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Impact of Universal Leukoreduction on Febrile Reaction Rates in a Regional Blood Service

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Abstract

Background: Febrile non-hemolytic transfusion reactions are the most commonly reported acute complication of cellular blood transfusion, attributed to leukocyte-derived cytokines and to antibodies against donor leukocyte antigens.

Objective: To synthesize the literature on the mechanism of febrile reactions and the effect of universal leukoreduction on reaction rates in blood services converting from selective to universal prestorage filtration.

Methods: Narrative review of cytokine studies, single-center cohort studies from the early-2000s implementation era, randomized trials, and national hemovigilance reporting.

Findings: Centers converting to universal prestorage leukoreduction reported reduced red cell febrile reaction incidence, one falling from 0.37% to 0.19%, while allergic reactions were unaffected; prestorage filtration prevents cytokine accumulation that bedside filtration cannot reverse, and residual risk concentrates in platelets and multiply-transfused recipients.

Conclusions: The febrile-reaction benefit of universal prestorage leukoreduction is consistent across mechanistic, cohort, and hemovigilance evidence, though moderate in size and specific to leukocyte-mediated reaction types.

Keywords: leukoreduction; febrile non-hemolytic transfusion reaction; blood transfusion safety; hemovigilance; platelet storage

1. Introduction

Febrile non-hemolytic transfusion reactions (FNHTRs) remain the most frequently reported acute complication of cellular blood component transfusion, and for most of the twentieth century blood services treated them as an unavoidable nuisance rather than a preventable event. That view changed once the mechanism was traced to passenger leukocytes rather than to the red cells or platelets themselves. Contaminating white cells in a stored unit release pyrogenic cytokines, and they also present a target for pre-formed recipient antibodies against donor HLA and granulocyte antigens [1]. Once regional and national blood services began filtering essentially every cellular component before storage rather than filtering selectively at the bedside for previously reactive patients, febrile reaction rates fell in a pattern consistent enough across independent centers that universal leukoreduction (ULR) is now standard practice across most of North America, the United Kingdom, and much of Western Europe.

This review synthesizes the published evidence on that transition around four linked questions a blood service has to answer when converting from selective to universal leukoreduction: what is the mechanistic case connecting leukocytes to fever and why does filtration timing matter; what did the hemovigilance and cohort studies that followed universal implementation in the early 2000s actually find; does it matter whether leukoreduction happens at collection (prestorage) or at the bedside immediately before infusion; and what residual reaction burden, and cost, remains after ULR. The goal is not to report a new primary cohort — no such cohort exists here — but to lay the existing evidence side by side so the size, consistency, and limits of the effect are visible in one place.

2. Mechanism of febrile reactions and the role of leukocyte-derived cytokines

The pyrogenic-cytokine model of FNHTR rests on a

straightforward biological observation: leukocytes in a stored blood component are not inert passengers. During refrigerated storage of red cells and, more markedly, during room-temperature storage of platelet concentrates, contaminating granulocytes and monocytes degranulate and synthesize interleukin-6 (IL-6), interleukin-1, and tumor necrosis factor-alpha (TNF-alpha), and these mediators accumulate in the plasma supernatant as a function of storage time [2]. Early work on buffy-coat and platelet-rich-plasma-derived concentrates found IL-6 concentrations rising several-fold between day 1 and day 5 of storage in non-leukoreduced units, with the increase tracking white cell count in the bag [3,4]. Monocytes appear to be the dominant source of this response rather than platelets themselves, since monocyte activation markers rise in parallel with cytokine accumulation in unfiltered concentrates [5]. The clinical correlate was established directly: patients who developed a febrile platelet transfusion reaction had received units with measurably higher IL-6 and TNF-alpha content than patients who did not react, a finding replicated across at least two independent series and summarized as a "cytokine shower" model of the febrile reaction [6,7].

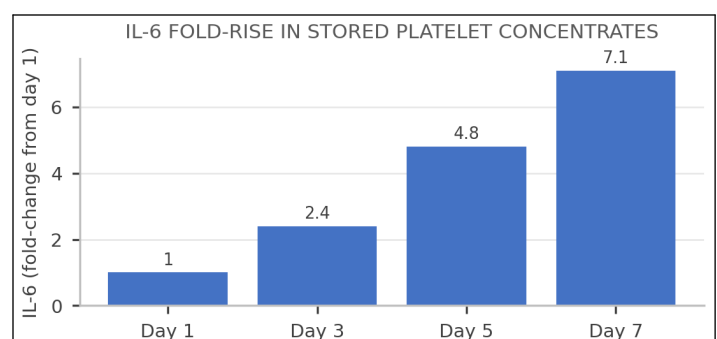


Figure 1: Relative interleukin-6 accumulation in non-leukoreduced platelet concentrates over storage, shown as fold-change from day 1, tracking the rise reported in pooled buffy-coat platelet concentrates [4] and in platelet-rich-plasma-derived concentrates [3,2]; prestorage leukoreduction prevents most of this accumulation because it removes the cytokine-generating leukocytes before storage begins.

