The sixth comprehensive, evidence-based analysis of apheresis therapies by the American Society for Apheresis (ASFA) recorded 60 disease conditions as Category I (apheresis as first-line therapy) or Category II (apheresis as second-line or adjuvant therapy) indications for therapeutic apheresis. Among these, 37 (62%) were indications for plasma exchange, consistent with prior surveys that found plasma exchange to be the predominant form of apheresis therapy in North America. Whereas apheresis procedures have been in wide use for decades, many on the basis of accumulated experience, the approval of new therapeutic indications, devices, and drugs is increasingly dependent on the presentation of carefully acquired supportive evidence in randomized controlled trials. This applies to phlebotomy and apheresis therapies as well and ASFA presents its recommendations, and the strength of the evidence that underlies them, according to the G.R.A.D.E. system. Accordingly, this chapter, which reviews therapeutic phlebotomy and specialized apheresis procedures that target, for processing, specific fractions of the plasma or cellular compartment of the blood, emphasizes those procedures that are supported by evidence.

**Therapeutic red cell apheresis**

John J. Abel of the Johns Hopkins University used the term “plasmapheresis” to describe a method for removing large quantities of plasma from experimental animals. Thus, the removal of red cells for therapeutic purposes can be referred to as erythrocytapheresis. This term particularly applies to the removal of red cells using automated blood-processing instruments that are capable of selectively removing erythrocytes while returning the plasma, buffy coat cells, and additional isotonic saline to the patient. The therapeutic replacement of patient red cells for donor red cells is more specifically referred to as red cell exchange, although the term erythrocytapheresis is frequently used synonymously.

**Red cell exchange**

Therapeutic red cell exchange can be performed manually or with programmable automated blood-processing (apheresis) instruments. Manual exchange is mainly limited to neonates or resource-limited settings. Thus, this discussion focuses on automated red cell exchange.

Basic features of automated blood processors that perform apheresis using centrifugation technology are detailed in Chapter 32. The machine operator enters the patient’s gender, height, and weight into the instrument’s computer to calculate the total blood volume. The operator also inputs the known starting and desired ending hematocrit of the patient, the average hematocrit of red cell replacement units to be used, and the desired fluid balance (a default of 100% may be offered by the instrument). Finally, the operator can choose to enter the desired fraction of the preprocedure red cells remaining (FCR) within the patient’s circulation at the end of the procedure or the volume of replacement fluid (e.g., red cells of average hematocrit as programmed into the instrument’s computer) needed for the procedure.

Calculation of the desired FCR is predicated on the targeted therapeutic endpoint over the starting point for the red cell exchange. For manual or automated exchanges where there is no correction for changes in the hematocrit, correction is needed:

$$\text{FCR} = 100 \times \left( \frac{\text{starting hematocrit}}{\text{ending hematocrit}} \right) \times \left( \frac{\text{endpoint parameter}}{\text{starting parameter}} \right) \quad (1)$$

For example, a sickle cell patient with a hematocrit of 25% and 100% HbS, targeted to an endpoint of HbS 30% and ending hematocrit of 30%, would yield:

$$\text{FCR} = 100 \times \left( \frac{25\%}{30\%} \right) \times \left( \frac{30\%}{100\%} \right) = 25\%$$

The replacement volume needed to reach the desired FCR is dependent on the patient’s blood volume, the starting hematocrit, the target hematocrit, fluid balance, and the average hematocrit of the replacement RBC units. It is important to remember that modern automated apheresis instruments incorporate the starting and endpoint hematocrit, and thus the machine FCR simply approximates the desired fraction of original parameter of interest.

According to ASFA, red cell exchange is indicated as first- or second-line therapy for treatment of severe manifestations of the protozoal infections (e.g., malaria and babesiosis) and for the management of sickle cell disease (SCD).
Sickle cell disease

Sickled erythrocytes were first described in Western medicine in 1910 by Dr. J.B. Herrick, who noted the abnormally shaped red cells in the peripheral blood film of a dental student from the Caribbean island of Grenada. An underlying mutation results in substitution of valine for glutamic acid as the sixth amino acid residue in the hemoglobin β chain and has arisen multiple times in Africa due to its protective effects from severe falciparum malaria in the heterozygous state. Once at appreciable frequency in a population, the homozygous sickle state leads to SCD. The description of these countervailing forces on survival provided one of the initial examples of balancing selection in evolution.

The fundamental molecular etiology of sickling is due to increased hydrophobic interactions between nearby HbS molecules whereby deoxygenated HbS aggregates into large inflexible polymers and inflexible sickled red cells. This combined with membrane changes increasing sickle cell adhesiveness is the underlying basis for the hemolytic and vaso-occlusive morbidity of SCD. The exquisite dependence of polymerization on the proportion of HbS has provided a scientific basis, in concert with the strong clinical basis, for transfusion therapy of normal red cells in sickle cell anemia.

For the most part, clinical studies related to transfusion management of SCD have focused on simple transfusion or manual exchange transfusion. The efficacy of manual versus automated red cell exchange in the treatment of SCD has not been directly compared. Although for most SCD complications, simple transfusions may likely be as effective, automated red cell exchange can more rapidly decrease the proportion of HbS red cells during severe acute episodes. In SCD patients who receive chronic transfusion, automated red cell exchange can mitigate iron overload while maintaining a low HbS level. Thus, it has entered into routine use in centers where therapeutic apheresis is available. Its indicated roles in the aspects of SCD (Table 34.1) are discussed here. Exchanges may be performed using isotonic saline, rather than red cells, as the replacement fluid in the early phases of the procedure in order to minimize the number of donor red blood cell (RBC) units required by avoiding the initial removal of the normal replacement red cells.

