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Indications for therapeutic apheresis in hematological disorders

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A B S T R A C T

The early apheresis devices were developed in 1930s, but therapeutic apheresis only became widely used decades later, when automated cell separators were introduced. Progress in technical development of these devices continues to this day. Initial use of therapeutic apheresis has not been evidence based. Documents such as the Guidelines by the American Society for Apheresis provided hematologist with better tools to assess the role of therapeutic apheresis in daily practice. This review focuses on the use of therapeutic apheresis in patients with hematological disorders. Four separate apheresis modalities most encountered by hematologists are discussed: therapeutic plasma exchange, therapeutic leukocytapheresis, red blood cell exchange, and extracorporeal photopheresis. Examples of indications are provided and discussed. The future of therapeutic apheresis and its role in different diseases is undergoing continuous re-evaluation as disease pathogenesis is better understood and new treatment options become available.

Introduction

Therapeutic apheresis relies on removal of whole blood with subsequent separation into components. A treated disease determines what blood elements are removed and what replacement fluid is being used. The replacement fluid is mixed with patient's remaining blood and reinfused to the patient. The apheresis devices, also called cell separators, were initially introduced in late 1930s but the significant progress moving from manual to automated procedures was made starting in 1980s. There are 3 mechanisms of action employed in cell separators: centrifugation, in which blood is separated by centrifugal force; filtration, in which blood is separated by cell size; and spinning membrane technology, in which blood is separated by a combination of filtration (ie, membrane) and centrifugation (ie, spinning). The latter technology is primarily used in collection of plasma (plasmapheresis) from healthy donors for further processing (eg, IgG, albumin, etc.). In the United States, the most used cell separators employ centrifugation, which allows for significant flexibility in utilization of these devices from therapeutic plasma exchange (TPE) to red blood cell exchange (Fig. 1).

Evidence-based indications for therapeutic apheresis

The introduction of therapeutic apheresis to routine medical treatments resulted in the use of this technology in a variety of diseases. The limited evidence often led to the use of apheresis whenever a treating physician had exhausted other therapeutic options and/or when pathophysiology of the condition was poorly or, not at all, understood.

The first attempt to summarize the evidence for appropriate use of apheresis came in 1986. Dr Harvey Klein (NIH/NHLBI) led the effort to identify and critically evaluate published evidence, and ultimately the first Special Issue of the *Journal of Clinical Apheresis* [1]. The first issue was followed by second (1993) [2,3] and third (2000) [4] which summarized published literature and assigned 1 of the 4 ASFA Categories to different diseases (Fig. 2). However, a limitation of this effort was the lack of consistent criteria for evaluation of evidence as well as somewhat subjective assessment of the role of apheresis in patients' treatment.

The subsequent special issues (2007, 2010, 2013, 2016, and 2019) changed the evaluation process in a significant way [5-11]. First, there were established criteria for evidence including inclusion of GRADE system in 2010 issue [12]. The evaluation of literature was standardized, and assignment of ASFA Categories as well as GRADE level becomes more transparent and predictable. The writing committee has been thoughtfully organized with 10 individuals, each serving on no more the than 3 issues (with some exceptions for guest editors). Furthermore, the output of this work was highly prescriptive with so-called "fact sheets" introduced in 2007 issue. The fact sheets have evolved slightly over the last 5 issues but in principle they provide for the systematic overview of the disease and the evidence for the utility of therapeutic apheresis. The writing committee also pays close attention to criteria for stopping the treatment, the issue which has not been adequately addressed in the past, often leading to apheresis treatments extending over months and years without any evidence of benefit.

