Review

Safety and effectiveness of apheresis in the treatment of infectious diseases: A systematic review

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ARTICLE INFO

SUMMARY

Objectives: Apheresis has been used as adjunctive treatment of severe *falciparum* malaria, loiasis and babesiosis. This systematic review aimed to investigate the safety and efficacy of apheresis in the treatment of these conditions.

Methods: MEDLINE, PUBMED, EMBASE and CINAHL databases were searched to identify studies published between January 1969 and March 2018 involving patients treated using apheresis for severe *falciparum* malaria, loiasis or babesiosis. Data extracted included details about the apheresis intervention, populations, study methods and outcomes relating to efficacy and safety.

Results: A total of 67 publications met the inclusion criteria and were included in the data synthesis, 36 for malaria (70 cases), 17 for babesiosis (22 cases) and 14 for loiasis (34 cases). Publications were case reports, case series, and cohort studies; there were no randomised controlled trials identified. Potential publication bias was considered to be high.

Conclusions: Systematic review of the literature suggests that apheresis may be a useful adjunct in the treatment of patients hospitalised for babesiosis, and prior to chemotherapy in loiasis with microfilarial count >8000 parasites/mL. Data does not support the use of apheresis in patients with severe *falciparum* malaria.

Introduction

Apheresis is the removal of a specific component of an individual's blood, with the remainder being returned to the individual. Apheresis may involve the removal of red blood cells (erythrocytapheresis), white blood cells (leukocytapheresis), plasma (plasmapheresis), or platelets (thrombocytapheresis). Currently, centrifugal apheresis is the preferred method whereby blood components are separated based on buoyancy. Modern automated apheresis systems are computer-controlled devices that undertake continuous removal, separation of the target component, and then return blood.[1] Advantages of apheresis over exchange transfusion include greater haemodynamic stability, lower risk of electrolyte imbalances, less chance of transfusion related complications including fluid overload, transfusion reactions and blood borne infections,[2] and speed such that a whole blood volume can be exchanged in 1.5 h[3] compared to 5 h with an exchange transfusion.[2] The primary drawback of apheresis is its limited availability, predominantly in specialist centres, typically in high income settings. Citrate reactions are the most likely adverse event and are a result of low blood calcium levels consequent on the use of citrate for anticoagulation. The vast majority of citrate reactions are mild and typically involve transient parasethiae around the mouth, nose, ears and extremities.[4] Very rarely citrate reactions may cause seizures or abnormal heart rhythms. If symptoms develop, they are treated with intravenous calcium, resulting in rapid resolution.

In the case of malaria, automated erythrocytapheresis, also known as red cell exchange (RCE), has been used with the rationale of reducing the parasitized red blood cell concentration by replacing *Plasmodium*-infected red cells with normal donor red cells. RCE, as well as exchange blood transfusion, were historically used as adjuncts to intravenous quinine therapy for severe *P. falciparum* malaria with hyperparasitaemia (parasitaemia >5%), as per WHO recommendations prior to the availability of intravenous artesunate.[5] The rapid parasite clearance resulting from artesunate therapy has resulted in exchange transfusion and RCE falling out

of favour as a treatment for malaria.[6,7] The question arises as to whether apheresis should be reconsidered as an adjunct to treatment for severe *falciparum* malaria in cases of hyperparasitaemia with coexisting artemisinin resistance as it was during the pre-artemisinin era.

Babesiosis is a rare potentially lethal vector-borne protozoan infection. The illness resembles malaria and, like malaria, *Babesia* parasites infect erythrocytes and can sequester.[8] Immunodeficient patients, particularly patients who are HIV infected, >50 years old, or with a history of malignancy and/or asplenia may develop severe babesiosis, which is a more serious illness, complicated by disseminated intravascular coagulopathy (DIC), acute renal failure and haemolytic anaemia. Most patients respond well to atovaquone and azithromycin or clindamycin and quinine (for severe cases).[9] It is thought that RCE acts by physically removing infected erythrocytes, thus lowering the parasite burden to a level where the immune system and antimicrobials can control the infection.

Loiasis is a parasitic infection spread by vectors including the deerfly (*Chrysops)* and is endemic to west and central Africa. Clinical manifestations include Calabar swellings (non-tender swellings around joints in arms and legs) and eye worm (visualisation of adult worm passing across the conjunctivae). Rare complications include renal impairment, pneumonitis, painful lymphadenopathy, scrotal swellings and pleural effusions.[10] Apheresis, as well as albendazole, can be used to reduce the parasite burden in loiasis prior to chemotherapy with diethylcarbamazine (DEC), with the aim of reducing the likelihood of treatment-induced side effects, particularly encephalopathy which can be fatal with high microfilarial counts (>30,000/ml).[11]

The purpose of this systematic review is to investigate the safety and effectiveness of apheresis as adjuvant treatment for malaria, loiasis and babesiosis. Although in each of these conditions there is a biologically plausible rationale for the use of apheresis, ethical and logistical issues mean there is a low likelihood that randomised control trials will be undertaken to assess the safety and efficacy of apheresis in the treatment of these conditions. Thus, this systematic review of the existing literature is aimed at providing as much guidance as possible. The use of apheresis as a treatment of medical conditions that may be caused or triggered by infection will not be assessed: for example, pulmonary hypertension secondary to leucocytosis in severe *Bordetella pertussis* infection, thrombotic thrombocytopaenic purpura, which is caused by *E.coli* 0157, or Guillain-Barre syndrome triggered by *Campylobacter jejuni* infection.

Methods

The complete protocol for this systematic review is included in Appendix 1, the methodology is summarised below.

