

*Review article***The role of blood microfilters in clinical practice**

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Abstract. Blood filters have been available since the 1930s. In this review we evaluate the role of microaggregate filters (MF) in certain transfusion complications, namely non-haemolytic febrile transfusion reactions (NHFT), pulmonary injury, thrombocytopenia, fibronectin depletion and histamine release. We review the latest generation of leucocyte depleting filters and discuss their role in preventing alloimmunisation, immunosuppression and CMV transmission. Finally, we provide a rationale for the role of blood microfiltration in the present day practice of intensive care medicine.

Key words: Microaggregate blood filters – Microaggregates – Leucocyte-depleting filters

Microaggregate blood filters, or microaggregate filters (MF), capable of removing microaggregate (MA) debris that would otherwise pass through standard 170 micron intravenous giving set filter have been developed from the mid 1960s. Microaggregate filters work on one of two principles: screen filtration or depth filtration [1].

Screen filters are screens with pores of a predetermined size and all particles larger than the pore size are held back. The screen is ideally made of a woven polyester material, the weave preventing movement between fibres thus maintaining a fixed pore size and the polyester material causing least damage to red cells [2]. During use the pore size becomes smaller due to plasma protein deposition on the screen [1] and therefore the potential exists to retain particles smaller than the pore size.

Depth filters work on the principle of adsorptive separation and to a lesser degree by mechanical separation. These filters consist of packed adsorptive material and

for filtration to be effective the adsorption force of the blood debris to the filter must be greater than the force acting in the direction of flow [1].

Eckert [1] has described the mechanism of action of these filters, highlighting that when coated with plasma the absorptive forces decrease and the filter becomes less efficient. In addition he states that other disadvantages of depth filters include prolonged contact with blood, and the possibility of unloading and channelling of particles already filtered. Wenz [3] has shown that these filters possess a larger dead space than screen filters leading to a greater red cell loss.

As a result of the advantages of screen filters over depth filters the clinical trend has been to use the former with depth filters rarely being used in modern day clinical practice.

Opinions on the role of microaggregate filters in routine clinical practice vary. Wenz [4] has stated – “All blood must be administered via a filtration device” and goes on to add “When is the microfiltration of whole blood and red cell concentrates essential? *Always*. When is it superfluous? A medical device which proves to have at least one advantage and no documented disadvantages is *never* superfluous”.

Others [5, 6] have shown their support for the above view by re-quoting him in their publications.

Derrington [7] however states “the use of microfiltration is probably an unnecessary expense and, where exsanguination is a risk may be positively dangerous” and adds “their routine use for transfusions, small or large, remains to be justified”.

The views expressed by Wenz and Derrington are not as divergent as they may appear. Both accept that all patients should get the benefit of doubt until the situation is further clarified. Whilst Derrington states that the expense of giving all patients the benefit of the doubt is probably unjustified on present evidence Wenz states that the benefits outweigh the potential disadvantages and justify the cost. To review this we will examine the formation of microaggregates and the complications they cause.

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Formation and effects of microaggregates

The early work on microaggregates concentrated on the formation of MA, and it was established that within a few hours of blood collection platelets begin to aggregate and form loosely bound structures [8]. After 24–48 h degenerating white blood cells (WBCs) get trapped in this structure and fibrin precipitation occurs resulting in a stable MA [5], a process which occurs in blood irrespective of the storage solution used. In the first week of storage, MA formation occurs faster in citrate, phosphate, dextrose anticoagulated blood (CPD) than in adenine, citrate, dextrose anticoagulated blood (ACD) [9]. However, after this time MA numbers are similar in both mediums and it has been estimated that by 2 weeks storage there are approximately 50–250 million microaggregates per unit [10]. Most recently blood stored in optimal additive solutions (Saline, adenine, glucose, mannitol, SAG-M) has been found to contain MAs and larger macroaggregates [6, 11]. Bolton [6] examined 321 units of unopened SAG-M blood and noted that 45.5% had particles visible to the naked eye and Robertson [11] reported that when the bags were examined by passing the blood through surgical gauze 85% of SAG-M units contained MA or macroaggregates.