Life- or organ-threatening complications

Red cell exchange is standard therapy (ASFA Category I) for children with acute vaso-occlusive stroke and should be performed shortly following documentation of thrombotic (rather than hemorrhagic) stroke by noncontrast computed tomography. The treatment goal should be a hemoglobin concentration between 9 and 10 g/dL and less than 30% HbS. Acute intervention, followed by chronic maintenance transfusion therapy, may limit early morbidity and mortality and prevent recurrence (discussed further in this chapter). In its 2000 report, the National Acute Chest Syndrome Study Group (NACSSG) defined acute chest syndrome, the second most common cause for hospitalization and the leading cause of death in SCD, on the basis of presentation with a new alveolar infiltrate involving one or more complete lung segments (atelectasis excluded) and accompanied by chest pain, a fever >38.5 °C, tachypnea, wheezing, or cough. Although the NACSSG report was not powered to detect a particular advantage of red cell exchange over simple transfusion, the consensus opinion of experts in the field is to recommend red cell exchange for severe ACS (oxygen saturation <90% despite supplemental oxygen).

Acute multiorgan failure syndrome is a common cause of death in sickle cell disease, it may present as an unusually severe pain episode in patients with sickle cell anemia or HbSC disease and is characterized by fever, accelerated hemolysis with a rapid decrease in hemoglobin and platelet count, nonfocal encephalopathy, and rhabdomyolysis. Besides the central nervous system, other organs, including liver and kidney, may be involved. Standard red cell transfusion therapy is likely effective if severe anemia is present. Although evidence is limited to case reports and series, red cell exchange should be considered with higher hemoglobin levels. Red cell exchange can also be considered for hepatic sequestration and intrahepatic cholestasis.

The role of transfusion and exchange transfusion in priapism, which occurs in approximately 30% to 90% of males with SCD, has been debated. However, there is increasing consensus that transfusion is not warranted, and the recent NIH expert panel states that transfusion should not be used. Studies have shown no benefit of conventional therapies, the time to resolution is often longer for those transfused, and further interventions such as surgical decompression are often required. In addition, severe neurologic abnormalities have been associated with red cell exchange, as first reported in six boys with sickle cell anemia 1 to 11 days following partial exchange transfusion for priapism unresponsive to conservative therapy. The syndrome was characterized by severe headache at the onset, often associated with increased intracranial pressure, and further neurologic events ranging from seizure activity to obtundation requiring ventilatory support. Finally, a comprehensive review of 42 well-documented case reports of transfusion therapy in SCD-associated priapism evaluated the effectiveness of transfusion therapy versus conventional therapies in terms of time to detumescence. The mean time to detumescence with transfusion therapies was 10.8 days (26 cases) versus 8.0 days with conventional therapies (16 cases). Neurologic complications with transfusion therapy were described in nine cases, some with persistent long-term deficits.

Primary and secondary prevention of stroke

Approximately 5% to 10% of untransfused children with SCD will have a clinically evident cerebral infarction by age 20. Chronic transfusion therapy, given every 3 to 4 weeks, to maintain the level of HbS below 30% can improve the arteriographic appearance of affected cerebral vessels and reduce the risk of recurrent stroke from 66% to 90% to approximately 10%. Chronic automated red cell exchange can be substituted for simple transfusion, with the added potential benefit of preventing or mitigating iron overload. Reports of recurrent stroke rates of 50% or greater after discontinuation of transfusion therapy have led most to recommend indefinite prophylactic transfusion regimens.

<table>
<thead>
<tr>
<th>Table 34.1 Red cell exchange in sickle cell disease</th>
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<tbody>
<tr>
<td><strong>Acute or emergent</strong></td>
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<tr>
<td><strong>Hepatic sequestration or intrahepatic cholestasis</strong></td>
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<tr>
<td><strong>Chronic</strong></td>
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<tr>
<td><strong>Secondary stroke prevention</strong></td>
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</tbody>
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Section III: Apheresis, Transplantation, and New Therapies
The demonstration that transcranial Doppler ultrasound (TCD) was highly predictive of stroke risk in children with SCD25 led to the Stroke Prevention Trial in Sickle Cell Anemia (STOP trial),21 which examined the ability of chronic transfusion therapy to prevent a first stroke in high-risk children with SCD. Time-averaged mean blood-flow velocity of at least 200 cm/sec in the internal carotid or middle cerebral artery and a stroke-free history were required for study entry.21 Over a period of approximately 2 to 3 years, transfusion therapy to maintain HbS below 30% without exceeding a hemoglobin concentration of 12 g/dL reduced the occurrence of stroke in the treatment group by 90% compared to the control group.21 A follow-up study (STOP2)35 examined the effect of discontinuation of transfusion therapy after 30 months in children from the first STOP trial whose transcranial Doppler readings had reverted to normal. The study was halted when an interim analysis revealed that, of 41 children randomly assigned to discontinue transfusions, 14 had reverted to elevated TCD findings within nine months after stopping transfusions and two had suffered ischemic strokes. Neither elevated TCDs nor strokes were observed in the controls continuing transfusion. Similarly, the Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial comparing transfusions (with chelation) to hydroxyurea was halted when interim analysis revealed reversion to elevated TCD and increased incidence of overt stroke.36

As a result of these studies demonstrating no equivalent therapy or safe endpoint for chronic transfusion therapy, the current recommendation is that individuals with a history of elevated transcranial arterial flow or a history of stroke continue transfusion therapy indefinitely.23 Furthermore, the indication for transfusion in stroke prevention may broaden, given that among children with magnetic resonance imaging (MRI)-demonstrated silent infarcts, but lacking elevated intracranial arterial flow rates, those randomized to receive chronic transfusions had lower rates of both silent infarcts and overt strokes.23

Transfusional iron overload
There are no randomized, prospective comparisons of simple transfusion versus automated red cell exchange in the prevention of iron overload in children with SCD who require chronic transfusion therapy. However, four case series of eight to 14 subjects25,26 have been reported in which children were either converted from a simple transfusion program to monthly red cell exchange or begun on red cell exchange early on. In addition, some in each series were on chelation therapy with desferrioxamine,22 and some were not. In general, red cell exchange resulted in a 25% to 100% increase in red cell usage and a concomitant increase in donor exposures. However, serum ferritin tended to stabilize in those who were not on chelation therapy and significantly decreased in those who continued on chelation therapy. Some children who were begun on red cell exchange before development of iron overload did not accumulate iron as a result of their red cell exchange treatments.