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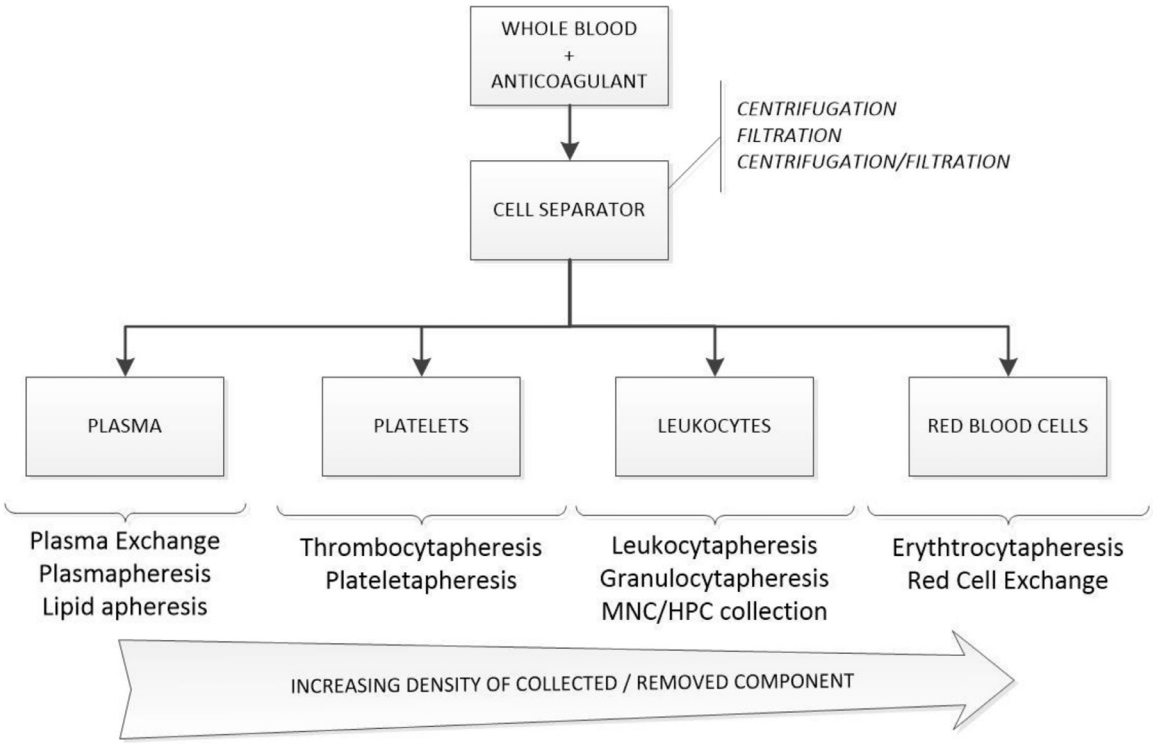

Fig. 1. Therapeutic apheresis procedures—nomenclature. HPC, hematopoietic progenitor cells; MNC, mononuclear cells.

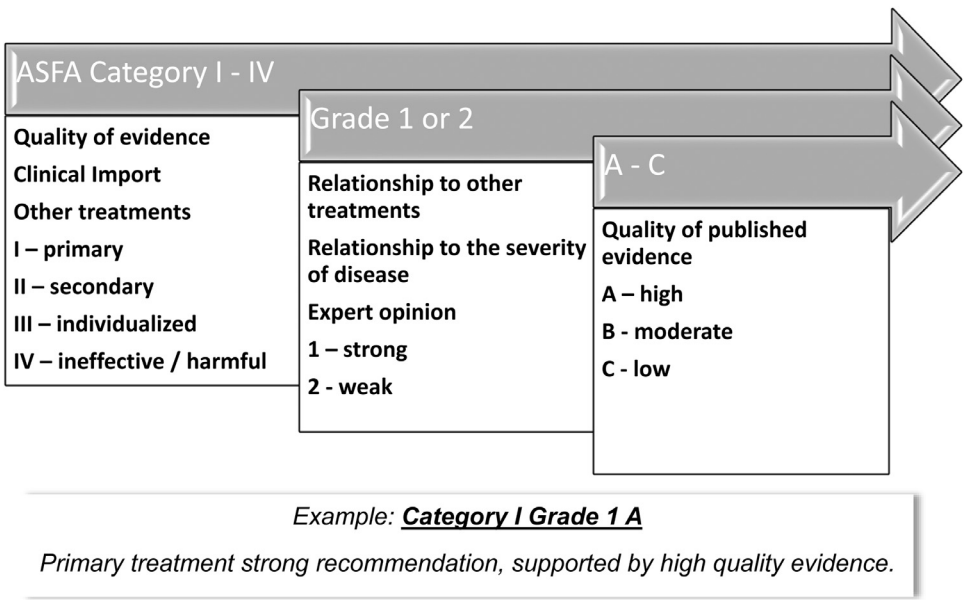

Fig. 2. American Society for Apheresis (ASFA)—categories and grading [5,9]. The figure summarizes the basic principles of ASFA Categories. The categories broadly determine the position of therapeutic apheresis in treatment of the disease; Grade reflects how group of experts "feel" about the use of therapeutic apheresis in the disease entity; and A-C denote the quality of published evidence.

This manuscript serves as introduction to the most recent, 2019 Special Issue of the *Journal of Clinical Apheresis* (8th edition) as the most authoritative source for evidence-based apheresis indications. The ASFA Categories are used worldwide and help apheresis practitioners to appropriately use this technology.