Search strategy and selection criteria

The search strategy aimed to find both published and unpublished studies in which male or female patients of any age were treated using apheresis for the following infectious diseases: severe *falciparum* malaria (including artemisinin-resistant *P. falciparum*), loiasis or babesiosis.

Only studies in which automated apheresis (erythrocytapheresis and plasmapheresis) was used were included. Studies that evaluated whole blood exchange transfusion were excluded. However data were included from reports where an individual patient received both exchange transfusion and apheresis and the relative outcomes of each could not be separated.

A two-step search strategy was utilized. An initial limited search of MEDLINE, PUBMED, EMBASE and CINAHL was undertaken as follows (searches #1 and #2 were combined using AND).

Search #1

Blood Component Removal [MeSH] OR Cytapheresis [MeSH] OR Plasma Exchange [MeSH] OR Plasmapheresis [MeSH] OR Plateletpheresis [MeSH] OR apheres* [ti.ab.kw] OR cytapheres* [ti.ab.kw] OR plateletpheris*[ti.ab.kw] OR thrombocytapheres*[ti.ab.kw] OR thrombocytophares*[ti.ab.kw] OR "red cell exchange" [ti.ab.kw]

Search #2

Malaria, Falciparum [MeSH] OR Loiasis [MeSH] OR Babesiosis [MeSH] OR "falciparum malaria"[ti.ab.kw] OR "plasmodium falciparum" [ti.ab.kw] OR loias* [ti.ab.kw] OR "Loa" [ti.ab.kw] OR babesi* [ti.ab.kw]

The indices of the following journals were hand searched: *Journal of Clinical Apheresis, Transfusion and Apheresis Science, Therapeutic Apheresis and Dialysis.* An analysis of the title, abstract, and keywords of all retrieved articles was undertaken to ensure the article fit inclusion criteria.

Secondly, the reference list of all identified reports and articles was searched for additional studies. Studies published in all languages were considered for inclusion in this review. Papers not written in English and identified as potentially relevant (based on their title and/or abstract) were translated as required. Because apheresis was introduced in the 1970s, searches were restricted to studies published from 1 January 1969 to 16 March 2018. Literature searches were not restricted to a type of study. Animal studies were excluded.

Data extraction and synthesis

The data extracted included specific details about the apheresis intervention, populations, study methods and outcomes of relevance to the review questions and objectives.

The characteristics of apheresis were recorded where documented including the apheresis protocol (e.g. number of cycles), apheresis equipment (e.g., Hemonetics™ model, COBE™ Spectra™, etc.), and continuous or discontinuous removal and replacement of blood cells.

The effectiveness endpoints recorded were specific to each disease and were based upon previous studies of disease. For malaria, the endpoints were the reduction in percentage parasitaemia, the clinical outcome (survival vs death), and complete recovery from severe malaria without lasting complications. For loiasis, the endpoints were the percentage reduction in microfilariae, reduction of microfilariae <8000/mL, and absence of adverse events from DEC treatment post apheresis. For babesiosis, the endpoints were the percentage reduction in parasitaemia and clinical outcome (survival vs death). The safety endpoints recorded were the number and type of adverse events and complications due to apheresis. If a range was given for parasitaemia, the middle of the range was selected as the value.

All data were entered in duplicate. Effect sizes expressed as weighted mean differences (for continuous data) and their 95% confidence intervals [95% CI] were calculated for analysis. Heterogeneity was explored using subgroup analyses based on the different study designs included in this review. Where statistical pooling was not possible, the findings were presented in narrative form including tables and figures to aid in data presentation where appropriate.

Results

Article screening

Description of included studies

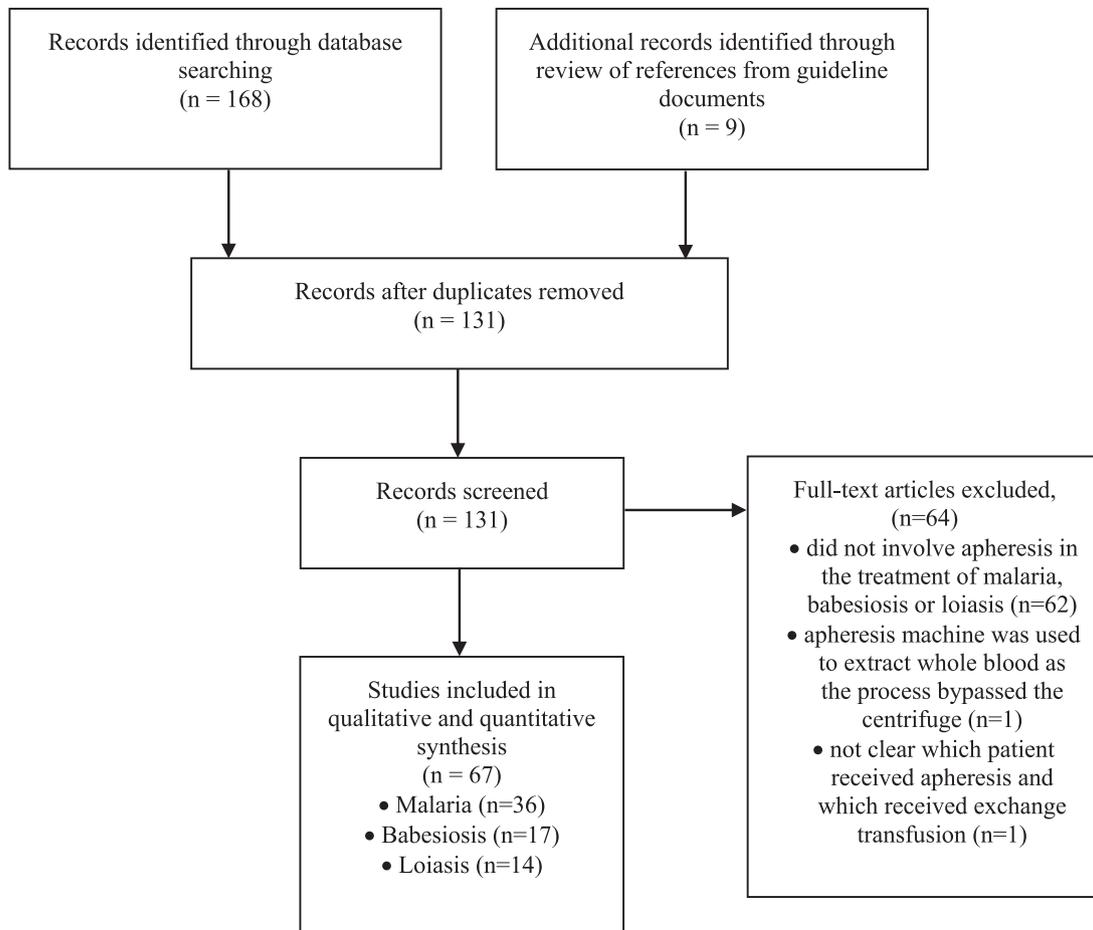A flowchart indicating the systematic selection of publications for inclusion in this review is presented in Fig. 1.