When the structure, size range and the numbers of MA in stored blood had been established, attention turned to the clinical effects of infusing such large numbers of MA. Initially work concentrated on the physical effects and sequelae of entrapment of the MA within the lung micro-vasculature [12, 13], however since then numerous other consequences have been highlighted.

Non-haemolytic febrile transfusion reaction

As a result of increased blood matching and development of the closed bag system, fever due to haemolytic reactions or infections are now very rare. The commonest 'adverse transfusion reaction' accounting for 70% of all transfusion related problems is now the intra- or post-transfusion pyrexia [14] of which most are due to a host reaction to donor leucocytes [15] and it has been shown that these can be successfully reduced by transfusing leucocyte poor red cell concentrates [3, 16, 17].

The incidence of the non-haemolytic febrile transfusion reaction in the "normal" hospital population has been estimated as being between 0.5% [15] and 6.6% [16]. It is higher in the chronically transfused patient [17] and can be as high as 45% in thalassaemia patients [3, 18]. In an attempt to control the high frequency of reaction many methods have been developed to prepare leucocyte poor red cell concentrates.

Unfortunately many of these are expensive, result in significant red cell wastage, decrease the shelf life of the unit, disrupt the sterile seal of the unit and are therefore unsuitable for routine hospital transfusion [19]. As a result, simple methods to produce leucocyte poor red cell concentrates have been recently described. These include the spin and filter method [14] and the spin cool and filter method [18] utilising the MF to remove the leucocyte containing MA.

Wenz [3] and later Parravicini [18] demonstrated that these methods significantly reduced the rate of NHFTR in chronically transfused patients. In a series of trials they demonstrated that MF alone caused a fivefold decrease in the rate of the NHFTR while centrifugation and filtration decreased the incidence by 98%. This further decrease in the incidence of NHFTRs is believed to occur as granulocytes, the cells implicated in causing these reactions, are incorporated into MAs during centrifugation and the resulting MAs can be removed by filtration.

Microaggregate induced pulmonary injury

Microemboli associated with blood transfusion or otherwise have been implicated as a causative factor in the development of Adult Respiratory Distress Syndrome (ARDS) [12]. Robb et al. [20] demonstrated in an endotoxic albino rat model that progressive occlusion of the pulmonary circulation caused by microemboli occurred with stable systemic arterial and venous blood pressures.

In another animal study, Davidson et al. [21] showed, that in dogs, the rise in pulmonary artery pressure and total body oxygen consumption associated with massive exchange transfusion could be prevented by using a MF, suggesting that exogenous microemboli are the causative agent. In 1979 Dhurandhuer et al. [22] also using an animal model, confirmed the efficacy of MF in preventing pulmonary microemboli and histopathological changes secondary to the microemboli. Connell et al. [23] obtained similar results and demonstrated the MF were effective by showing that transfusion of washed red cells gave no additional protection to the lung.

Human studies have supported these results. Eckert [1] demonstrated histopathologically that MA were present in the lungs of brain dead patients following a 2000 ml blood transfusion and Ruel et al. in two separate studies [12, 13] found that traumatised patients, receiving massive blood transfusion with the MA removed by 40 µm filtration, demonstrated a much lower incidence of clinical ARDS than those who received blood through a giving set containing the standard 170 µm clot screen.

Despite these studies the definitive role of MF in prevention of human lung injury needs further clarification. The animal studies show both the role of MA in lung injury and the role of MF in preventing this. However, human studies are less conclusive and the significance of the Reul studies needs to be tempered by the small numbers involved. As yet no prospective randomised human study has demonstrated improved outcome following the use of microfilters.