Therapeutic plasma exchange

The rationale for the use of TPE relies on its ability to remove a pathologic substance (eg, cryoglobulins, autoantibodies, immunoglobulins, etc.) quickly and efficiently. Substances with low volume of distribution and/or tightly bound to albumin are removed most effectively. Another benefit of TPE is the use of replacement fluid for lost plasma proteins with normal, functional proteins. The most used replacement fluids remain 5% albumin and fresh frozen plasma.

TPE is rarely the only treatment modality in the care of the patient. The timing of TPE must be coordinated with other therapies as not to affect their efficacy. It is important to note that plasma exchange, in addition to removing pathologic sub-

Table 1
Therapeutic plasma exchange in hematological disorders—indications [5].

ASFA category	Disease	Specific indication	Category/Grade
Category I	Catastrophic antiphospholipid syndrome (CAPS) Severe presentation		I/2C
	Hyperviscosity in hypergammaglobulinemia	Symptomatic	I/1B
		Prophylaxis pre Rituximab	I/1C
	Thrombotic microangiopathy, complement mediated	Factor H autoantibody	I/2C
	Thrombotic microangiopathy, drug associated	Ticlopidine	I/2B
	Thrombotic microangiopathy, thrombotic thrombocytopenic purpura (TTP)		I/1A
Category II	Autoimmune hemolytic anemia, severe	Severe cold agglutinin disease	II/2C
	Cryoglobulinemia	Severe/symptomatic	II/2C
	Myeloma cast nephropathy		II/2B
	Transplantation, HSCT; ABO incompatible (ABOi)	Major ABOi HPC(Marrow)	II/1B
		Major ABOi HPC(Apheresis)	II/2B
Category III	Autoimmune hemolytic anemia, severe	Severe warm autoimmune	III/2C
	Coagulation factor inhibitors		III/2C
	Erythropoietic protoporphyria; liver disease		III/2C
	Hemophagocytic lymphohistiocytosis (HLH); Hemophagocytic syndrome; Macrophage activating syndrome		III/2C
	Heparin-induced thrombocytopenia and thrombosis (HIT/HITT)	Precardiopulmonary bypass	III/2C
		Thrombosis	III/2C
	Immune thrombocytopenia (ITP)	Refractory	III/2C
	Post-transfusion Purpura		III/2C
	Red Cell Alloimmunization	Treatment; Pregnancy GA <20 wks	III/2C
	Thrombotic microangiopathy, coagulation mediated	THBD, DGKE and PLG mutations	III/2C
	Thrombotic microangiopathy, complement mediated	Complement factor gene mutations	III/2C
	Thrombotic microangiopathy, drug associated	Clopidogrel	III/2B
	Thrombotic microangiopathy, infection associated	STEC-Hemolytic Uremic Syndrome (HUS), severe	III/2C
		pHUS	III/2C
	Thrombotic microangiopathy, transplantation associated		III/2C
	Transplantation, HSCT; ABO incompatible (ABOi)	Major/Minor ABOi with pure red cell aplasia	III/2C
	Transplantation, HSCT, HLA desensitization		III/2C

stances, also removes from the circulation proteins, glycoproteins, lipoproteins, and coagulation factors. The large proteins are more likely to be affected as their extravascular presence is limited. The effect on smaller molecules is less pronounced and, if present, mostly due to the use of anticoagulants such as citrate which chelates cations (eg, calcium, magnesium). Calcium supplementation is frequently used in apheresis procedures where significant amount of citrate is returned to patient's circulation. The intravenous route of administration is most convenient without any significant side effects, while patients receiving calcium supplementation by mouth may complain of gastrointestinal discomfort.

Table 1 summarizes all TPE indications in hematological disorders as identified by ASFA in 2019. It is important to note that there are only a few category I indications, but these are also those most often confronted by the practicing hematologist. In this short review, I will concentrate on the progress which has been made in the treatment of thrombotic thrombocytopenic purpura (TTP) as well as challenges which we face selecting the optimal treatment plan for our patients [13].

Introduction of TPE to the armamentarium of treatment options for TTP was a paradigm shift, with mortality plummeting from 90% to below 10% [13]. It was an example of *ex juvantibus* approach: without good understanding of the pathophysiology of this disease, we were able to show dramatic change in mortality using TPE with plasma as replacement fluid. Since then much energy has been expended to improve upon this therapy without appreciation of its mechanism. Only in the late 1990s have we learned the critical role played by ADAMTS-13 and its deficiency, both acquired and familial. Introduction of immunosuppression (eg, corticosteroids) and monoclonal antibodies (eg, anti-CD20) allowed to decrease the risk of recurrence of TTP. However, patients still require on average 6 to 9 TPE procedures with plasma replacement.