Fig. 1. PRISMA flowchart indicating the systematic selection of publications for inclusion in this review.

Malaria-related articles consisted of 19 case reports, 15 case series and 2 cohort studies. There were 5 studies that involved plasmapheresis only, 5 studies with plasmapheresis and RCE, and the remaining 23 studies involved RCE only.

Babesiosis-related articles consisted of 14 case reports and 3 case series. Loiasis-related articles consisted of 10 case reports and 4 case series. Additionally, personal correspondence from Dr. Thomas Nutman from the National Institutes of Health outlining his experience with the use of apheresis in treatment of loiasis was included.

Risk of bias

Apheresis is predominantly undertaken in high-resource settings, and also in institutions with sophisticated facilities and trained staff that improve the likelihood of survival (such as access to an intensive care unit and renal replacement therapy).

There are no randomised control trials assessing the use of apheresis in the treatment of any of the three diseases under study. This is primarily a reflection of the relatively low number of cases of severe *falciparum* malaria, severe babesiosis and loiasis in locations, where apheresis is available. Thus, the potential bias is large as only case reports, case series and cohort studies have been published.

Publication bias will likely play a large part as studies that demonstrate perceived improvement of tolerance of apheresis and survival are more likely to be published. Although we included studies published in languages other than English (following translation), there may be a bias towards articles published in English as the journals where index searching was used published in English

only. However, only one additional article was identified using the index searches of journals.

Summary of study findings

Summary tables containing individualised data for all patients included in the study for all three conditions can be found as supplementary material.

Apheresis in treatment of malaria

A total of 36 suitable publications were identified that included data on 70 patients, with a total of 87 apheresis procedures. Individual data were available on 73 procedures and grouped data on 14 procedures. An additional 7 patients only underwent plasmapheresis, with a total of 14 procedures. The remainder of patients either underwent RCE alone or RCE and plasmapheresis. Of the 70 patients, 19 were from case reports, 42 were from case series and 9 were from cohort studies. All patients had confirmed severe malaria as per WHO criteria.[12] Table 1 summarises the main findings.

In several studies, parasitaemia estimates were not explicit (e.g. >70% or <1%); in these cases parasitaemia levels were designated as 70% and 1% respectively. There were seven patients where the peak parasitaemia was described as greater than a specific value. In such cases this may be an underestimate of peak parasitaemia. For a similar reason, it is possible that the level of parasitaemia reduction may also have been underestimated. Of the five (7.1%) patients who were reported to not have completely recovered, two (2.9%) died. One patient had what the authors described as "minimal organ damage", one had persistent memory impairment and

Table 1
Apheresis in treatment of malaria.

Demographics	
Number of patients	70
Number of male patients	44 (62.9%)
Median age (IQR) in years	40 (26–49)
Number of apheresis procedures	87
Blood tests	
Median pre-apheresis haemoglobin (IQR) g/dL	9.8 (6.7–12)
Median platelets nadir (IQR) $\times 10^9$/L	27 (16–44)
Parasitaemia	
Median (IQR) peak parasitaemia	28% (14.5–46.5)
Median% reduction (IQR) in parasitaemia for all apheresis procedures	80% (68.4–90)
Median% reduction (IQR) in parasitaemia for 1st apheresis procedure per patient ($n = 50$)	80% (68.4–90.9)
Median% reduction (IQR) in parasitaemia for 2nd apheresis procedures per patient ($n = 44$)	76.8% (42.9–90)
Log_{10} reduction (IQR) in parasitaemia for all apheresis procedures	1.61 (1.2–2.3)
Log_{10} reduction (IQR) in parasitaemia for 1st apheresis procedure per patient ($n = 50$)	1.6 (1.2–2.4)
Log_{10} reduction (IQR) in parasitaemia for 2nd apheresis procedure per patient ($n = 44$)	1.46 (0.56–2.30)
Safety of apheresis	
Number of patients with AEs related to apheresis	3 (4.3%)*
Number of patients with AEs possibly related to apheresis	3 (4.3%)*
Clinical outcome	
Number of patients who made a full recovery	65 (92.9%)
Number of patients who died	2 (2.9%)
Number of patients who experienced complications	3 (4.3%)

* The presence or absence of AEs was only specified for 35 patients; the percentage is based on the assumption that if AEs were not specified than none occurred. IQR=interquartile range; AEs= adverse events.