Thrombocytopenia

Thrombocytopenia associated with massive blood transfusion is well recognised [24]. This was presumed to be due to a simple dilutional effect, however recent work [25–27] have shown that a significant fall in platelet counts in excess of that expected by simple haemodilution occurs with transfusions of a few units of blood.

Examining this in detail, Lim et al. [26] showed that anaemic and thrombocytopenic patients exhibited a significant decrease (41.7%) in platelet count after receiving

a 3 unit transfusion of SAG-M blood through a standard blood giving set. The same patients receiving another 3 unit transfusion, at a different time, through a MF had a resulting platelet count fall of only 4.6%. Using radio labelled platelets Bareford [27] showed that the degree of splenic sequestration of the platelets was significantly reduced when blood was transfused through a MF as compared to a standard giving set and could account for the difference in overall platelet levels. He also showed that washed red cells have no further advantage emphasising the role of MA rather than any plasma constituent in causing the splenic sequestration.

More recently Hart et al. [28] have shown that the maximal transfusion induced thrombocytopenia affect is not seen until 72 h post-transfusion. A consequence of this effect being time dependent is that a number of patients may have a platelet count within an acceptable range at 24 h post-transfusion but not at 72 h and therefore extended observation would be advisable.

This effect may also be of significance in intensive care and surgical patients whose platelet count may be falling due to sepsis, infection, operational procedure or trauma.

Fibronectin depletion

Fibronectin is an opsonic circulating glycoprotein which has a role in coating invading organisms and debris and presenting them to the reticulo-endothelial system (RES) for clearance from the circulation [29]. Following blood transfusion through a normal giving set there is a significant drop in fibronectin levels [29, 30], whilst transfusing blood through a MF prevents this fall [30]. The method by which this occurs is not known but is probably due to host fibronectin adhering to transfused MA and being prematurely removed from the circulation by the RES [27, 31].

In fibronectin depleted septic patients replenishing fibronectin levels has been shown to be beneficial in improving gas exchange in the lung and oxygen utilisation by tissues [32] presumably as the result of an improved pulmonary and systemic microcirculation.

Histamine release

Histamine levels are higher than normal in stored blood [33]. There is a further rise of histamine at the time of transfusion probably due to a combination of warming and contact with the drip tubing [33]. This further rise in histamine is mediated through basophil degranulations [33] and transfusing the blood through a MF decreases the number of infused basophils and thus reduces the rise of histamine [34]. The importance of this in the general population has not been established but coupled with the other transfusion related problems the cumulative effect within some patient groups may be important.

Potential problems of microfilters

Microfiltration of blood is essentially unphysiological. It places a varying burden on cellular elements [1] and can

potentially trigger chemical reactions in response to contact with a foreign surface [7]. Five potential problems exist with MF:

- exsanguination;
- haemolysis;
- release of foreign particles;
- platelet retention;
- complement activation.

Exsanguination

In the bleeding, critically hypovolaemic patient, the time taken to prime the filter can delay rapid blood volume replacement. However, the priming of a filter usually takes less than 1 min and once in place does not slow down transfusion time [2]. It has been shown that resistance to flow when a screen filter is present in line alone is not significantly different from that offered by simple giving sets [2]. However, increasing resistance to flow necessitating MF exchange may occur after 3–4 units of whole blood have passed through a depth filter and 7–8 units of whole blood through a screen filter [2].

Haemolysis

Screen MF (which work by filtration through a fixed size pore) appear to be free of the problem of haemolysis while depth filters (which work on the principle of adsorptive filtration) cause a degree of haemolysis especially with older blood [2, 35]. In a case report a 20 μm MF was associated with massive haemolysis and resulted in a death, however subsequent analysis of this report suggests that a neonate MF was improperly used in an infant resulting in massive haemolysis [36–38].

Release of foreign particles

In a review on MF, Derrington [7] quotes a reference by Eckert [1] as stating that foreign particles can be released into the blood stream during microfiltration. Scrutiny of Eckert's paper however failed to reveal any mention of this problem.