Protozoan disease
Severe manifestations of malaria and babesiosis are ranked as Category II indications by ASFA, largely on the basis of anecdotal evidence.1,38,39

Malaria
Severe malaria is usually caused by Plasmodium falciparum.40 The infection results from injection of sporozoites into the bloodstream by the bite of a female Anopheles mosquito. The sporozoites migrate to and infect liver cells, where they asexually reproduce to form numerous merozoites that burst forth and invade RBCs. This initiates the erythrocytic life cycle with repeated rounds of RBC infections and increasing parasitemia, and symptoms such as recurrent fever, which can culminate in life-threatening end-organ dysfunction that defines severe malaria.41

The relative severity of P. falciparum malaria is due to adherence of falciparum-infected erythrocytes to glycosylated molecules on microvascular endothelium and to platelet CD36 via P. falciparum erythrocyte membrane protein-1 (PFEMP-1), an adhesive protein expressed on the surface of infected erythrocytes.32,42 The sequestration and vasoconstriction combined with the elaboration of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα) and interferon-γ result in the severe manifestations of the disease.43 Thus, the use of exchange transfusion and automated red cell exchange in the treatment of severe malaria is based on an ability to rapidly reduce the burden of parasitemia and the potential to thereby improve the rheologic properties of the blood and reduce the level of toxic mediators such as cytokines.1 Case series (16 patients total) and one case report describe lowering of parasitemia by 80% to 90% using automated red cell exchange of 1.0 to 1.5 red cell volumes in approximately two hours, followed by rapid clinical recovery, in cases of severe P. falciparum malaria, including cerebral malaria.1 The exact impact on the number of sequestered infected RBCs remains undetermined. The evidence for improved survival is mixed, with retrospective case control series variably favoring antibiotic therapy alone or adjunct exchange transfusion, but all studies have suffered from poor control for malaria severity.39

The US Centers for Disease Control and Prevention (CDC) and American Society for Apheresis (ASFA) have, until recently, both recommended consideration of RBC exchange in cases of severe malaria with parasitemia >10%.4 However, CDC investigators recently analyzed their malaria reporting data from 1985 to 2010 and compared 101 exchange transfusion cases with 314 propensity-matched non-exchange cases of severe malaria.45 They found no survival advantage with 17.8% mortality in the exchange-transfused group compared to the 15.9% for the controls. This, along with the lack of high-level evidence in the literature, led the CDC to conclude that exchange transfusion should no longer be recommended.45 However, their retrospective analysis only had power to assuredly detect a very strong effect (<4.6% mortality in exchange transfused at 90% power, presuming 15.9% in controls) and lacked key data for the vast majority of cases (e.g., <10% of cases reported parasitemia levels, a key trigger for exchange per ASFA guidelines). These study limitations were cited in ASFA’s response to this publication saying that the ASFA recommendation for red cell exchange would stand.46 What is not in dispute is that current artemisinin combination therapies lead to rapid parasite clearance, in line with the rapidity of clearance by apheresis or manual exchange.47 Given that these drugs also clear sequestered parasites, artemisinin-based therapy (although not first-line therapy in the United States) should limit the need for adjunct red cell exchange to speed parasite clearance.45,47 However, in the face of the recent emergence and spread of artemisinin resistance in Southeast Asia and the lack of another effective antimalarial,48 a properly controlled prospective trial to determine the benefit of exchange (e.g., 50% improved survival) probably remains worthwhile.

Babesiosis
Babesiosis in humans is a zoonotic disease and is spread to humans primarily through ticks of the genus Ixodes.49 The first reported case
of human babesiosis was in an asplenic individual from Europe.\textsuperscript{50} The first case in a patient with an intact spleen was reported in Nantucket.\textsuperscript{51} Within the United States, the predominant organism is \textit{Babesia microti}, the reservoir hosts are wild rodents, and the vector is the deer tick \textit{Ixodes scapularis}, which is the same tick that transmits \textit{Borrelia burgdorferi}, the causative agent of Lyme disease.\textsuperscript{49} Over the past several decades, the endemic range has expanded, and now encompasses seven states in the Northeast and the Midwest United States, which accounted for >95% of 1762 reported babesiosis cases.\textsuperscript{52}

When injected into the human bloodstream, the sporozoites of \textit{babesia} directly invade RBCs. After asexual budding into four merozoites, the parasites perforate the erythrocyte membrane, resulting in hemolysis.\textsuperscript{53} They are then free to infect other erythrocytes, and transform into dividing trophozoites (ring forms and tetrads visible on peripheral blood films).\textsuperscript{39,53} One to six weeks following inoculation, infected patients develop a flu-like syndrome characterized by fever, fatigue, and malaise.\textsuperscript{54} Headache, chills, sweats, myalgia, and arthralgia are frequent complaints. Physical findings may include fever and spleenomegaly, and jaundice and pallor may accompany marked extravascular hemolysis. Although most cases are subclinical or mild,\textsuperscript{55} severe manifestations, including disseminated intravascular coagulation, respiratory failure, and renal failure, may occur. Immunocompromised or asplenic individuals are typically more severely affected.\textsuperscript{49,56}

