.91%, respectively.
A randomized control trial to compare mortality in recipients of leucoreduced and non-leucoreduced whole blood transfusion in patients with cancer in Uganda	BMC cancer	Okello et al.,2024	Clinical Trial	This study failed to demonstrate any mortality difference in patients with cancer transfused with leucoreduced or non-leucoreduced whole blood in a sub-Saharan African setting, though the pre-specified sample size was underpowered for the study given the observed mortality rate.

Source: Authors of the study.

Twelve studies[9,15,18,19,33,40–45,49] suggested that leukoreduction is beneficial in preventing in-hospital mortality rates, alloimmunization to HLA antigens, preventing the risk of CMV transfusion transmission, protective factor against FNHTR after RBC and platelet concentrate transfusions, decreased transfusion related immunomodulation. However, two studies[46,47] showed no benefit to completely eliminating parasitic transmission risk and not altering the development of clinically significant RBC alloimmunization. Because of issues regarding study design, data analysis, and other factors, these findings are still a subject of debate. On the other hand, one study[69] was published that reported evidence of does not have a favourable cost-effectiveness ratio in relation to the occurrence of FNHTR. One randomized control trial study[48] found a failed to demonstrate any mortality difference in patients with cancer transfused with leucoreduced or non-leucoreduced whole blood in a sub-Saharan African setting.

Leukoreduction can be performed in two ways: prestorage filtration or poststorage filtration. The most widely used method in Europe and the USA is prestorage leukoreduction, where leukocytes are removed before they can contribute to storage lesions in RBC or cause transfusion reactions in platelets and RBC. This approach offers improved quality control, has not been linked to acute hypotensive episodes, and eliminates the need for transfusion services to manage filter inventories or for nursing staff to handle multiple blood administration protocols.

Leukoreduction has been shown to decrease the incidence of febrile reactions and other adverse effects associated with transfusions, as well as result in a reduced need for hospitalization. Patients with compromised immune systems, such as those undergoing cancer treatment, may particularly benefit from leukoreduction, showing better clinical outcomes.

By reducing complications such as febrile transfusion reactions, transmission of latent infections, and alloimmunization, leukoreduction minimizes the need for additional treatments and hospitalizations. This can translate into lower healthcare costs by decreasing the length of hospital stays, reducing the need for further interventions, and improving patient outcomes. Additionally, the prevention of long-term complications in patients requiring multiple transfusions, such as those with chronic conditions, can lead to significant savings over time. Thus, the initial investment in leukoreduction technology can be offset by these long-term benefits, improving both patient safety and financial efficiency.

The clinical benefits of leukocyte reduction far outweigh its potential drawbacks, and without cost considerations, most transfusion medicine professionals would strongly support the implementation of ULR through pre-storage filtration. However, some argue that, in the absence of sufficient data demonstrating universal benefits, the technology should be applied selectively, targeting only those patients who would clearly gain from this intervention.

DISCUSSION

Several studies indicate that reducing leukocyte counts offers additional clinical benefits, including shorter hospital stays, reduced antibiotic usage, and enhanced platelet transfusion efficiency[49–51]. Since 1990, European countries such as Germany, the United Kingdom, Ireland, and Portugal have implemented leukoreduction to prevent complications like transfusion reactions and the transmission of cCJD[52,53]. Prions are infectious proteins associated with a variety of progressive and fatal neurodegenerative diseases collectively referred to as transmissible spongiform encephalopathies[54,55]. The contamination of leukocytes in blood increases the risk of abnormal prion protein transmission, the probable causative agent of the new variant of vCJD[56,57].

Similarly, Canada has adopted leukoreduction to mitigate TRIM[58]. In contrast, leukoreduction is not widely practiced in Brazil, mainly in public health services. Brazilian legislation prioritizes recommending leukoreduction for specific patient groups but does not specify the timing of filtration, whether before or after storage[21].

Studies indicate that a significant percentage of healthy blood donors carry *Chlamydia pneumoniae* in their blood. The clinical significance of these findings is unknown; however, the eradication of these bacteria has been confirmed in leukoreduced units through real-time PCR and immunostaining tests that identified bacteria trapped in the filter mesh[59,60].

Leukoreduction reduces up to 42% of the infectivity associated with infectious prions. Modifications to specific prion surface affinity have been developed to enhance filtration efficiency for this purpose[24,57]. Some European countries and the United Kingdom have implemented universal leukodepletion under this risk[61].

In Brazil, clinical screening eliminates individuals with a diagnosis of CJD, a family history of CJD, significant residency in the United Kingdom or the Republic of Ireland after 1980, those who have received growth hormone or other non-recombinant pituitary-derived drugs, bovine insulin use, corneal and dura mater transplants, and those who have received blood component transfusions in the United Kingdom after 1980[14,61].