With depth filters however a theoretical possibility of this problem does exist as it is not possible to flush individual filters during manufacture. This is not the case with screen filters.

Platelet retention

Microaggregate filtration has been reported to remove viable platelets when fresh whole blood is transfused through them [7]. To examine this Snyder et al. [39] studied the effect of MF on donor platelets when fresh whole blood or platelet concentrates were transfused through them. They showed with platelet concentrates that there were no significant numerical, biochemical or in vitro functional changes in donor platelets passed through either depth or screen microaggregate filters. In contrast it was found that when whole blood was transfused through depth filters a significant number of platelets were trapped in the filter resulting in a fall in the platelet

count reaching the transfusion recipient. This did not occur with screen filters.

Complement activation

The possibility of MF causing complement induced endogenous MA formation and consequent pulmonary injury has been raised [7]. Yellon [40] demonstrated a 17% rise in C3 when nylon filter material was incubated with heparinised blood for 60 min. The relevance of such findings were investigated by Snyder [41] who found less than 10% rise in C3 when filter material was incubated with heparinised blood and less than 3% rise when incubated with citrated blood. The difference between anticoagulant types is not surprising as citrate acts by chelating Ca^{++} and Mg^{++} , essential ions for both the coagulation and complement cascades.

The clinical significance of the perceived rise in complement was also investigated by Snyder who related the experimental work to the clinical setting and passed citrated blood through a MF and once more observed a less than 3% rise in C3 levels and no C6 activation [41]. From this they concluded that the passage of citrated blood through a MF does not pose a clinical risk and does not represent a problem of MF.

Animal studies support the above conclusion [22]. Dogs sacrificed 48–144 h after receiving a massive exchange transfusion through a MF showed no evidence of microemboli in the lungs. This indicates that any endogenous MA load secondary to complement activation is too small to be detected histologically in the lungs of these animals and therefore not of consequence.

In conclusion none of the potential problems suggested to be associated with MF, are of clinical significance. Screen MF cause less haemolysis of older blood and less

of a reduction in the platelet count of transfused whole blood than depth filters.

Leucocyte depleting blood filters

Filtration through a MF of blood stored for two weeks results in removal of approximately 90%–95% of the leucocytes providing a typical residual count in the order of $8 \pm 3.7 \times 10^8$ /unit [14]. This process has been found to be successful in preventing many transfusion related complications, as discussed, but other problems of cytomegalovirus (CMV) transfer, alloimmunisation and immunosuppression, require a greater degree of leucocyte depletion.

Immunosuppressed patients, transplant recipients and chronically transfused patients are particularly prone to these complications.

As the CMV resides solely in the leucocyte, minimising the number of transfused leucocytes will decrease the incidence of transfusion associated CMV transmission. The evidence for the efficacy of leucocyte depletion in preventing CMV transmission is presented in Table 1.

Transfusion of leucocytes is also believed to be central to the pathogenesis of transfusion associated alloimmunisation and immunosuppression [24]. Prevention of these problems require leucocyte depletion to less than $1-5 \times 10^6$ /unit [42]. The evidence for the efficacy of leucocyte depletion in preventing alloimmunisation associated platelet refractoriness is reviewed in Table 2.

To help prevent these problems in recent years a new generation of leucocyte depleting filters have been developed which allow high level removal of leucocytes from red cells or platelets at the time of transfusion [42]. These filters have been designed to deplete blood products of

Table 1. Leucocyte depletion of random red cells and platelets prevents transmission of cytomegalovirus (CMV) to immunocompromised CMV seronegative recipients