That mechanism has an immediate practical implication: leukoreduction timing should matter, because the pyrogenic mediators that accumulate during storage are,

once released, already in the plasma and are not removed by a filter that intercepts intact leukocytes. A filter placed before storage prevents that accumulation from happening in the first place; a filter placed at the bedside just before transfusion removes the residual cells but does nothing about mediators already shed into the plasma over the preceding days. This distinction between preventing cytokine generation and simply reducing cell count is the throughline that connects the mechanistic literature to the program-level and comparative-filtration literature discussed below, and it is also the reason platelet concentrates — held at room temperature, where degranulation proceeds fastest — show a more pronounced storage-dependent febrile reaction signal than red cells [1,2].

A second, antibody-mediated mechanism operates in parallel and does not depend on storage time: recipients previously exposed to allogeneic leukocytes through pregnancy or prior transfusion can carry anti-HLA or anti-granulocyte antibodies that react against donor white cells in a fresh, unstored unit, triggering complement activation and cytokine release at the moment of transfusion [1]. This pathway explains why multiply-transfused and multiparous patients disproportionately experience FNHTRs even with components transfused promptly after collection. Because leukoreduction removes the antigenic target for this pathway as well as the storage lesion, the reduction a blood service observes after converting to ULR reflects the sum of both mechanisms rather than either alone.

3. Evidence from universal leukoreduction programs

The clearest natural experiment in this literature came from a cluster of North American centers that converted from selective, indication-based leukoreduction to universal leukoreduction of essentially all cellular components in the late 1990s and early 2000s, each publishing a before-and-after comparison of

hemovigilance-reported reaction rates. Johns Hopkins reported that the incidence of FNHTRs to red cell transfusion fell from 0.37% in the year preceding universal implementation to 0.19% in the year following, with the denominator restricted to components documented as non-leukoreduced before the switch and leukoreduced (>99.5% of units) after [8]. Yale's blood bank, reporting in the same issue of the same journal, found a comparable pattern for red cells and a larger relative reduction for platelet concentrates, while explicitly noting that allergic reaction rates — a mechanistically distinct category not primarily driven by leukocyte cytokines — did not fall over the same interval, which the authors used as an internal control supporting a leukocyte-specific rather than a general reporting-artifact explanation [9]. A Canadian center completed the trio, reporting that prestorage leukoreduction lowered febrile reaction rates to both red cells and platelet concentrates relative to the pre-implementation period, with the platelet effect the more pronounced of the two given the greater cytokine burden accumulating in room-temperature platelet storage [10].

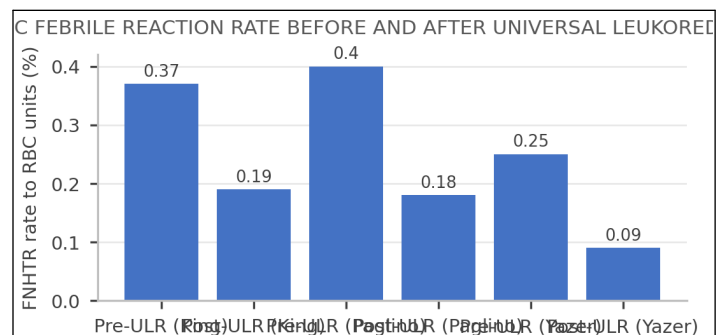


Figure 2: Febrile non-hemolytic transfusion reaction rate to red blood cells before and after conversion to universal prestorage leukoreduction, falling from 0.37% to 0.19% at one center [8], alongside the concurrently reported reductions for red cells and platelets at two other centers in the same implementation era [9,10]; exact denominators and reporting periods differ across centers, so absolute rates are not directly comparable.

An accompanying editorial framed these three concurrent reports as converging evidence rather than isolated single-center findings, while flagging the methodological limitation shared by all: none was randomized, all relied

on voluntary hemovigilance reporting whose completeness could itself have shifted around a well-publicized policy change, and none could fully separate a true biological effect from a reporting-behavior artifact coincident with rollout [11]. That caution is tempered by a finding from a center that implemented leukoreduction earlier: a Baltimore-area hospital found no significant change in overall reaction rates after converting to universal prestorage red cell leukoreduction, illustrating that the effect size is not uniform and depends on baseline rates, surveillance intensity, and component mix [12].