One of the major challenges in clinical practice is to correctly diagnose patients with thrombotic microangiopathies (TMA), and especially with acquired TTP as it carries significant morbidity and mortality. Recently, a new tool was proposed which helps to predict the likelihood that a patient with TMA has an ADAMTS-13 level below 10%, which is strongly correlated with TTP. The tool, called PLASMIC score, assigns points for presence or absence of easily measurable and/or discernable variables [14]. The higher the score, the greater the preanalytical (before measurement of ADAMTS-13) likelihood of low ADAMTS-13 levels. There is an easily accessible calculator at https://www.mdcalc.com/plasmic-score-ttp. The score considers the following variables: platelet count; hemolysis index; active cancer; history of solid organ or stem cell transplant; mean corpuscular volume; international normalized ratio; and creatinine and assigns 1 or 0 points for each. The maximum score is 7. A PLASMIC score of greater than or equal to 6 denotes high risk of low ADAMTS-13 with recommendation for ADAMTS-13 testing, hematological consultation, and immediate plasma exchange. A score of 4 or lower suggests pursuing other diagnosis, while scores of 5 places the patient in the intermediate category, for which close observation is recommended. The PLASMIC score, although not perfect, provides a systematic evaluation of patients suspected of TTP.

An interesting twist in this story came from a different approach to thinking about the disease. Rather than looking at the loss of ADAMTS-13 activity, the research focuses on the result of this deficiency, which accelerates binding of von Willebrand multimers to platelets and causes microthrombosis. The latter leads to thrombocytopenia, hemolytic anemia, and tissue ischemia. The

newly approved an anti-von Willebrand factor humanized, bivalent variable-domain-only immunoglobulin fragment, caplacizumab, interrupts the interactions between von Willebrand factor multimers and platelets. Though this approach does not address the cause of the disease, it does significantly limit its effects on platelets and tissues. In randomized controlled trial (HERCULES), where 10 mg of caplacizumab was administered intravenously prior to initiation of TPE followed by 10 mg daily subcutaneously for 30 days thereafter, the median time of normalization of platelet count was shorter [15]. Other secondary outcomes were also favorable for caplacizumab arm vs placebo. Interestingly, there was statistically significant decrease in the rate of recurrence of TTP (12% vs 38%, caplacizumab vs placebo) as well as lower rate of refractory disease. Not unexpectedly the mucocutaneous bleeding was more common in treatment arm vs placebo. It was noted by some that the clinical benefit of earlier platelet recovery may not be cost effective (2.69 days [95% confidence interval {CI}, 1.89-2.83] vs 2.88 days [95% CI, 2.68-3.56], $P = .01$) despite being statistically significant. This randomized study was followed by reports of the results from open label studies, which showed to be efficacious and well tolerated in patients with acquired TTP who experienced a disease exacerbation [16]. Although, caplacizumab shows great promise in treating patients with acquired TTP (aTTP), it is unclear if it will be widely used. The primary concerns include a very high cost, safety, and efficacy [17]. These practical considerations also may limit introduction of other targeted therapies. As noted above diagnosis of aTTP still remains difficult and though a significant progress has been made by introduction of better and more predictable diagnostic tools, it could be a costly mistake to initiate treatment with caplacizumab in a patient who does not have aTTP. Likely, we will continue to use daily TPE with some combination of steroids and anti-CD20 therapy.

Other indications for TPE are listed in Table 1. The readers are referred to the ASFA Guidelines for perusal of individual fact sheets to learn more about individual indications [5].

Therapeutic leukacytapheresis

The clinical manifestations attributed to an elevated white blood cell (WBC) count in patients with leukemia can be grouped into 3 categories: leukostasis syndrome, tumor lysis syndrome, and early mortality. Because these manifestations are not mutually exclusive, it is useful to keep all 3 in mind when considering the potential benefits of therapeutic leukocytapheresis [18].

Clinically appreciable leukostasis typically manifests by organ dysfunction related to microvascular obstruction and consequent patchy ischemia. The most common symptoms are neurologic abnormalities and pulmonary insufficiency. Both presentations often lead medical team to seek emergent leukocytapheresis in order to reverse the pathologic changes resulting from small vessel occlusion by masses of leukemic cells, with or without attendant thrombosis and sometimes with hemorrhage distal to the occlusion [19]. The increased blood concentration of WBCs was believed to increase whole blood viscosity. However, as shown in Fig. 2, a reduced hematocrit keeps whole blood viscosity in the normal range in most patients with leukemia [20,21], unless it is raised by red cell transfusion [22] before the WBC count has decreased. Recent studies emphasize reduced deformability, cytokine secretion, and altered adherence properties of blasts or other primitive cells compared with the mature cells that normally circulate [23,24]. These observations support hypothesis that the load of circulating blasts better correlates with clinical symptoms than total WBC count. There is also observed a patient specific variability in relationship between the absolute circulating blast count and development of clinical symptoms [25]. Approximately 5% of patients with acute myelogenous leukemia (AML) develops leukostasis [26]. Autopsy studies have revealed microscopic correlates of leukostasis in a majority of AML patients whose WBC count exceeded 200,000/μL [27]. In most other clinically evident cases of leukostasis, the blast count exceeds 100,000/μL, but the syndrome is occasionally suspected in patients with a blast count in the 50,000 to 100,000/μL range [25]. The size of cells also matters. Leukostasis is rarely observed until the WBC count reaches the 250,000 to 300,000/μL range [24]. Other hematological malignancies with smaller, more mature cells requires even higher counts [23,28,29] (Fig. 2).