Table 2
Characteristics of malaria patients treated using apheresis.

	NR excluded	NR interpreted as not present
Cerebral malaria	33/62 (53.2%)	33/70 (47.1%)
Pulmonary oedema	24/58 (41.4%)	24/70 (34.3%)
Renal failure	39/64 (60.9%)	39/70 (55.7%)
Hyperbilirubinaemia	31/44 (70.5%)	N/A
DIC	16/39 (41.0%)	N/A
Hyperlactaemia*	12/16 (75%)	N/A
Hypoglycaemia	5/27 (18.5%)	N/A

* included a cohort study with 5 patients with a median lactate of 5.1 mmol/L. NR = not recorded; DIC=disseminated intravascular coagulopathy.

one developed persistent renal impairment (creatinine 165 µmol/L), peripheral neuropathy and retinopathy all thought to be secondary to malaria. One of the patients who died had a Glasgow Coma Scale (GCS) 3/15, and pinpoint pupils at presentation, suggesting that this patient's condition was unsalvageable. The patient who was reported to have persisting memory impairment, had a GCS of five prior to RCE, and required intensive supportive treatment, including mechanical ventilation, vasopressor support with norepinephrine, and dialysis.

Of the 62/70 (88.6%) patients where antimalarial drug treatment was documented, only 9/62 (14.5%) included artemisinin-based therapy. A significant number of studies did not record (NR) whether their patients had cerebral malaria, pulmonary oedema or renal failure. Although it could be argued that these were not reported because they were absent, this cannot be stated with certainty. Hence, for cerebral malaria, pulmonary oedema and acute kidney injury, we carried out an additional analysis where NR is interpreted as not present (see Table 2). However, it must be emphasised that this additional analysis is likely to mean that we underestimate the frequency of these conditions.

The reporting of other complications, such as hyperbilirubinaemia, hyperlactataemia, hypoglycaemia and coagulopathy may have also been incomplete; they require blood testing for diagnosis. However as the absence of reporting is less likely to represent true absence, they are not included in the additional analysis (Table 2).

There were only three adverse events thought to be related to apheresis. These events were all transient hypotension; in one patient this was treated by fluid resuscitation and two others were simply monitored until resolution. Pulmonary oedema was later seen in two of these patients, although the reports suggest this was unlikely to have been related to apheresis.[3,13] Of note, all 3 patients who had adverse events related to apheresis survived without any complications. Acute Respiratory Distress Syndrome (ARDS) occurred post RCE in 3 of the 6 patients in a case report by Molla et al.[14] The authors comment that it is not clear if the ARDS was related to RCE or malaria; all had hyperparasitaemia (23%, 58% and 80%), and drug treatment began shortly before apheresis.

It is notable that there were no adverse events reported in patients with anaemia or thrombocytopenia: Hb levels were not reported to be reduced in the 3 patients who developed hypotension (12.0 g/dL, 13.7 g/dL and NR).

Apheresis in treatment of babesiosis

A total of 17 suitable publications were identified that included data on 22 patients who underwent a total of 29 RCE and 4 plasmapheresis procedures. Table 3 summarises the main findings.

No adverse events were reported although this was only specified for four out of 33 (12.1%) procedures. There were 4 deaths; one of the deaths occurred 5 days, and another 6 days after the blood film became negative for *Babesia*. One patient had a background of chronic relapsing pancreatitis secondary to acute fulminant alcoholic pancreatitis, and was due to have a total pancreatectomy or a biliary diverting procedure, but due to intraoperative complications a gastrojejunostomy was performed instead and the patient contracted transfusion related babesiosis. *Babesia* parasitaemia improved from 30% to 6.6% following initiation of quinine and clindamycin and two RCE procedures. However, the patient's bilirubin continued to increase despite the insertion of a biliary drain and the decision was made to withdraw active treatment. In the final case the authors believed that the cause of death was myocardial infarction. In this case, babesiosis was thought to be a contributing factor. It is not possible to ascertain the true effect that babesiosis had in each of these deaths.

Table 3
Apheresis in treatment of babesiosis.

Demographics	
Number of patients	22
Number of male patients	16 (72.7%)
Median age (IQR) in years	64.5 (47–67)
Number of apheresis procedures	33
Parasitaemia	
Median% Reduction (IQR) in parasitaemia for all apheresis procedures	71.4% (60–91.7)
Median% Reduction (IQR) in parasitaemia for 1st apheresis procedure per patient (n = 15)	83.3% (57.6–96.7)
% Reduction in parasitaemia for 2nd apheresis procedure per patient (n = 2)	50%, 95%
Safety of apheresis	
Number of patients with AEs related to apheresis	0[*]
Clinical outcome	
Number of patients who died	4 (18.2%)

[*] The presence or absence of AEs was only specified for 4 patients. IQR = interquartile range; AEs = adverse events.

Table 4
Apheresis in treatment of loiasis.