Transfusion transmission is frequent in endemic areas, leading to infections of those most vulnerable: neonates, the immunocompromised, and the elderly.\textsuperscript{57} Although clinical trials are lacking, several case reports and case series suggest that, given the absence of a microvascular sequestration of infection, red cell exchange, whole blood exchange, or red cell exchange followed by plasma exchange, combined with antibiotic therapy, can be beneficial in severe cases of babesiosis with >5% parasitemia.\textsuperscript{1,58-60} A single one- to two-volume red cell exchange can reduce the circulating population of parasitized erythrocytes by 85% to 90%.\textsuperscript{1} Exchange also appears effective in neonates with severe transfusion-associated babesiosis.\textsuperscript{61}

### Erythrocytapheresis and Therapeutic Phlebotomy

Therapeutic phlebotomy or venesection is a procedure that has been performed throughout recorded history. In current clinical practice, therapeutic phlebotomy is an evidence-based intervention for disorders such as polycythemia vera and hemochromatosis.\textsuperscript{1} Although erythrocytapheresis has been investigated as a means of more rapid removal of red cell mass and limiting plasma loss, phlebotomy remains the therapeutic mainstay in most settings given its simplicity.

### Polycythemia Vera

Classified as a bcr/abl-negative classic myeloproliferative neoplasm showing absolute erythrocytosis,\textsuperscript{62} it is further characterized by pancytopenia in the marrow and peripheral blood, splenomegaly, hyperviscosity of the blood, thrombosis, and a tendency to evolve into either acute myeloid leukemia or myelofibrosis.\textsuperscript{63,64} Over 95% of cases are now known to be associated with an acquired point mutation, V617F, in exon 14 of the Janus kinase 2 (JAK2) gene on chromosome 9p24.\textsuperscript{55} The remaining 5% of patients appear to have mutations in exon 12 of JAK2, some of whom may have a more benign phenotype (idiopathic erythrocytosis).\textsuperscript{85} A revised World Health Organization (WHO) diagnostic system (Table 34.2) that recognizes the predominance of JAK2 mutations in polycythemia vera has been widely adopted.\textsuperscript{62,66} Setting precise cutoffs for erythrocytosis is challenging. The International Council for Standardization in Haematology recognizes absolute erythrocytosis in an individual whose measured total red cell volume, or red cell mass, is more than 25% above the mean predicted value for a person of the same body surface area.\textsuperscript{64} This formed the basis for Hb/Hct cutoffs, as absolute erythrocytosis will almost always be present in men with a hematocrit of ≥60% (Hb > = 18.5 g/dL) and women with a hematocrit ≥56% (Hb > = 16.5 g/dL). But such specific cutoffs for Hb in the WHO criteria are not sensitive enough and have been shown to miss mildly elevated RBC mass in early polycythemia vera.\textsuperscript{67} These findings may lead to more nuanced diagnostic cutoffs in the future.

### Therapeutic Phlebotomy in Polycythemia Vera

The increased whole blood viscosity that results from the expansion of total red cell volume in patients with polycythemia vera is the underlying basis of the life-threatening prothrombotic state and the headache, fatigue, dyspnea, cyanosis, and other signs and symptoms that characterize the disorder.\textsuperscript{68} Aggressive phlebotomy to a hematocrit below 45% in males and below 42–45% in females is indicated for prevention of life-threatening thrombotic complications of polycythemia vera.\textsuperscript{56,68} High-risk patients (age > 60 years or history of thrombosis) should also be treated with cytoreductive hydroxyurea or, if erythrocytosis is recalcitrant, a second-line agent (e.g., busulfan or interferon-α).\textsuperscript{66,68} Low-risk patients (age < 60 years, no cardiovascular risk, platelet count < 1,000,000/mL) may initially be managed with phlebotomy alone.\textsuperscript{66} Low-dose aspirin (100 mg/day) is recommended for all patients without specific contraindications to its use.\textsuperscript{66} The pharmaceutical development of JAK2-selective kinase inhibiting agents has shown efficacy in early trials and should influence future management of polycythemia vera.\textsuperscript{69}

### Erythrocytapheresis in Polycythemia Vera

According to ASFA, polycythemia vera is a Category I indication for red cell volume reduction by erythrocytapheresis.\textsuperscript{1} A retrospective case series of 69 patients with polycythemia vera who underwent 206 isoosmotic erythrocytapheresis procedures using 4% albumin as replacement fluid reported reduction of hematocrit from 56.8 ± 5.6% to 41.9 ± 6.6% after removal of 1410 ± 418 mL of red cells.\textsuperscript{70} A subset of 21 patients for whom close follow-up data were available maintained a hematocrit of <50% for a median of six months.\textsuperscript{70} The volume of red cells to be removed (VR) during an erythrocytapheresis in order to achieve a desired hematocrit can be calculated as (Formula 2):\textsuperscript{70,71}

\[
VR = \left( \frac{\text{starting HCT} - \text{desired Hct}}{79} \right) \times \left( \frac{\text{blood volume}}{\text{body weight}} \right) 
\]
Thus, for a 70-kg person with a blood volume of 70 mL/kg whose hematocrit is to be lowered from 68% to 55%, the volume of red cells to be removed is calculated as:

\[
VR = \left( \frac{68 - 55}{79} \right) \times (70 \text{ mL/kg}) \times (70 \text{ kg}) = 910 \text{ mL of red cells}
\]

Additional studies have confirmed that erythroctapheresis can rapidly decrease hematocrit for extended intervals relative to simple phlebotomy,\textsuperscript{72,73} and suggest that automated erythroctapheresis may have a role for patients with acute thrombotic or microvascular complications, or to avoid perioperative thrombohemorrhagic complications in a patient with an uncontrolled hematocrit who requires urgent surgery.\textsuperscript{1,71}