Table 2
Leukocytapheresis/thrombocytapheresis in hematological disorders [5].

ASFA category	Disease	Specific indication	Category/ Grade
Category II	Hyperleukocytosis	Symptomatic	II/2B
	Thrombocytosis	Symptomatic	II/2C
Category III	Hyperleukocytosis	Prophylactic or secondary	III/2C
	Thrombocytosis	Prophylactic or secondary	III/2C

Hyperleukocytosis correlates with a poorer prognosis in acute and chronic leukemia, even without development of leukostasis, which may explain the lack of appreciable long-term benefit of emergent leukocytapheresis on overall survival [30]. Other complications, such as an increased risk for hyperuricemia and other manifestations of tumor lysis syndrome can be exacerbated by cytotoxic chemotherapy for leukemia [31] (Fig. 3).

The lack of controlled studies to assess the true role of leukocytapheresis leaves hematologists with accepting the dogma that lowering the WBC count by leukocytapheresis can reverse symptoms of leukostasis. The relative absence of high-quality data is reflected in the ASFA categorization of leukocytapheresis as listed in Table 2. Leukocytapheresis could be considered as secondary treatment for leukemia patients with signs of leukostasis, especially for patients who have acute leukemia and whose blast counts exceed 100,000/μL. There is, however, no strong support for prophylactic leukocytapheresis, which is now category III with Grade 2C, clearly leaving this indication only for selected patients, whose WBC count is expected to remain high for several days before chemotherapy is instituted [24,25].

It remains unclear whether prophylactic leukocytapheresis to lower the WBC count before the initiation of chemotherapy can prevent or meaningfully reduce the severity of tumor lysis syndrome. Controlled studies that address this point are lacking. There are multiple observational case series which seem to indicate that there is limited, if any, impact of prophylactic leukocytapheresis on overall survival or even the frequency of development of tumor lysis syndrome [32-34]. Approximately half of the patients with acute leukemia develop intracranial hemorrhage. Leukocytapheresis and cranial irradiation in patients with hyperleukocytic AML did not affect the incidence of intracranial hemorrhage or provide a survival benefit [35].

Therapeutic leukocytapheresis can be performed with most centrifugal apheresis instruments. Emergent leukocytapheresis in patients with inadequate peripheral venous access requires emergent placement of a dual-lumen central venous apheresis catheter, which can be challenging in an acutely ill patient with thrombocytopenia. When deciding whether to perform leukocytapheresis in a patient who does not have the leukostasis syndrome, the physician should balance the possible benefits of the procedure against the risks of emergent central line placement and the possible detriment that may arise from delays in implementing pharmacologic cytoreduction with hydroxyurea and in starting definitive chemotherapy [24,25]. Additional information on technical considerations related to performing optimal therapeutic leukocytapheresis need to be considered, though efficacy of the procedure is