Demographics	
Number of patients	34
Number of male patients	25 (74%)
Median age (IQR) in years	32 (27–41)
Number of apheresis procedures	61
Microfilaraemia	
Median% reduction (IQR) in microfilaraemia per apheresis procedure for all apheresis procedures	51.7% (28.9–70.8)
Median% reduction (IQR) in microfilaraemia for 1st apheresis procedure n = 24)	60.3% (27.4–82.5)
Median% reduction (IQR) in microfilaraemia for 2nd apheresis procedure (n = 9)	38.2% (32.6–50.4)
Median% reduction (IQR) in microfilaraemia for 3rd apheresis procedure (n = 10)	52.2% (36.7–64.7)
Median absolute reduction (IQR) in microfilaraemia per apheresis procedure for all apheresis procedures	2400 (1250–6750) microfilariae/ml
Median absolute reduction (IQR) in microfilaraemia for 1st apheresis procedure (n = 24)	2450 (1110–7100) microfilariae/ml
Median absolute reduction (IQR) in microfilaraemia for 2nd apheresis procedure (n = 9)	6600 (2370–7200) microfilariae/ml
Median absolute reduction (IQR) in microfilaraemia for 3rd apheresis procedure (n = 10)	1515 (1200–4900) microfilariae/ml
Number of patients with pre-apheresis microfilariae count >8000/ml with successful reduction to <8000/ml by apheresis	9/12 (75%)[*]
Safety of apheresis	
Number of patients with AEs related to apheresis	12 (35.3%)[#]
Clinical outcome	
Number of patients with DEC related AEs post apheresis	3 (8.8%)

Median (IQR) percentage and absolute reduction in microfilaraemia for the 1st, 2nd and 3rd apheresis procedures could only be calculated if pre and post-apheresis microfilarial count data were available for the procedure. Out of 61 apheresis procedures, 18 had missing microfilarial count data.

[*] Only assessable in 12 patients; in the remaining patients it was not possible to confirm that this target was met as the patients either had microfilaremia <8000/ml prior to apheresis, or data on microfilaremia were incomplete.

[#] The presence or absence of AEs was only specified for 28 patients; the percentage is based on the assumption that if AEs were not specified than none occurred. IQR = interquartile range; AEs = adverse events; DEC = diethylcarbamazine.

Apheresis in treatment of loiasis

A total of 14 identified publications included data on 34 patients with a total of 61 apheresis procedures. Table 4 summarises the main findings.

The generally accepted aim of apheresis in loiasis is to reduce the microfilariae level to as low as possible prior to anti-filarial therapy, with efforts made to target <8000/ml (although this level has been chosen relatively arbitrarily).[11,15] In 22 patients it was not possible to confirm that this target was met, as the patients either had microfilaremia <8000/ml prior to apheresis, or data on microfilaremia were incomplete. In the 12 patients that could be assessed, 9/12 (75%) reached this target. In the other three patients, there was a substantial reduction in parasitaemia (15,000 to 10,666, 37,500 to 20,000 and 21,900 to 8900).

A total of 12 patients were reported to have experienced adverse events related to apheresis. The most common adverse event was a reduction in platelet count. Other adverse events include reductions in lymphocyte count, haemoglobin and haematocrit. Lastly, difficultly in venous access was experienced in an obese woman (body mass index 40.1) and short-lived generalised weakness occurred following the procedure.

Personal communication from Dr. Thomas Nutman from the National Institutes of Health was also received. Since 1987, 72 apheresis procedures have been carried out in 50 patients, most of whom had microfilariae levels >1000/ml. No adverse events related to apheresis have been reported. The team typically aims for a 7 Litre apheresis procedure focused at the monocyte interface (Buffy coat) for maximal microfilarial yield. No reliable data on reduction in parasitaemia are available, given that multiple types of apheresis equipment were used over this 30 year period and standardized assessment of microfilarial counts were not performed on all individuals. It was also noted that carrying out procedures at midday

and re-checking the microfilarial level 24 h post apheresis is the only real way to provide accurate results about microfilarial clearance through apheresis because of the natural diurnal periodicity of microfilaremia.

Discussion

The aim of this review was to analyse the safety and efficacy of apheresis in the treatment of severe *P. falciparum* malaria, severe babesiosis and loiasis. The review highlights the relative lack of high quality, prospective studies for all three diseases.

Malaria

Assessing the effectiveness of parasite reduction was difficult because many studies did not report parasite counts immediately before or after RCE; in some cases they were taken more than 24 h after the procedure. This is compounded by sequestration of infected erythrocytes during the second half of the *P. falciparum* life-cycle, making the relative contribution of apheresis, sequestration or drug effect difficult to determine.[16–20] Moreover, the timing of drug treatment relative to apheresis was rarely documented. The median 80% (IQR 68.4-90) reduction in parasitaemia per apheresis procedure may therefore overestimate the true reduction.[21] It should be noted that, independent of parasite clearance, other potential benefits of apheresis such as removal of toxins or cytokines[22,23] could help improve overall prognosis; this could explain the clinical improvements experienced following plasmapheresis.[23–25]

Complete recovery in 65/70 (92.9%) of patients in our analysis, was an interesting finding given that, the literature suggests, malaria patients treated with apheresis are typically more unwell than the general population with severe malaria.[26,27] Specifically, this is evidenced by a higher Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) 2 score (26 versus 17)[26] and a higher initial median parasitaemia (46.5% vs 7.3%) in apheresis treated patients compared to those who were not treated using apheresis.[27] Anecdotally, several cases describe RCE as rescuing patients who were rapidly deteriorating,[28] or clinical improvement soon after RCE or plasmapheresis.[24,25] Plasmapheresis has also been used as an adjunct to antimalarial therapy,[24,25,29] with or without RCE and as a potential treatment for thrombotic microangiography[24] and associated renal failure.[24,29] However, the numbers are relatively small making interpretation of therapeutic benefit very difficult.