Study	No. and nature of initially seronegative patients	Residual WBCs leucocytes-depleted groups		CMV infection post transfusion	
		RBCs	Platelets	Control	Leuco deplet
Verdonck [44]	29 Bone marrow transplant	$< 1 \times 10^6$ /unit (BCR + Erypur)	CMV seronegative	N/A	0/29
de Graan Hentzen [45]	61 Acute leukemics	$< 2 \times 10^7$ /unit (BCR + Erypur)	$< 2 \times 10^8$ /6 unit pool	N/A	0/61
Murphy [46]	20 Acute leukemics	$< 8 \times 10^6$ /unit (Imugard)	Mean 2×10^8 /PC (centrifugation) or mean 1×10^7 /PC (dual stage harvesting)	2/9	0/11
Gilbert [47]	72 Neonates	94%–99% Removal (Imugard)	Not administered	9/24	0/30
de Graan Hentzen [48]	55 High dose chemoradiotherapy and BMT	$< 1 \times 10^6$ /unit	Seroneg	N/A	0/55
de Graan Hentzen [49]	59 Remission induction	$< 1 \times 10^6$ /unit	1×10^7	N/A	0/59
	192 Cardiac surgery	1.1×10^9	Not given	14/80 (17.5%)	9/112 (8%)
de Graan Hentzen [49]	59 Haematologic malignancy patients	Mean 1.4×10^6 /unit	$< 1 \times 10^7$ /4–6 units	N/A	0/59
	86 Cardiac surgery patients			10/86	N/A
Bowden et al. [50]	17 Autologous BMT	99.9% Removal Pall RC100	99.9% Pall PL100	N/A	0/17

BMT, Bone marrow transplant; BCR, buffy coat removed; N/A, not available

Table 2. Refractoriness by using standard platelets and leukocyte-depleted platelets: review of literature (after Saarinen: Blood Jan 1989, pp 512–517)

Study	No. of patients		Contaminating leukocytes/unit		Refractory state	
	A	B	A	B	A	B
Eernisse [51]	27	68	500×10^6	5×10^6	93%	24%
Schiffer [52]	48	50	65×10^6	12×10^6	19%	16%
Murphy [53]	31	19	1060×10^6	60×10^6	23%	5%
Sniecinski [54]	20	20	530×10^6	6×10^6	50%	15%
Andreu [55]	35	34	64×10^6	6×10^6	47%	21%
Brand [56]		335		5×10^6		9%
Myllylä [57]	18	21	200×10^6	$< 1 \times 10^6$	6%	0%
Saarinen [58]	21	26	200×10^6	$< 1 \times 10^6$	52%	0%

A, Standard platelets; B, leukocyte-free/depleted/poor platelets

leucocytes by adsorbing the leucocytes in addition to filtering out microaggregates. Compared to MF they are more expensive, transfusion times are longer and are designed to allow only 1 or 2 units of red cells per filter. As a result of these constraints, use is currently restricted to the chronically transfused, those patients particularly at risk of alloimmunisation and those immunosuppressed patients at risk of developing CMV associated disease. If however the immunosuppressive effect of the foreign leucocyte is implicated in post operative infections and recovery rates, as has been recently suggested [43], the role of leucocyte depleting filters may need to be re-evaluated.

Conclusion

It is the authors' view that from the evidence presented, at the present time, the beneficial effects of MF in the chronically transfused, the thrombocytopenic and those receiving massive blood transfusions, is sufficient to recommend their routine use in these patients. The authors also believe that the routine use of MF in critically ill patients at risk of developing sepsis, ARDS and Multi-Organ Failure, is also justified until such time that a definitive trial disproves the benefit in this situation.

The routine use of MF in patients not at risk of ARDS and Multi-Organ Failure for a single or two unit transfusion is more contentious. In this population the hosts ability to clear a MA load and maintain an appropriate plasma fibronectin level should be adequate. Similarly a drop in platelet levels in patients with previously normal platelet counts and a functioning bone marrow is likely to be of little significance.