There has been a decrease in the incidence of transfusion-transmitted malaria in recent years. This accompanies the increased use of leukocyte filters and the fact that Brazil has well-defined clinical

criteria to prevent transmission. In endemic areas, screening for *Plasmodium* or its antigens is mandatory[62,63].

Studies provide evidence that leukocyte reduction filters are effective in reducing the number of parasites in infected blood, such as *Trypanosoma cruzi*, and this effectiveness partly depends on the concentration of parasites in the infected blood[62,64]. The mechanisms of *Trypanosoma cruzi* retention by leukocyte filters were evaluated, and concentrated samples of RBC and platelets were infected with the parasite and then filtered to measure removal capacity, showing a reduction of approximately 3 log[64].

The prevalence of positive serology for visceral leishmaniasis in asymptomatic individuals has been observed in endemic areas[46,65]. There are few cases in the literature suggesting transfusion as a probable cause of transmission of this disease[44]. Cardo (2006) demonstrated a substantial reduction in this parasite after filtration in intentionally contaminated blood[62].

Transfusion-related acute lung injury has been associated with transfusions of donor anti-leukocyte antibodies that react with alloantigens in the recipient's leukocytes. This potentially fatal complication occurs more frequently with blood donations from multiparous women. The use of leukocyte removal filters has been described as a way to mitigate this risk[66,67].

The leukoreduction process of cellular blood components, performed using leukocyte retention filters and potentially housing microorganisms, offers clear clinical benefits to recipients of allogeneic blood transfusions[44,68].

Khan et al.[18] conducted a prospective observational cohort study in 2020 to examine the immunomodulatory effects of leukocytes following transfusion in patients undergoing cardiac surgery and the overall outcomes. They found that BC depletion, which reduces leukocytes by only 1 log, is insufficient to prevent the post-transfusion TRIM effect in cardiac surgery patients, compared to leukofiltration, which achieves a 4-log reduction[18].

Chien and colleagues[45] conducted a retrospective study to evaluate and compare transfusion reactions between pre-storage and post-storage leukoreduced apheresis platelets. They found that pre-storage leukoreduction not only decreased the incidence of transfusion reactions but also reduced the release of inflammatory cytokines from leukocytes and lowered the risk of virus transmission by preventing the release of intracellular organisms from leukocytes during storage[45].

Hebert et al.[49] evaluated clinical outcomes following the implementation of ULR in Canada through a retrospective cohort study conducted across 23 academic and community hospitals (n=14,786). While the study did not show an increased risk of nosocomial infections, it did reveal a significant reduction in in-hospital mortality (p=0.04) after ULR was introduced. The authors noted that, assuming a 7% mortality rate during the control period, the reduced odds of death indicated by the findings would result in one life saved for every 120 patients receiving leukoreduced blood instead of non-leukoreduced blood. This outcome was consistent across all subgroups and varying levels of blood exposure. Additionally, the study found that ULR was associated with a lower frequency of febrile episodes and reduced use of antibiotics[49].

In costly, non-mandated blood safety policies, such as URL of RBC, physicians must decide whether to offer the novel product or stick with the conventional option. While leukoreduced blood is of higher quality than non-leukoreduced blood, the overall effectiveness of ULR has not been clearly established. The reduction in the rate of FNHTR is the only well-documented clinical safety benefit. This benefit can be relatively easily quantified in terms of cost when using leukoreduced blood products outside a narrowly defined group of at-risk patients[69].

Although the transfusion process is not without risks, despite the accumulated scientific knowledge and the current health regulations in place, this work aimed to identify the main practical

implications that leucoreduction can offer to patients, such as: reduced frequency and severity of NHFTRs, reduced risk of CMV transmission, reduced risk of HLA-alloimmunization and platelet refractoriness, reduced infectious risk associated with immunomodulation and reduced direct risk of transfusion-transmission bacteria.

The promotion of health through the use of leukocyte filters emerges as a strategy for prevention and improvement of medical care quality, positively impacting both patients and the efficiency of the healthcare system. Thus, ULR highlights the critical need for authoritative, evidence-based guidelines that establish standardized practices across all areas of transfusion medicine, including blood collection, component preparation, pre-transfusion testing, and screening for transfusion-transmitted diseases. Blood banks must take responsibility for ensuring optimal blood safety, guided by objective needs, clinical outcomes, and cost-effectiveness. Furthermore, it is essential to emphasize that blood safety involves a balance between the cost-effective implementation of safety measures and the appropriate utilization of blood components.

CONCLUSION

URL has no clinical disadvantages. The only downside is a relatively modest cost that is more than compensated for by the overall savings to the healthcare system. Therefore, an essential aspect of enhancing patient care is finding a way to implement URL for red cell and platelet transfusions.

It is concluded that while leukocyte filters offer several benefits in hemotherapy, the implementation of universal leucodepletion is not yet mandatory in many countries. Further studies are needed to assess the cost-effectiveness of this measure.

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