Adverse events were rare, even in patients with thrombocytopaenia or anemia. Some RCE procedures were complicated by transient hypotension,[13,30] with most cases resolving without intervention or following fluid resuscitation,[30] all patients made a full recovery from malaria. Molla et al[14] reported a case series involving 6 patients with severe *P. falciparum* treated with RCE. Three patients developed ARDS post RCE requiring mechanical ventilation. The authors could not determine if the ARDS was due to malaria or RCE but all three were at high risk of ARDS as they had hyperparasitaemia (23%, 58% and 80%) and multiple features of severe malaria including cerebral (2/3), renal (3/3) and DIC (2/3). All patients who experienced possible adverse events from apheresis completely recovered.

Our review specifically focused on the use of apheresis and not whole blood exchange transfusion. A comprehensive review on exchange transfusion in severe malaria demonstrated no difference in outcome with overall mortality rates of 17.8% and 15.9% for exchange transfusion and non-exchange transfusion respectively (odds ratio 0.84; 95% CI 0.44-1.60).[31] This review, and to a greater extent, the introduction of fast acting artesunate treatment, was influential in leading to a change in WHO and CDC guidelines to rec-

ommend that exchange transfusion not be used in severe malaria. The majority of patients identified in the review were not treated with artemisinin based therapy. The more rapid decline in parasite counts mediated by artemisinin based therapy means that the therapeutic effect of apheresis may have been lower if a greater number had received artemisninin-based therapy.

Tan et al. assessed exchange transfusion as a whole and did not distinguish between manual and automated exchange.[31] The authors did comment on apheresis techniques, but the commentary largely focused on the rate of adverse events from apheresis reported by a 1999 study by Mcleod et al[32] with an overall complication rate of 10.3% in 78 procedures. This is greater than the complication rate observed in our study of 3/87 (3.4%) procedures.

A clinician may be faced with a patient with severe *P. falciparum* from an area of high prevalence for artemisinin resistance and a high parasitaemia, or alternatively they may not have access to artesunate in a timely manner or be unable to use artesunate, for example in the case of allergy (very rare[33,34]). Given the low rate and short-lived nature of adverse events experienced during apheresis (3/70 [4.3%] patients), in such circumstances it may be considered as adjunctive treatment. If apheresis is undertaken and hypotension occurs, it would be more appropriate to stop the procedure given the data supporting the conservative use of intravenous fluid treatment in the management of severe malaria infection.[35] RCE should be carried out at least 3–4 h post artesunate dosing to avoid removal of artesunate and its metabolite dihydroartemisinin.[27,36,37] Apheresis should only be used where there is local expertise and should not delay artesunate treatment. The spread of artemisinin resistance may mean that apheresis could assume a renewed place in the treatment of severe *P. falciparum* in the future.[38]

Overall, the published data indicate that the use of apheresis in the context of severe *P. falciparum* is safe and may have some therapeutic benefit. However, given the lack of randomised control studies, there is insufficient evidence to support the general application of apheresis as an adjunct, use of apheresis as routine treatment, or its establishment in resource limited settings solely for the treatment of severe malaria.

Babesiosis

The use of RCE and apheresis in babesiosis have mainly been extrapolated from evidence in malaria. *Babesia*-infected patients with high parasite loads have been treated with adjunctive whole blood exchange transfusion, or apheresis-mediated RCE, to reduce parasite burden. Patients hospitalised with babesiosis have a mortality of 6–9%, with case fatality rates of up to 21% in immunocompromised patients.[8,39,40] However, the patients in this review appear to reflect the severe end of the spectrum, with a median parasitaemia pre-apheresis of 20.25% compared to median parasitaemia levels of 7.6% to 15.1% in most studies.[8,39,40] All but one of the patients identified during this review had identifiable risk factors for immunosuppression, and 4/22 patients died.

In terms of the safety of RCE in severe babesiosis, no adverse events related to RCE were reported. Furthermore, the low mean (SD) haemoglobin level pre-apheresis 7.6 g/dl (2.2 g/dl) suggests the procedure is safe and well tolerated even at low haemoglobin levels.

Guidelines from the Infectious Diseases Society of America suggest that RCE should be carried out in anyone with renal, liver, respiratory failure, significant haemolysis or high parasitaemia.[41] They advise that one RCE volume is sufficient, as it replaces 85–90% of the patient's RBCs; this is the same advice given by the American Society for Apheresis (AFSA).[42] ASFA suggests RCE for *Babesia*-infected patients with parasitaemia >10%, or with significant comorbidities such as significant haemolysis, DIC, pulmonary,

renal or hepatic compromise. In *Babesia*-infected patients who are asplenic, RCE is recommended even in asymptomatic patients. In addition, plasmapheresis is recommended for critically ill asplenic patients not responding to chemotherapy or RCE, or with severe coagulopathy.[42] The data these recommendations are based on is considered weak.

With the high reliance on case reports and lack of randomised control trials, the available data are not of sufficient quality to support the routine use of RCE in babesiosis. However, given the high mortality rate in immunosuppressed hospitalised patients, the lack of adverse events from the apheresis procedure, and the low number of *Babesia*-related deaths identified in this review, the data suggests RCE may be considered by clinicians as a useful adjunct to standard chemotherapy in hospitalised patients with *Babesia* infection (especially those with immunosuppression). Plasmapheresis may be considered if there is evidence of haemolytic anaemia, or if there are specific concerns regarding renal failure (e.g. in the context of renal transplant).