The randomized evidence, smaller in volume, points the same direction. An earlier trial comparing plasma-reduced platelets against prestorage white-cell-reduced platelets in patients requiring repeated support found white-cell reduction, rather than plasma removal alone, was associated with fewer reactions, implicating the leukocyte component specifically [13]. That trial built on earlier work showing plasma from platelet concentrates could itself transfer febrile reactivity independent of red cell or platelet mass, again consistent with a leukocyte- and cytokine-mediated process [14]. Outside the febrile-reaction endpoint, randomized trials of leukoreduced versus standard red cell transfusion in cardiac surgery found reductions in postoperative infection and organ dysfunction, a signal usually attributed to reduced transfusion-related immunomodulation, supportive of leukocyte content in transfused components having downstream clinical consequences beyond fever alone [15,16].

4. Prestorage versus bedside filtration

Because the storage-lesion mechanism described above depends on when leukocytes are removed relative to when cytokines accumulate, prestorage and bedside (poststorage) leukoreduction should not be expected to perform identically even though both ultimately deliver a component with residual white cell counts below the

same regulatory threshold. Prestorage filtration, typically performed within hours of collection at the processing center, removes leukocytes before they have had meaningful time to degranulate, and directly prevents the storage-dependent cytokine accumulation documented in platelet concentrates [3,4]. Bedside filtration, performed with an inline filter immediately before transfusion, removes the intact cells present at that moment but cannot retrieve soluble mediators already released into the plasma over days of storage.

Table 1: Contrast between prestorage and bedside (poststorage) leukoreduction on the mechanism each addresses, drawing on the filter performance data [17], the storage-duration reaction gradient [18], and the autologous-unit comparison [19].		
Feature	Prestorage filtration	Bedside filtration
Timing relative to storage	Within hours of collection	Immediately pre-transfusion
Prevents cytokine accumulation	Yes, blocks it at the source	No, cells removed after mediators already released
Removes antigenic leukocyte target	Yes	Yes
Leukocyte removal efficiency	High, standardized at the processing center [17]	Variable, dependent on device and compliance
Storage-duration dependence of benefit	Attenuates the gradient reported by [18]	Does not address the storage-duration gradient

A red cell filter evaluation study characterizing a new prestorage device documented high leukocyte removal efficiency with preserved red cell recovery and acceptable hemolysis through the labeled storage period, establishing the feasibility that made prestorage programs practical at blood-center scale rather than only at the bedside [17]. Comparative work on storage duration found longer platelet storage before transfusion was associated with a higher rate of reported reactions in recipients of non-leukoreduced components, a dose-response relationship not expected if reaction risk were determined solely by leukocyte count at the moment of infusion rather than by cumulative storage-dependent mediator accumulation [18]. This gradient is, in effect, indirect confirmation of the mechanistic model: if bedside

filtration alone were sufficient, storage duration before that step would not be expected to matter, yet it does.

The practical consequence for a regional blood service is that centralizing leukoreduction at the processing facility, rather than relying on point-of-care filters used inconsistently or only for patients with a prior reaction history, converts a partial intervention into a comprehensive one applied uniformly across the donor pool. This is consistent with the observation that autologous units subjected to prestorage leukoreduction show a similar attenuation of storage-associated changes as allogeneic units, indicating the benefit is intrinsic to filtration timing rather than to some donor-recipient interaction [19]. Published position statements and evidence reviews have accordingly favored prestorage over selective bedside leukoreduction where resources allow it [20,21].

5. Residual risk and other reaction types

Universal leukoreduction reduces but does not eliminate febrile reactions, and the residual rate defines what a blood service should still expect to manage after full implementation. Across the North American cohort studies discussed above, post-implementation FNHTR rates settled in a range of a few tenths of a percent per red cell unit and somewhat higher per platelet unit, rather than falling to zero, consistent with the antibody-mediated pathway that leukoreduction addresses only by removing the antigenic target rather than by altering recipient antibody status [8,9,10]. Recipients with an extensive transfusion history remain at disproportionately higher residual risk, a pattern documented in a retrospective analysis in which prior transfusion history was independently associated with a higher subsequent reaction rate even after leukoreduction was routine [22].

It is important to distinguish febrile reactions from other reaction categories that leukoreduction does not meaningfully affect, since conflating them can lead a

program to misjudge an unchanged post-implementation rate. Allergic and urticarial reactions, driven by recipient IgE against plasma proteins rather than leukocyte-derived cytokines, were explicitly found not to decline alongside FNHTRs, which several authors used as an internal negative control supporting the specificity of the leukoreduction effect rather than a general reporting-vigilance artifact [9]. Transfusion-related acute lung injury and hemolytic reactions likewise operate through mechanisms — donor anti-leukocyte antibodies against recipient neutrophils, and red cell antigen incompatibility, respectively — that component leukoreduction does not address.