Although studies on the non-haemolytic febrile transfusion reaction have been performed in chronically transfused patient, it seems reasonable to assume that the use of MF will decrease the incidence of this reaction in other hospital populations as the mechanisms are the same in all groups. It would similarly decrease the incidence of histamine mediated problems.

In conclusion, it appears that the use of microfilters is warranted in a broad array of intensive care settings, and the authors believe that in the evidence from the liter-

ature the routine use of microaggregate filters is warranted in the critically ill patient.

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References

- Eckert G (1980) Prevention of pulmonary microembolism during blood transfusion by means of fine mesh filters. *Anaesthesia*. *Intensivther Notfallmed* 15:201–206
- Buley R, Lumley J (1975) Some observations on blood microfilters. *Ann Coll Surg Engl* 57:262–267
- Wenz B (1983) Microaggregate blood filtration and the febrile transfusion reaction. *Transfusion* 23:95–98
- Wenz B (1986) When is microfiltration of whole blood and red cell concentrate essential? When is it superfluous. *Int Forum Vox Sang* 50:63–64
- Lloyd GM, Marshall L (1986) Blood microaggregates, their role in transfusion reactions. *Intensive Care World*, 3:119–122
- Bolton DT, Peeters A (1988) Microaggregates and filtration. Correspondence. *Anaesthesia* 43:330–331
- Derrington C (1985) The present status of blood filtration. *Anaesthesia* 40:334–347
- Wright G (1974) ACO and CPO blood preservation. *Lancet* II:173
- Wright G (1975) The causes and effects of blood cell aggregates. International Symposium on the Fine Screen Filtration of Stored Blood, pp 21–32
- Lowe GD (1981) Filtration in IV therapy. A review of the clinical and technical aspects of intravenous fluid and blood filtration, in four parts. Part III: Clinical aspects of blood filtration. *Br J IV Ther* 2:28–38
- Robertson M, Boulton F, Doughty R, MacLennan JR, Collins A, McClelland DBL, Prowse CV (1985) Macroaggregate formation in optimal additive red cells. *Vox Sang* 49:259–266
- Reul GJ, Beal AC, Greenberg S, (1974) Protection of the pulmonary vasculature by fine screen blood filtration. *Chest* 66:4–9
- Reul GJ, Greenberg SD, Lefrak EA (1973) Prevention of post traumatic pulmonary insufficiency fine screen filtration of blood. *Arch Surg* 106:386–394
- Wenz B, Gurtlinger KF, O'Toole AM, Dugan EP (1980) Preparation of granulocyte poor red blood cells by microaggregate filtration: a simplified method to minimise future transfusion reactions. *Vox Sang* 39:282–287
- Perkins HA, Payne R, Ferguson J, Wood M (1966) Non haemolytic febrile transfusion reactions. Quantitative effect of blood components with emphasis on isoantigenic incompatibility of leucocytes. *Vox Sang* 11:578–600
- Mollison PL (1979) *Blood transfusion in clinical medicine*, 6th edn. Blackwell P, p 1033
- Milner LV, Butcher K (1978) Transfusion reactions reported after transfusion of red blood cells and of whole blood. *Transfusion* 18:493–495
- Parravicini A, Rebulli P, Apuzzo J, Wenz B, Sirchia G (1984) The preparation of leucocyte poor red cells for transfusion by a simple cost effective techniques. *Transfusion* 24:508–509
- Meryman HT and Hornblower H (1986) The preparation of red cells depleted of leucocytes. Review and evaluation. *Transfusion* 26:101–106
- Robb HJ, Mongulis RR, Jalo CM (1972) Role of pulmonary microembolism in the haemodynamics of endotoxic shock? *Surg Gynecol Obstet* 135:777–783
- Davidson IJ, Barret A, Miller E, Litwin S (1975) Pulmonary microembolisms associated with massive transfusion. *Ann Surg* 181:51–57
- Dhurandhur HN, Brown C, Barrett J, Litwin S (1979) Pulmonary structural changes following microembolism and blood transfusions. *Arch Pathol Lab Med* 103:335–340
- Connell RS, Swank RL, Webb MC (1973) Pulmonary microemboli