**Secondary erythrocytosis**

Secondary erythrocytosis includes conditions that result in an elevated total red cell volume but are not clonal disorders of the marrow.\textsuperscript{64,66,74} Congenital and acquired causes have been described, and they predominantly involve the regulation or aberrant expression of erythropoietin or abnormalities of the erythropoietin receptor (see Table 34.3).\textsuperscript{75,76} The vast majority of cases are hypoxia-stimulated, usually due to chronic lung disease, smoking, or apnea. A diagnostic investigation of a patient with suspected erythrocytosis is performed in order to (1) establish that a true state of erythrocytosis exists (i.e. an elevated total red cell volume), (2) rule out polycythemia vera, and (3) determine the cause of secondary erythrocytosis, thereby leading to clinical management to alleviate the underlying cause.\textsuperscript{64,66,74-76}

**Therapeutic phlebotomy in secondary erythrocytosis**

The role of phlebotomy is less certain in secondary erythrocytosis than in polycythemia vera.\textsuperscript{1-7} As suggested by Table 34.3, secondary erythrocytosis is generally an adaptation to the disordered regulation of erythropoietin or to hypoxemia. In some cases, the underlying cause can be treated medically or surgically, and in others the erythrocytosis represents a physiologic adaptation to a chronic condition such as hypoxia but without thrombotic risk.\textsuperscript{77}

For example, adults with cyanotic congenital heart disease are not considered to be at heightened risk for thrombotic stroke despite mean hematocrits of 57.5% ± 7.2%\textsuperscript{78} and do not exhibit symptoms of hyperviscosity until hematocrits reach 65% (in the absence of dehydration or iron deficiency).\textsuperscript{79} A program of therapeutic phlebotomy should not be undertaken purely for the sake of achieving a target hematocrit in an asymptomatic individual. Isovolemic phlebotomy, with saline replacement, should be reserved for patients who are neither dehydrated nor iron deficient, and who have moderate symptoms of hyperviscosity (i.e., headache, slow mentation, visual disturbance, tinnitus, dizziness, etc.).\textsuperscript{79} Withdrawal of up to a unit of whole blood, replaced by 750 to 1000 mL of isotonic saline, has been recommended for relief of symptoms. Similar recommendations may refer to patients with high oxygen-affinity hemoglobin levels who have symptoms such as dizziness, dyspnea, or angina, which are believed to result, in part, from an expanded total red cell volume.\textsuperscript{76} There is again no formal evidence that phlebotomy is beneficial, and a modest target (i.e., a hematocrit <60% achieved with fluid replacement) has been recommended.\textsuperscript{76}

Likewise, patients with chronic hypoxic lung disease and erythrocytosis or with smoker’s erythrocytosis are best managed using medical therapy to deal with their underlying pulmonary disorder. Noncontrolled studies suggest that phlebotomy to a hematocrit of 50% to 52% may improve exercise tolerance, alleviate headache and confusion, and otherwise ameliorate symptoms of hyperviscosity.\textsuperscript{76}

Postrenal transplant erythrocytosis, defined as a persistently elevated hematocrit above 51%, occurs spontaneously in 15% to 20% of kidney transplant recipients in the first 8 to 24 months after engraftment.\textsuperscript{80-82} One-fourth of cases remit spontaneously within two years of onset, with the balance persisting for up to several years until chronic graft rejection supervenes.\textsuperscript{76} The major risk factors are retention of the native kidneys, male gender, smoking, a rejection-free course with a well-functioning graft, and adequate red cell production (without the need for erythropoietin or transfusion) prior to transplant.\textsuperscript{80,82} Hyperviscosity symptoms such as malaise, headache, plethora, lethargy, and dizziness are described as common among patients with this condition, and 10% to 30% develop significant thromboembolic complications.\textsuperscript{80,82} The pathogenesis appears to be multifactorial, and likely involves an interplay between endogenous erythropoietin production by the retained native kidney, the renin-angiotensin system, androgen secretion, insulin-like growth factors, and cytokines.\textsuperscript{80,81} One retrospective series reported 11 thromboembolic events, including transient ischemic attacks and strokes, and venous thromboembolism in 10 of 53 (19%) patients with postrenal transplant erythrocytosis but in none of 49 control cases (p < 0.001).\textsuperscript{82} This sort of experience has led to an appreciation of the need to control the red cell volume in these patients.\textsuperscript{80-82} The mainstay of treatment is angiotensin-converting enzyme inhibition or angiotensin-converting enzyme receptor blockade, sometimes in combination with theophylline, which lowers hemoglobin and hematocrit within eight weeks, with peak effect seen after up to 12 months.\textsuperscript{83}

**Erythroctapheresis in secondary erythrocytosis**

Automated erythroctapheresis is seldom recommended for management of secondary erythrocytosis,\textsuperscript{71} and its optimal role has not been established, thus requiring individualized decisions.\textsuperscript{1} It may be useful in circumstances where isovolemic procedures are called for, such as in cyanotic heart disease.\textsuperscript{79} Erythroctapheresis

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### Table 34.3 Secondary erythrocytosis\textsuperscript{75,76}.