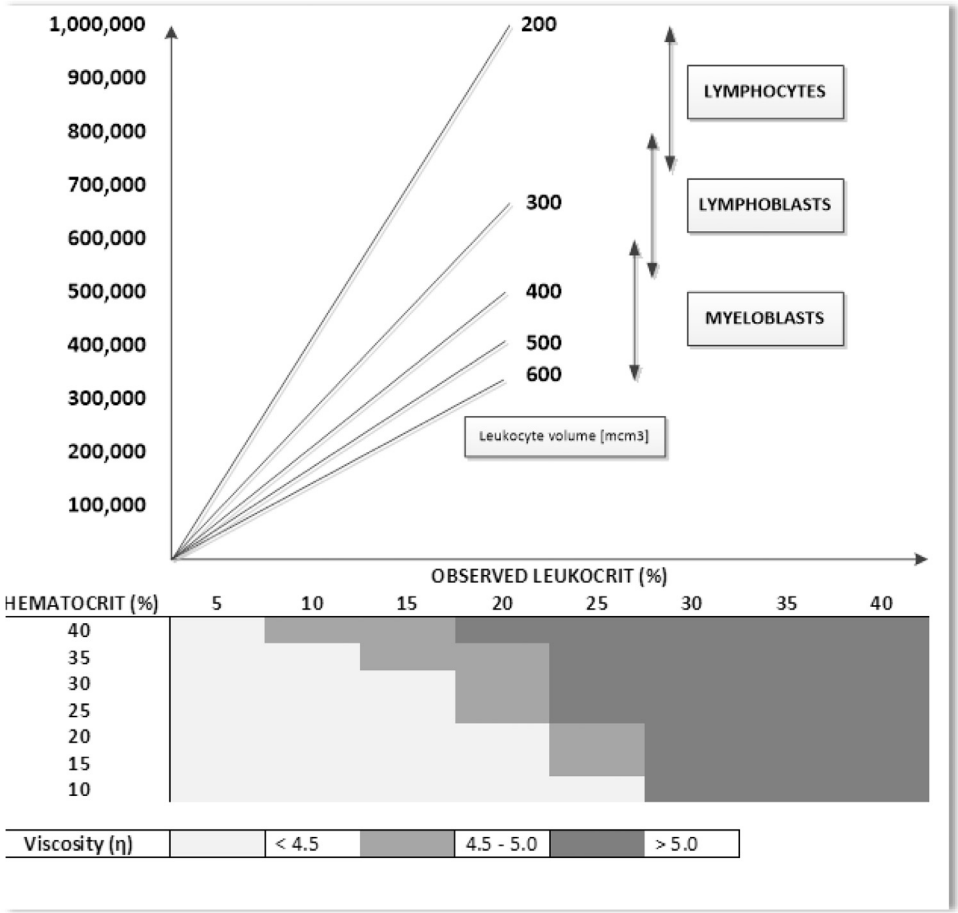

Fig. 3. Relationship between leukocytosis and likelihood of clinically apparent leukostasis. The risk of clinically relevant leukostasis that may require leukocytapheresis depends on hematocrit and observed leukocrit (eg, the volume of white blood cells (WBC) after centrifugation, expressed as percentage of the whole blood volume). As the observed leukocrit increases, so does the risk of leukostasis without a change in hematocrit. However, increasing hematocrit (eg, transfusion of red blood cells or intravascular fluid depletion) with stable WBC mass may also result in leukostasis. The size and density of WBCs affects the observed leukocrit, as also shown in this figure. The measured whole blood viscosity (η) increased as hematocrit and observed leukocrit increases. Blood viscosity below 4.5 carries a lower risk of clinically significant leukostasis; however, the leukostasis is multifactorial. *Figure drawn by the author and previously published in Cytapheresis: In: Therapeutic Apheresis: A Physician's Handbook. 5th ed. Crookston KP, King KE, eds. Bethesda, MD: AABB, 2017:75 (used with permission)* [18]*; The data for this figure are derived from Lichtman MA, Rowe JM. Hyperleukocytic leukemias: rheological, clinical, and therapeutic considerations. Blood 1982;60:279-83.*

highly variable due to patient's individual characteristics, types of cells to be removed, and technical limitations of the cell separator [18]. Importantly, transfusion of red blood cells (irradiated and leukoreduced) can be considered in patients with severe anemia and cardiac or pulmonary disease, when the WBC concentration is sufficiently lowered during the procedure to decrease the risk of leukostasis [18].

Thrombocytapheresis is now used rather sparingly with development of new medications which can ameliorate thrombocytosis. Elevated and unresponsive to therapy platelet count can be acutely reduced using thrombocytapheresis, which is a modified procedure typically used for collection of apheresis platelets from healthy donors (ie, plateletapheresis). Symptomatic thrombocytosis received category II indication, while prophylactic thrombocytapheresis carries category III indication. Both indications have weak recommendation based on a limited literature (Table 2) [5].

Red blood cell exchange

The use of cell separators to exchange a patient's red blood cells has major advantages over simple transfusion [36]. First, replacement of patient's red blood cells reaches 50% to 80% and second, exchange decreases the risk of development of iron overload by concurrent removal of dysfunctional cells. Simple or apheresis-based phlebotomy, that is, erythrocytapheresis, is used exclusively in patients with either iron overload (eg, hemochromatosis; transfusional iron overload) or erythrocytosis (eg, polycythemia vera, secondary erythrocytosis). These also gained ASFA indications as noted in Table 3.