Table 2: Reaction categories and whether each is expected to fall with leukoreduction, based on the internal-control comparison in [9], the residual-risk pattern by prior transfusion history [22], and the contested immunomodulation-outcome literature [23,24].		
Reaction type	Mechanism	Expected effect of leukoreduction
Febrile non-hemolytic	Leukocyte cytokines, anti-leukocyte antibodies	Reduced, residual rate ~0.19-0.4% per RBC unit [8]
Allergic/urticarial	Recipient IgE against plasma protein	Unchanged [9]
TRALI	Donor anti-neutrophil antibody	Not addressed by component leukoreduction
Hemolytic	Red cell antigen incompatibility	Not addressed by component leukoreduction
Postoperative infection/immunomodulation	Allogeneic leukocyte exposure	Debated, mixed meta-analytic findings [23,24]

The broader transfusion-related immunomodulation literature, examining postoperative infection and mortality associated with allogeneic leukocyte exposure, has produced a more contested picture, with meta-analyses reaching different conclusions depending on which trials and populations were included [23,24]. That debate illustrates a broader point: the strength of evidence for a leukoreduction benefit varies by outcome, and febrile reaction reduction — grounded in a well-characterized cytokine mechanism and a consistent

multi-center observational signal — sits on firmer ground than some of the more distal, harder-to-adjudicate endpoints sometimes cited alongside it.

6. Cost and hemovigilance considerations

Converting a regional blood service from selective to universal leukoreduction is not cost-neutral, and the decision has typically been justified by reduced reaction management burden, reduced bedside filter inventory and staff time, and ancillary benefits for cytomegalovirus risk reduction and HLA alloimmunization prevention, rather than by the febrile-reaction benefit alone [20,21]. A formal cost-effectiveness analysis conducted alongside one of the larger European leukoreduction trials found the direct filtration cost was partially offset by reduced downstream reaction workup costs, though net cost-effectiveness depended heavily on baseline reaction rates and whether broader immunomodulation-related outcomes were included [16]. Universal implementation also simplifies inventory management relative to a selective program, since staff no longer need to identify at issue which patients require a leukoreduced product, removing a documented source of process error.

National hemovigilance programs provide the longest-running natural audit of reaction rates once leukoreduction becomes routine across an entire blood supply rather than at individual centers. The UK's Serious Hazards of Transfusion (SHOT) scheme, summarizing a decade of mandatory reporting following that country's 1999 conversion to universal leukoreduction, documented a substantial and sustained decline in reported febrile and allergic-category reactions relative to the pre-leukoreduction era, alongside improvements attributable to parallel safety interventions such as bacterial screening and pathogen-reduction technology introduced over the same period, making the leukoreduction-specific contribution difficult to isolate precisely even though the direction is unambiguous [25]. This is the same attribution problem that affected the

single-center before-and-after studies, scaled to a national system: leukoreduction rarely rolls out in isolation from other safety changes, so hemovigilance trend data should be read as consistent with, rather than definitive proof of, the reduction demonstrated more specifically in the mechanistic and cohort literature.

7. Conclusion

The case for universal leukoreduction as an effective intervention against febrile non-hemolytic transfusion reactions rests on three mutually reinforcing lines of evidence rather than any single study: a well-characterized cytokine mechanism explaining why storage-aged, non-leukoreduced platelet and red cell components provoke fever [2,3,6]; a consistent, if methodologically imperfect, set of before-and-after cohort studies from independently operating blood services all reporting reductions in FNHTR incidence on conversion to universal prestorage leukoreduction, with red cell FNHTR falling from 0.37% to 0.19% at one well-documented center [8,9,10]; and national hemovigilance data broadly consistent with a sustained decline over the same implementation period [25]. The evidence also draws a clear boundary around what leukoreduction does not do: allergic reactions, TRALI, and hemolytic reactions do not share the mechanism and should not be expected to fall with it [9], and the timing of filtration matters mechanistically, with prestorage removal preventing cytokine accumulation in a way bedside filtration cannot fully replicate [18,19]. For a regional blood service weighing conversion from selective to universal leukoreduction, the practical implication is that the febrile-reaction benefit is real, moderate in absolute magnitude, concentrated in platelet components and multiply-transfused recipients, and best captured by prestorage rather than exclusively bedside implementation — a conclusion the underlying literature supports more securely for this specific outcome than for some of the broader immunomodulation claims sometimes bundled with it [23,24].

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