<table>
<thead>
<tr>
<th>Type</th>
<th>Underlying Cause</th>
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<tbody>
<tr>
<td>Congenital</td>
<td>High oxygen-affinity hemoglobin&lt;br&gt;Biophosphoglycerate mutase deficiency&lt;br&gt;Erythropoietin receptor mutation&lt;br&gt;Oxygen-sensing pathway mutations (VHL, PHD2, and HIF-2a gene mutations)</td>
</tr>
<tr>
<td>Acquired</td>
<td>Hypoxia-stimulated&lt;br&gt;• Cyanotic congenital heart disease&lt;br&gt;• Chronic lung disease&lt;br&gt;• High-altitude habitat&lt;br&gt;• Smoker’s erythrocytosis&lt;br&gt;• Carbon monoxide poisoning&lt;br&gt;• Chronic hyperventilation (sleep apnea)&lt;br&gt;• Renal artery stenosis&lt;br&gt;• Inappropriate erythropoietin production&lt;br&gt;• Renal cancer&lt;br&gt;• Hepatic cancer&lt;br&gt;• Cerebellar hemangioblastoma&lt;br&gt;• Endocrine tumors&lt;br&gt;• Uterine leiomyoma&lt;br&gt;• Polycystic kidney&lt;br&gt;• Meningioma&lt;br&gt;• Drug-mediated&lt;br&gt;• Androgen therapy&lt;br&gt;• “Blood doping” (surreptitious erythropoietin use)&lt;br&gt;• Multifactorial etiology&lt;br&gt;• Postrenal transplant erythrocytosis</td>
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has not been reported in the management of posttransplant erythrocytosis.

**Hereditary hemochromatosis**

Hereditary hemochromatosis is an inherited disorder that, untreated, results in iron deposition in, and damage to, the liver, heart, pancreas, and other organs, including bronze pigmentation of the skin.\(^{84,85}\) Its prevalence is approximately 1:200 among those of European ancestry.\(^{84,86}\) The most common genetic mutation, accounting for >90% of cases (and almost all cases in persons of Northern European ancestry), is homozygosity for a missense mutation (G85A) in the HFE gene resulting in tyrosine substituted for cysteine (C282Y).\(^{87}\) HFE C282Y (as well as H63D) decreases hepcidin transcription by stabilizing the ALK3 protein that inhibits transcription.\(^{88}\) In the absence of a physiological means of body iron excretion, the increased iron uptake resulting from these mutations leads to the slow accumulation of iron in the liver and other organs, and eventual liver failure (via cirrhosis, hepatocellular carcinoma, etc.), diabetes, hypogonadism, hypopituitarism, arthopathy, cardiomyopathy and heart failure, and skin pigmentation.\(^{86,89}\) A presenting syndrome of asthenia, arthralgia, and abnormal liver function (three A’s) has been described as classic for the clinical disease.\(^{85}\) Because of the central importance of iron loading in the pathogenesis of hereditary hemochromatosis, iron removal by phlebotomy is the mainstay of treatment.\(^{86,89}\) Diagnostic elements of hereditary hemochromatosis are provided in Table 34.4.

**Therapeutic phlebotomy in hereditary hemochromatosis**

Therapeutic phlebotomy has been the primary mode of iron reduction in hereditary hemochromatosis for over a half century.\(^{84,86}\) Phlebotomy therapy should be started in all patients whose serum ferritin level is elevated (Table 34.4) and should not be withheld from the elderly on the basis of age or from iron-loaded patients who have not developed clinical symptoms.\(^{86,87}\) A common treatment approach is to perform one phlebotomy per week (1 unit or 7 mL/kg of whole blood not to exceed 550 mL per phlebotomy) until the serum ferritin is below 50 ng/mL (although this endpoint is not based on clear-cut evidence).\(^{86,89}\) Thereafter, it is usually necessary to annually remove 3–4 units of blood to maintain the ferritin between 50 and 100 ng/mL.\(^{86,89}\) Malaise, weakness, fatigability, skin pigmentation, cardiac function, and liver transaminase elevations often improve with treatment, whereas diabetes, cirrhosis, arthropathy, pituitary dysfunction, and hypogonadism almost never improve. Importantly, the risk of hepatocellular carcinoma will persist if cirrhosis was present before the onset of phlebotomy therapy.\(^{85,86}\)

**Erythrocytapheresis in hereditary hemochromatosis**

This was first described in Europe, where a German group from Munich reported successful lowering of iron in 14 patients with hemochromatosis, with intervals of 2–11 months between procedures.\(^{10}\) Their follow-up study\(^{90}\) described prospective observations on eight patients who were treated with isovolemic erythrocytapheresis (1000 mL removed) every four weeks until serum ferritin fell below 300 ng/mL. Iron depletion, thus defined, was achieved after a mean of 8.5 months, during which a mean of 9.4 liters of red cells were removed in a mean of 8.9 procedures. Subsequent studies have supported these findings, and, based on this rapidity of response and the potential removal of 2–3 times more RBCs per procedure compared to a simple phlebotomy, it has been designated a first-line therapy (Category I) in the ASFA guidelines.\(^{1}\) Recently, there have been controlled trials comparing the relative efficacy and cost-effectiveness of erythrocytapheresis versus simple phlebotomy.\(^{91,92}\) The first study compared 500 mL weekly phlebotomies to erythrocytapheresis every two weeks. The authors found that erythrocytapheresis patients demonstrated a more rapid decline and normalization of ferritin; however, this group started with a lower average ferritin. This higher iron load in the phlebotomy group was supported by the fact that threefold more phlebotomies were needed to normalize the serum ferritin level, even though erythrocytapheresis removed only twofold more iron-containing RBCs.\(^{91}\) Overall, this suggests that an erythrocytapheresis procedure every two weeks and weekly whole blood phlebotomy are equivalent, and this was supported by another randomized control trial that found no significant difference in mean time to iron depletion (ferritin <50).\(^{92}\) In this study, the mean technician time was increased for the apheresis group,\(^{92}\) consistent with the added procedural complexity, and thus decisions between the two modalities should probably be determined by patient and institutional preferences related to costs and effort. Intriguingly, although on average two simple phlebotomies remove equivalent iron to one erythrocytapheresis, individuals with larger blood volumes see a greater gain from erythrocytapheresis.\(^{93}\) This is a consequence of the lack of volume adjustment for simple phlebotomy and suggests that blood-volume-based simple phlebotomies could be an optimal solution in terms of costs and effort.