There are 3 groups of diseases hematologists will encounter where red blood cell exchange may be indicated. The first group consists of hemoglobinopathies, such as hemoglobin S or hemoglobin C; the second group includes enzymatic deficiencies leading to increased hemolysis (eg, pyruvate kinase deficiency); and the third group encompasses infectious diseases which may lead to increased hemolysis as well as higher rate of complications during treatment (eg, babesiosis, malaria).

Table 3 summarizes indications for red blood cell exchange [5]. Category I indications include patients with sickle cell disease either with acute presentation (eg, stroke) or chronic treatment for stroke prophylaxis. Both indications garnered Grade 1 with variable level of supporting literature. It is unclear if with additional studies and our expanding knowledge on acute stroke in sickle cell disease current indications will withstand the test of time [5,6].

Hematologists are peripherally involved in the treatment of babesia and malaria but need to be aware of potential use of red blood cells exchange as a tool to decrease blood parasitemia. The RBC exchange is used in very severe forms of these infections

Table 3
Red blood cell exchange/erythrocytapheresis in hematological disorders [5].

ASFA category	Disease	Specific indication	Category/Grade
Category I	Hereditary hemochromatosis	(Erythrocytapheresis)	I/1B
	Polycythemia Vera	(Erythrocytapheresis)	I/1B
	Sickle Cell Disease, acute	Acute stroke	I/1C
	Sickle Cell Disease, non-acute	Stroke prophylaxis	I/1A
Category II	Babesiosis	Severe presentation	II/2C
	Sickle Cell Disease, acute	Acute chest syndrome, severe	II/1C
	Sickle Cell Disease, non-acute	Pregnancy	II/2 B
		Recurrent vaso-occlusive pain crisis	II/2B
Category III	Erythrocytosis (Secondary)	(Erythrocytapheresis)	III/1C
	Erythropoietic protoporphyria; liver disease		III/2C
	Malaria	Severe	III/2B
	Red cell alloimmunization prevention	Exposure to RhD+ red blood cells	III/2C
	Sickle Cell Disease, acute	Other complications	III/2C
	Sickle Cell Disease, non-acute	Pre-operative management	III/2A
	Transplantation, HSCT; ABO incompatible (ABOi)	Minor ABOi HPC(A)	III/2C

where there is a significant parasitemia accompanied by developing or present complications.

Extracorporeal photopheresis

Extracorporeal photopheresis (ECP) is a unique apheresis technology as it combines cellular selection with extracorporeal cell treatment. The addition of psoralen-based compound and illumination with UV light leads to initiation of apoptosis in the collected cells. The reinfusion of treated cells produces an immunologic response in the patient either by generating cytotoxic T cells or regulatory T cells. The actual immunologic mechanism employed in this response continues to be investigated. The initial target cells were malignant cells in cutaneous T cell lymphoma (CTCL) but with time ECP has been employed in different diseases, most notably graft-vs-host disease (GvHD).

ECP is performed either as one procedure (so-called “online” treatments, the only modality currently available in the United States) or as 2 separate procedures (“off line” treatment in which cells are first collected in a cell separator and then exposed to UV radiation in a light box). In another variation of the offline procedure, light exposure is followed by cryopreservation, allowing multiple infusions from a single mononuclear cell collection. In some institutions, a mini-ECP is used, in which leukocytes are collected from whole blood, treated with UV light and reinfused to the patient. The offline procedures are particularly popular in continental Europe as they do not require additional investment in online equipment and are thus less expensive. Recently, some manufacturers have created a therapeutic platform which combines the benefits of online and offline treatment with intricately linked 2 devices (eg, widely available cell separator and customized lightbox). Unfortunately, at present, these devices are only available in Europe.

The mechanism by which ECP exerts its beneficial effect has been a source of debate. There are several leading hypotheses, but immunomodulation seems to be the primary pathway. Some propose testing the hypothesis that generation of dendritic cells may play important role [37].

Indications for ECP (Table 4) have not changed significantly over the last decade, primarily due to limited studies in new hematological disorders. There is also a significant competition in this space from new targeted therapies for lymphomas as well as GvHD. Despite these new developments, ECP is still widely used for both CTCL and GvHD. This popularity can be attributed to an excellent safety profile. However, many patients require implanted central venous access devices to be able to undergo ECP. The typical course of ECP in GvHD starts with 12 weeks of 2 treatments per week which then can be tapered to less frequent treatments or discontinued [37]. The frequency of treatments in CTCL varies between 2 treatments per week every 2 to 4 weeks. As this is primarily a palliative modality, some patients remain on this treatment for months or years and only discontinue it when the disease progression ensues.

Table 4
Extracorporeal photopheresis in hematological disorders [5].