Loiasis

Apheresis is aimed at reducing the microfilarial load prior to treatment with DEC, reducing the likelihood of treatment related encephalopathy.[11,15] This review demonstrated a median (IQR) parasitaemia reduction of 51.7% (28.9–70.8%) across all apheresis procedures where both pre- and post-procedure data are available. Given the diurnal variation and potential for microfilariae to migrate from the periphery, it cannot be assumed that this reduction is solely due to apheresis, but it is highly likely to be contributing.

Safety data suggests apheresis is an acceptable intervention as long as subjects have relatively normal platelet and haemoglobin counts. Given the clinical benefits of reducing the parasite count prior to anti-filarial treatment, and the good safety profile, the data support apheresis for the treatment of *Loa loa*-infected patients with high microfilarial counts.

General considerations

The study endpoint was parasite clearance for malaria and babesiosis and microfilarial clearance for loiasis. This does not allow any firm conclusion for other biological benefits of RCE or plasmapheresis, or indeed clinical outcome. Indeed any observed clinical improvement post apheresis could also be due to a delayed effect from the curative chemotherapy therapy. Of course it is important to remember that non-circulating parasites will not be removed during apheresis, and hence return to the circulation. Thus, increases in parasite burden following apheresis may not necessarily signify failure of apheresis, and repeat apheresis should not be ruled out.

This study assessed all the original published data on the use of apheresis in the treatment of malaria, babesiosis and loiasis. No randomised trials were identified and only cohort studies, case series and case reports were available, reflecting the fact that most of these conditions are rare in resource rich settings where apheresis is available. Study findings were most relevant to high resource settings where the majority of apheresis procedures took place. In particular, the frequency of adverse events could be higher if apheresis was used in low resource settings. Overall, the small sample sizes, lack of hard clinical endpoints and limitations of study design issues make it extremely difficult to clearly identify beneficial or harmful effects of adjunctive apheresis on clinical outcome in any of the three conditions. More data may become available should apheresis become established in resource poor settings for the treatment of other conditions such as sickle cell disease, potentially allowing RCTs in severe *P. falciparum* or loiasis, although these would be challenging. There is no doubt that standardised

recording and publication of data for any patients treated with apheresis would be valuable.

Conclusion

Existing data suggests that apheresis may be a useful adjunct to chemotherapy in the treatment of patients hospitalised for *Babesia*, and prior to chemotherapy in loiasis with microfilarial count >8000 parasite/mL on the basis of reduction of parasite counts, but there are no clear clinical benefits. Our review does not currently support the use of apheresis in patients with severe *P. falciparum* malaria.

Declaration of Competing Interest

The authors declare to competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.09.014.

References

1. Ward DM. Conventional apheresis therapies: a review. *J Clin Apher* 2011;**26**:230–8.
2. van Genderen PJ, Hesselink DA, Bezemer JM, Wismans PJ, Overbosch D. Efficacy and safety of exchange transfusion as an adjunct therapy for severe *plasmodium falciparum* malaria in nonimmune travelers: a 10-year single-center experience with a standardized treatment protocol. *Transfusion* 2010;**50**:787–94.
3. Macallan DC, Pocock M, Bishop E, Bevan DH, Parker-Williams J, Harrison T, et al. Automated erythrocytapheresis in the treatment of severe *falciparum* malaria. *J Infect* 1999;**39**:233–6.
4. Holig K, Kramer M, Kroschinsky F, Bornhauser M, Mengling T, Schmidt AH, et al. Safety and efficacy of hematopoietic stem cell collection from mobilized peripheral blood in unrelated volunteers: 12 years of single-center experience in 3928 donors. *Blood* 2009;**114**:3757–63.
5. World Health Organisation Severe *falciparum* malaria. *Trans R Soc Trop Med Hyg* 2000;**94**(Suppl 1):S1–90.
6. Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate versus quinine for treatment of severe *falciparum* malaria: a randomised trial. *Lancet* 2005;**366**:717–25.
7. Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, et al. Artesunate versus quinine in the treatment of severe *falciparum* malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010;**376**:1647–57.
8. Krause PJ, Gewurz BE, Hill D, Marty FM, Vannier E, Foppa IM, et al. Persistent and relapsing babesiosis in immunocompromised patients. *Clin Infect Dis* 2008;**46**:370–6.
9. Vannier E, Krause PJ. Human babesiosis. *N Engl J Med* 2012;**366**:2397–407.
10. Gibbs RD. Loiasis: report of three cases and literature review. *J Natl Med Assoc* 1979;**71**:853–4.
11. Awadzi K, Gilles HM. Diethylcarbamazine in the treatment of patients with onchocerciasis. *Br J Clin Pharmacol* 1992;**34**:281–8.
12. World Health Organisation (WHO). *World Helath Malaria Report*. Geneva: WHO; 2017.
13. Harris P, Price S, Senthuran S, Cochupanachimootil J, Norton R. Automated erythrocytapheresis for severe *falciparum* malaria. *Intern Med J* 2011;**41**:60–3.