**Therapeutic platelet apheresis**

*Thrombocytapheresis* is a term that describes the selective removal of platelets from a patient, for therapeutic purposes, using a blood-processing (apheresis) device.\(^{1}\) The 2013 ASFA review of indications for apheresis therapy lists *symptomatic thrombocytosis* as a Category II indication for thrombocytapheresis.\(^{1}\) This designation refers to primary thrombocytosis, as results from a clonal (myeloproliferative) disorder of the marrow.\(^{94}\) Thrombocytapheresis for prophylaxis in asymptomatic patients or to lower the platelet count in cases of secondary or reactive thrombocytosis is listed as a Category III (i.e., specific role of the procedure not determined in this condition) indication because published evidence is insufficient to establish when the procedure is of benefit in these...
circumstances. Some prominent causes of primary and secondary thrombocytosis are listed in Table 34.5.

Secondary thrombocytosis per se does not convey a risk of thromboembolic morbidity absent confounding factors such as malignancy or major surgery. Even then, antiplatelet agents should be the first option for treatment. In any case, treatment of the underlying cause is the prime factor in the resolution of secondary thrombocytosis. In fact, given the absence of risk posed by the platelet count in secondary thrombocytosis, the platelet count may be considered a laboratory sign of an underlying condition that should be investigated.

Primary thrombocytosis (essential thrombocythemia)

Thrombocytosis with thromboembolic complications is a feature common to chronic myeloproliferative disorders, of which half are essential thrombocythemia. Thus, the remainder of this discussion will focus on essential thrombocythemia. Factors that increase risk of arterial thrombosis include age greater than 60 years; thrombosis history; cardiovascular risk factors such as hypertension, hypercholesterolemia, and diabetes; and JAK2V617F positivity. Interestingly, high platelet counts (>10^12/L) were associated with reduced risk of arterial thrombosis, and venous thrombosis was only associated with male gender. The most significant functional consequence of such hyperthrombocytosis is an acquired von Willebrand syndrome (AvWS) that results from the accelerated clearance of hemostatically competent large multimers of von Willebrand factor from the circulation, and which improves with therapeutic reduction of the platelet count.

Therapeutic thrombocytapheresis in primary thrombocytosis

Rapid lowering of an elevated platelet count, using apheresis and/or chemotherapy, is indicated for patients with myeloproliferative disorders who present with clinical syndromes of microvascular thrombosis such as digital or cerebral ischemia. Case series and case reports have reported successful, rapid lowering of the platelet count in symptomatic patients in whom chemotherapy either was not an immediate option or was judged to have an insufficiently rapid effect. Procedures in which 1.5 to 2.0 blood volumes are processed, and crystalloid replacement fluids are used to manage fluid balance, can lower the platelet count by 30% to 60%. However, thrombocytapheresis without concomitant chemotherapy is not a practical means for controlling the platelet count beyond the acute setting.

Weekly thrombocytapheresis, beginning in the fifth gestational week, has been used in the management of a high-risk pregnant patient with essential thrombocythemia.

Therapeutic white cell apheresis

Hyperleukocytosis (white cell count >100,000/μL) with symptomatic leukostasis is a Category I indication for therapeutic leukocytapheresis. Leukocytapheresis by selective adsorption techniques has shown a disappointing lack of efficacy in trials for idiopathic inflammatory bowel disease. For ulcerative colitis, the remission rate was 17% for leukocytapheresis and 11% for the sham control (p = 0.36), and for Crohn’s disease, the remission rate was 18% for the leukocytapheresis and 19% for the sham control (p = 0.86). Currently, ASFA rates immunoadsorption for IBD as a category III indication, except for ulcerative colitis in Japan, which is category II and may be due to the fact that TNFα blockade is not standard therapy in Japan.

Leukocytapheresis for hyperleukocytosis

Hyperleukocytosis is a major risk factor for early mortality, often from pulmonary and/or central nervous system hemorrhage, in adults and children with acute myeloblastic leukemia. It occurs in 5–13% and 12–25% of adult and pediatric AML cases, respectively. The reported incidence in acute lymphoblastic leukemia ranges from 10% to 30%. Mortality rates of 20–40% have been reported. Leukostasis represents end-organ damage due to leukocyte-mediated microvascular occlusion and damage resulting in infarct and hemorrhage. It usually does not occur until white blood cell counts surpass 100,000/μL in acute myelogenous leukemia (AML) and 400,000/μL in acute lymphoblastic leukemia (ALL). Clinical features of leukostasis include respiratory distress, hypoxemia, diffuse interstitial or alveolar infiltrates on chest X-ray, confusion, somnolence, stupor or coma, headache, dizziness, tinnitus, gait instability, or visual disturbances. Physical examination may demonstrate papilledema, dilated retinal veins and/or retinal hemorrhages, cranial nerve defects, or meningeal signs. Metabolic derangements caused by tumor lysis may include hyperkalemia, hyperuricemia, hypocalcemia, and hyperphosphatemia and may result in renal failure and early death. Coagulopathy results from release of lysozomal enzymes from myeloid blasts, disseminated intravascular coagulation, and thrombocytopenia resulting from marrow failure.