ASFA category	Disease	Specific indication	Category/Grade
Category I	Cutaneous T cell lymphoma (CTCL); Mycosis fungoides; Sezary syndrome	Erythrodermic	I/1B
Category II	Graft vs Host Disease (GvHD)	Acute	II/1C
		Chronic	II/1B
Category III	Cutaneous T cell lymphoma (CTCL); Mycosis fungoides; Sezary syndrome	Non-erythrodermic	III/2C

Cutaneous T cell lymphoma

CTCL, where malignant helper CD4+ cells are typically found in circulation in addition to skin involvement, was the first disease studied using ECP and showing its clinical benefit. The rationale behind ECP in CTCL was based on earlier experience with observed clinical response to UVA irradiation of skin after 8-MOP ingestion (psoralen-UVA treatment). The subsequent extension of this observation with removal, irradiation, and reinfusion of 5% to 10% of circulating MNCs on 2 consecutive days each month led to unprecedented disease regression in some patients, albeit usually after a delay of some months (typically 4-12 months). The magnitude of clinical response could not have been explained by simple destruction and induced apoptosis irradiated tumor cells. Additional observations suggested that ECP elicits, enhances, or otherwise modulates host immune responses to the tumor [37]. These initial findings support additional studies looking at ECP in other diseases. In a report evaluating results from 242 patients with CTCL reported in nine North American studies, the complete response rates were 23% to 50%, while partial response rates up to 60% [37]. Long-term follow-up of treated patients suggested a better median survival than that seen in historical controls. Patients with relatively recent onset of diffuse skin disease (erythroderma) and little disease-induced immunosuppression benefited the most from ECP.

As disease progressed the response in patients with longstanding disease, localized skin plaques or involvement of lymph nodes and viscera was less favorable [38,39]. Interestingly, a decrease in the number of circulating Sézary cells correlated with clinical response.

The cell separator/illuminator device (Therakos' UVAR) was approved by FDA in 1987 for treatment of CTCL. Currently, Therakos' Cellex is the only approved device in the United States, while in Europe in addition to Cellex other devices are used for performing ECP with online approach (ie, Amicus Blue System, Fresenius Kabi) in addition to several offline illuminators available from different manufacturers. The CTCL with erythrodermic presentation remains the only category I indication for ECP, while CTCL with nonerythrodermic involvement is considered category III indication (Table 4). There has been a significant progress in development of other therapies in CTCL over the last decade making ECP less frequently used in more advanced disease. However, ECP is still a therapy of choice in many patients with initial presentation and may delay progression of the disease, but ECP's role may change with development of competing therapies (and better understanding of pathophysiology of CTCL including the role of CCR4 receptor and potential therapeutic agents) [40,41].

Graft-vs-host disease

GVHD may develop following allogeneic hematopoietic stem cell transplantation. The organs most involved include skin, liver, and gastrointestinal tract. Acute and chronic GvHD do not only differ by the time post-transplant when they appear (ie, acute within 100 days while chronic after 100 days from transplant) but also by presentation and pathomechanism [42,43]. Despite application of prophylaxis, both forms of GvHD still occur with the incidence of each as high as 40% following Human Leukocyte Antigen-matched sibling transplants and 70% following matched unrelated transplants [42-44].

ECP was introduced to treatment schema of GvHD over 2 decades ago, after some improvement was noted with the use of phototherapy and psoralen-UVA. Currently, chronic GvHD is the most common diagnosis among patients receiving ECP treatment [37,45]. Literature reviews revealed mean improvement in ECP-treated patients of 85% with skin involvement, 56% with liver involvement, and 63% with GI involvement [46].

Similar patterns of response have been noted in more recent uncontrolled series as well [47-50]. Improvement is noted sooner in GVHD than in CTCL, with apparent responses being evident in a matter of weeks. Survival is also thought to be improved [44]. The precise contribution of ECP to treatment of GvHD is difficult to study as only a few controlled studies have been performed and patients are often receiving other concurrent therapies.

A large, randomized, phase II controlled trial was reported in 2008 [51]. The treatment was performed over the course of 12 weeks. This study and its results till this date support the use of ECP, but results of the primary end point (change in the total skin score) did not show statistically significant difference. There were secondary outcomes which seemed to favor ECP. Based on these results standard care, ECP is considered category II for both acute and chronic GvHD with strong support for both indications as a secondary therapy [5].

Conclusions

Indications for therapeutic apheresis in hematological disorders are quite broad and include multiple apheresis modalities. The role of apheresis in different diseases is undergoing dramatic changes as disease pathogenesis is better understood and new treatment options become available. At the same time, there are diseases where apheresis role is well established and difficult to replace at this time. As we continue to assess role of apheresis in the care of our patients, indications established by ASFA provide a great support for evidence-based practice.

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