- after blood transfusions. An electron microscope study. *Am Surg* 177:40–50
24. Miller RD, Robbins TO, Tang MJ, Barton SL (1971) Coagulation effects associated with massive blood transfusion. *Ann Surg* 174:794–801
 25. Monnucci PM, Federici AB, Sirchia A (1982) Haemostasis testing during massive blood replacement. *Vox Sang* 42:113–132
 26. Lim S, Boughton BJ, Bareford D (1989) Thrombocytopenia following routine blood transfusion: micro-aggregate blood filters prevent worsening thrombocytopenia in patients with low platelet counts. *Vox Sang* 56:40–41
 27. Bareford D, Chandler ST, Hawker RJ, Jackson N, Smith M, Boughton BJ (1987) Splenic platelet sequestration following routine blood transfusion is reduced by filtered/washed blood products. *Br J Haematol* 67:177–180
 28. Hart S, Bareford D, Smith N, MacWhannel, Lanchbury E, Boughton B (1990) Post-transfusion thrombocytopenia: its duration in splenic and asplenic individuals. *Vox Sang* 59:123–124
 29. Saba TM, Jaffe E (1980) Plasma fibronectin (opsonic glycoprotein): its synthesis by vascular endothelial cells and role in cardiopulmonary integrity after trauma as related to reticuloendothelial function. *Am J Med* 68:577–594
 30. Snyder EL, Mosher DF, Hezzey BA, Bock J, Golenwsky G (1980) Effect of blood transfusion on plasma fibronectin. *Anaesthesiology* 53 (Abstract S191)
 31. Snyder EL, Mosher DF, Hezzey BA, Golenwsky G (1981) Effects of blood transfusion on in vivo levels of plasma fibronectin. *J Lab Clin Med* 98:336–341
 32. Scovill WA, Saba TM, Blumenstock FA, Bernard H, Powers SR (1978) Opsonic surface binding glycoprotein therapy during sepsis. *Ann Surg* 188:521–529
 33. Frewin DB, Jonsson JR, Head RJ, Russell WJ, Beal RW (1984) Histamine levels in stored human blood. *Transfusion* 24:502–504
 34. Frewin DB, Jonsson JR; Davis KG, Beilby AM, Haylock DN, Beal RW, Russell WJ (1987) Effect of microfiltration on the histamine levels in stored human blood. *Vox Sang* 52:191–194
 35. Dunbar RW, Price KA, Cannarella CF (1974) Microaggregate blood filters: effect on filtration time, plasma haemoglobin and fresh blood platelet counts. *Anaesth Analg* 53:577–583
 36. Langhurst DM, Gooch WM, Castello RA (1983) In vitro evaluation of a paediatric microaggregate blood filter. *Transfusion* 23:170–177
 37. Schmidt WF, Kim HC, Schwartz E, Tomassini N (1982) RBC destruction caused by a micropore blood filter. *J Am Med Assoc* 248:1629–1632
 38. Linko GE (1983) Microaggregate filters and neonate patients. *Transfusion* 23:537–548
 39. Snyder EL, Mezzey A, Cooper-Smith M, Jones R (1981) Effects of microaggregate blood filtration on platelet concentrated in vitro. *Transfusion* 21:427–434
 40. Yellon RF, Vernick S, Golub AH (1981) Complement activation by blood micro-filters. *Transfusion (Abstract)* 21:610–611
 41. Snyder EL, Root RK, McLeod B, Dalmaso AP (1983) Activation of complement by blood transfusion filters. *Vox Sang* 45:288–293
 42. Meryman HT (1989) Transfusion induced alloimmunisation and immunosuppression and the effect of leucocyte depletion. *Transfusion Med Rev* 3:180–193
 43. Tartter PI (1988) Blood transfusion and infectious complications following colorectal cancer surgery. *Br J Surg* 75:789–792