14. Molla S, de La Rubia J, Arriaga F, Fernandez MJ, Carpio N, Marty ML. Role of exchange transfusion in patients with severe *falciparum* malaria: report of six cases. *Haematologica* 2001;**86**:208–9.
15. Boussinesq M, Gardon J, Gardon-Wendel N, Chippaux JP. Clinical picture, epidemiology and outcome of *loa*-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon. *Filaria J* 2003;**2**(Suppl 1):S4.
16. Bryan AW, Qian Q, Kirby JE. Photo quiz: a man with fever and headache. *J Clin Microbiol* 2017;**55**:351.
17. Zhang Y, Telleria L, Vinetz JM, Yawn D, Rossmann S, Indrikovs AJ. Erythrocytapheresis for *plasmodium falciparum* infection complicated by cerebral malaria and hyperparasitemia. *J Clin Apher* 2001;**16**:15–18.
18. Boctor FN. Red blood cell exchange transfusion as an adjunct treatment for severe pediatric *falciparum* malaria, using automated or manual procedures. *Pediatrics* 2005;**116**:e592–5.
19. Fraser IP, Cserti CM, Dzik WH. Case records of the massachusetts general hospital. case 32-2006. A 3-year-old girl with fever after a visit to Africa. *N Engl J Med* 2006;**355**:1715–22.
20. Siegenthaler N, Giraud R, Bendjelid K. Erythrocytapheresis and sublingual micro-vascular flow in severe malaria. *Clin Hemorheol Microcirc* 2010;**46**:299–304.
21. Sanz LM, Crespo B, De-Cozar C, Ding XC, Llergo JL, Burrows JN, et al. *P. falciparum* in vitro killing rates allow to discriminate between different antimalarial mode-of-action. *PLoS ONE* 2012;**7**:e30949.
22. Winters JL. Plasma exchange: concepts, mechanisms, and an overview of the American society for apheresis guidelines. *Hematol Am Soc Hematol Educ Program* 2012;**2012**:7–12.
23. Lapinski TW, Prokopowicz D, Miegoc H, Kalinowska A, Nahorski WL. Plasmapheresis in the treatment of tropical malaria. *Rocz Akad Med Bialymst* 1999;**44**:254–9.
24. Ou TY, Chuang CY, Chen CD, Cheng CY. Therapeutic plasma exchange in the treatment of complicated *plasmodium falciparum* malaria: a case report. *J Clin Apher* 2018;**33**:419–22.
25. Bolandard F, Hommel D, Hulin A. [Plasma exchange and severe *plasmodium falciparum* malaria. apropos of 2 cases]. *Cah Anesthesiol* 1995;**43**:371–3.
26. Auer-Hackenberg L, Staudinger T, Bojic A, Locker G, Leitner GC, Graninger W, et al. Automated red blood cell exchange as an adjunctive treatment for severe *plasmodium falciparum* malaria at the Vienna general hospital in Austria: a retrospective cohort study. *Malar J* 2012;**11**:158.
27. Calvo-Cano A, Gomez-Junyent J, Lozano M, Castro P, Cid J, Nicolas JM, et al. The role of red blood cell exchange for severe imported malaria in the artesunate era: a retrospective cohort study in a referral centre. *Malar J* 2016;**15**:216.
28. Mainwaring CJ, Leach MJ, Nayak N, Green ST, Jones DA, Winfield DA. Automated exchange transfusion for life-threatening *plasmodium falciparum* malaria-lessons relating to prophylaxis and treatment. *J Infect* 1999;**39**:231–3.
29. Bambauer W. [Plasmapheresis or exchange transfusion in severe tropical malaria?]. *Dtsch Med Wochenschr* 1985;**110**:1953.
30. Watanaboonyongcharoen P, Park YA, Poisson JL, Brecher ME. Rapid increases in parasitemia following red cell exchange for malaria. *J Clin Apher* 2011;**26**:315–19.
31. Tan KR, Wiegand RE, Arguin PM. Exchange transfusion for severe malaria: evidence base and literature review. *Clin Infect Dis* 2013;**57**:923–8.
32. McLeod BC, Sniecinski I, Ciavarella D, Owen H, Price TH, Randels MJ, et al. Frequency of immediate adverse effects associated with therapeutic apheresis. *Transfusion* 1999;**39**:282–8.
33. Mohapatra MK, Srinivas D, Kar AK, Murmu M. Anaphylactic reaction to intravenous artesunate. *J Assoc Physicians India* 2009;**57**:183–4.
34. Dube SK, Panda PS, Agrawal GR, Singh DK. Anaphylaxis to artesunate? *Indian J Crit Care Med* 2012;**16**:55–7.
35. Hanson J, Anstey NM, Bihari D, White NJ, Day NP, Dondorp AM. The fluid management of adults with severe malaria. *Crit Care* 2014;**18**:642.
36. Vyas N, Avery BA, Avery MA, Wyandt CM. Carrier-mediated partitioning of artemisinin into *plasmodium falciparum*-infected erythrocytes. *Antimicrob Agents Chemother* 2002;**46**:105–9.
37. . *Summary of product characteristics: artesunate 60 mg for injection*. Guilin Pharmaceutical Co. Ltd.; 2013.
38. Ashley EA, Dhorda M, Fairhurst RM, Amaratunga C, Lim P, Suon S, et al. Spread of artemisinin resistance in *plasmodium falciparum* malaria. *N Engl J Med* 2014;**371**:411–23.
39. Hatcher JC, Greenberg PD, Antique J, Jimenez-Lucho VE. Severe babesiosis in long island: review of 34 cases and their complications. *Clin Infect Dis* 2001;**32**:1117–25.
40. White DJ, Talarico J, Chang HG, Birkhead GS, Heimberger T, Morse DL. Human babesiosis in New York State: review of 139 hospitalized cases and analysis of prognostic factors. *Arch Intern Med* 1998;**158**:2149–54.
41. Wormser GP. Hematogenous dissemination in early Lyme disease. *Wien Klin Wochenschr* 2006;**118**:634–7.
42. Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the use of therapeutic apheresis in clinical practice- evidence-based approach from the writing committee of the American society for apheresis: the seventh special issue. *J Clin Apher* 2016;**31**:149–62.