 44. Verdonck LF; de Graan-Hentzen YCE, Dekker AW, Mudde GC, de Gast GC (1987) Cytomegalovirus seronegative platelets and leukocyte-poor red blood cells from random donors can prevent primary cytomegalovirus infection after bone marrow transplantation. *Bone Marrow Transplant* 2:73–78
 45. de Graan Hentzen YCE, Gratama JW, Mudde GC, van Loon AM, Verdonck LF, Willemze R, Brand A, de Gast GC (1987) Prevention of primary cytomegalovirus infection during induction treatment of acute leukemia using at random leucocyte poor blood products. *Br J Haematol* 66:421
 46. Murphy MF, Grant PCA, Hardiman AE, Lister TA, Waters AH (1988) Use of leucocyte poor blood components to prevent cytomegalovirus (CMV) infections in patients with acute leukemia. *Br J Haematol* 20:253–255
 47. Gilbert G, Hayes K, Hodson IL, James J (1989) Prevention of transfusion acquired cytomegalovirus infections in infants by blood filtration to remove leucocytes. *Lancet* 1:1228–1231
 48. de Graan Hentzen YCE, de Gast GC, Gratama JW, Brand A, Verdonck LF, Mudde GC (1989) Prevention of primary CMV infection by leukocyte depletion of blood products. 2nd International Cytomegalovirus Workshop, p 13
 49. de Graan Hentzen YCE, Gratama JW, Mudde GC, Verdonck LF, Houbiers JGA, Brand A, Sebens FW, van Loon AM, The TH, Willemze R, de Gast GC, (1989) Prevention of primary cytomegalovirus infection in patients with haematologic malignancies by intensive white cell depletion of blood products. *Transfusion* 29:757–760
 50. Bowden RA, Sayers MH, Cays M (1989) The role of blood product filtration in the prevention of transfusion associated cytomegalovirus infection after marrow transplant. 42nd Annual Meeting AABB.
 51. Eernisse JG, Brand A, (1981) Prevention of platelet refractoriness due to HLA antibodies by administration of leukocyte-poor blood components. *Exp Haematol* 9:77–81
 52. Schiffer CA, Dutcher JP, Aisner J, Hogge D, Wiernik PH, Reilly JP (1983) A randomized trial of leukocyte-depleted platelet transfusions to modify alloimmunisation in patients with leukaemia. *Blood* 62:815–820
 53. Murphy MF, Metcalfe P, Thomas H, (1986) Use of leukocyte-poor blood components and HLA matched platelet donors to prevent alloimmunization. *Br J Haematol* 62:529–539
 54. Sniecinski I, O'Donnell NR, Nowicki B, (1988) Prevention of refractoriness and HLA alloimmunisation using filtered blood products. *Blood* 71:1402–1407
 55. Andreu G, Dewailly J, Leberre C, Quarre MC, Bidet ML, Tardivel R, Devers L, Lam Y, Soreall E, Boccaccio C, Piard N, Bidet JM, Genetet B, Fauchet (1988) Prevention of HLA immunization with leucocyte poor packed cells and platelet concentrates obtained by filtration. *Blood* 72:964–969
 56. Brand A, Claas FHJ, Voogt PJ, Wasser MNJM, Eernisse JG, (1988) Alloimmunisation after leukocyte depleted multiple random donor platelet transfusions. *Vox Sang* 54:160–166
 57. Myllyla G, Ruutu R, Oksanen V, Kekomaki R, Rasi V, (1986) 19th Congr Int Soc Blood Transfusion, Australia (Abstract)
 58. Saarinen TM, Kekomaki R, Siimes M, Myllyla G (1990) Effective prophylaxis against platelet refractoriness in multitransfused patients by use of leucocyte-free blood components. *Blood* 75:512–517

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