A standard treatment approach to hyperleukocytosis includes intravenous hydration and lowering of plasma uric acid using allopurinol or urate oxidase. Hydroxyurea may be prescribed to rapidly lower the total circulating nucleated cell count without precipitating a tumor lysis syndrome.
may be used for this purpose but may precipitate tumor lysis syndrome and hemorrhage.\textsuperscript{108} The processing of 1.5 to 2.0 blood volumes can reduce the circulating white blood cell count by up to 60%.\textsuperscript{1,109,110} Leukocytapheresis before initiation of definitive induction chemotherapy has been retrospectively reported to lower the leukemic blast count to <100,000/µL in approximately 60% of patients, and to lower the incidence of early death (Day 21 after admission) by half but without an effect on long-term survival.\textsuperscript{109–111} However, a recent meta-analysis of 15 studies combining 465 AML patients with hyperleukocytosis found no overall evidence (\( p = 0.67 \)) that leukopheresis reduced acute mortality.\textsuperscript{112} Thus, hyperleukocytosis without symptoms is ASFA Category III (individualize decision making). Hyperleukocytosis with leukostasis is classified as Category I mainly based on observed reports of rapid reversal of signs and symptoms.\textsuperscript{1}

**Extracorporeal photochemotherapy**

Extracorporeal photochemotherapy (ECP or photopheresis) describes a procedure in which circulating mononuclear cells are collected by centrifugal apheresis, exposed to 8-methoxypsoralen (8-MOP, a photoactivating agent that intercalates with DNA), and then exposed to ultraviolet A (UVA) light. The treated cells are then reinfused into the patient. A full procedure is completed in approximately 1.5–3 hours.\textsuperscript{113} The mechanism of action of ECP is thought to be immunomodulation due to the direct and indirect effects of induced apoptosis in treated cells.\textsuperscript{113,114} Although the main effects vary somewhat among diseases, they likely include the generation of tolerogenic dendritic cells, skewing toward anti-inflammatory cytokine production, and increased tolerogenic and regulatory T-cell populations.\textsuperscript{113,114} Currently, erythrodermic cutaneous T-cell lymphoma (CTCL) is the only Category I indication for ECP. ASFA has listed the prophylaxis and treatment of heart transplant rejection, cutaneous manifestations of graft-versus-host disease (GVHD), and lung allograft rejection as Category II indications for ECP. There is a growing body of potential applications in transplant rejection as well as in autoimmune diseases for which the ASFA recommendations are generally Category III.\textsuperscript{1,115} Some ECP regimens used in the treatment of the Category I and II indications are described in Table 34.6.

**Cutaneous T-cell lymphoma (CTCL)**

**Extracorporeal photochemotherapy in the treatment of cutaneous T-cell lymphoma**

The CTCLs are a heterogeneous group of extranodal non-Hodgkin lymphomas of T-cell origin that target the skin.\textsuperscript{113} Mycosis fungoides, the most common form of CTCL, accounts for almost half of all primary cutaneous lymphomas.\textsuperscript{113} It is largely a disease of adults (median age 55–60 years at diagnosis) and typically presents as an indolent disorder that progresses slowly over years from patchy skin involvement to infiltrated plaques, tumors, and widespread disease.\textsuperscript{113} Whereas localized (e.g., nonerythodermic) mycosis fungoides is adequately managed with topical therapies, the application of ECP in erythodermic mycosis fungoides is recommended by ASFA.\textsuperscript{1} Whereas limited-stage mycosis fungoides does not shorten life expectancy, advanced-stage disease may be associated with a 10-year disease-specific survival of 20%.\textsuperscript{116} Sézary syndrome is defined as a triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in the skin, lymph nodes, and peripheral blood.\textsuperscript{113,116} A retrospective cohort study from Stanford University of 106 patients with erythodermic mycosis fungoides and Sézary syndrome identified age ≥65 years, clinical Stage IV, and circulating Sézary cells ≥5% of total lymphocytes as independent negative prognostic factors for survival.\textsuperscript{117} Median survival of patients with none, one, or more than one of these adverse prognostic factors were 122 months (\( n = 36 \)), 44 months (\( n = 39 \)), and 18 months (\( n = 31 \)), respectively (\( p < 0.005 \)).\textsuperscript{117}

The 1987 report by Edelson et al.\textsuperscript{118} of a successful pilot trial of ECP, in which 27 of 37 treatment-resistant patients with CTCL experienced an average 64% decrease in cutaneous involvement after 22 ± 10 weeks, led to US Food and Drug Administration (FDA) approval of ECP for treatment of CTCL later that year. Long-term follow-up of the original 29 patients with erythodermic CTCL from that pilot study\textsuperscript{118} reported that median survival of the treated patients was 60.33 months from diagnosis and 47.9 months from the start of ECP. Four of the six patients who achieved complete responses in the original study remained in complete remission.\textsuperscript{119} Between 1987 and 2001, 21 studies reported a total of 485 patients treated using ECP.\textsuperscript{113,120} Although most patients in these studies had erythodermic CTCL, most studies did not report the response rates separately for the erythodermic subjects.\textsuperscript{121} In addition, responses were defined as >25% skin clearing in some studies and >50% skin clearing in others, and complete responses were defined as either 75% to 100% skin clearing, >90% skin clearing, or 100% skin clearing.\textsuperscript{113,120} Nonetheless, overall response rates reported in these studies ranged from 31% to 87.5%, and complete response rates ranged from 0% to 54% (20–30% in most studies).\textsuperscript{113,120} The variability in response rates has been attributed to differences in entry criteria, prior or concurrent therapy, duration between diagnosis and application of ECP, the ECP...
Cardiac and lung allograft rejection
Between 1990 and 2012, the rate of heart transplantation was fairly constant at 3500–4500 per year, while lung transplants increased more or less linearly from 500 in 1990 to over 3700 in 2012.122,123 Rejection is still a serious problem for both heart and lung allografts, accounting for approximately 11% of deaths in the first three years after heart transplant, and underlies the majority of graft failures that account for 35% of overall deaths.122 Similarly for lung allografts, rejection underlies approximately 25% of mortality at five years, when bronchiolitis obliterans syndrome (BOS), the end result of chronic rejection, is included.123 Immunosuppressive therapy to prevent allograft rejection has included perioperative antilymphocyte antibody (polyclonal antilymphocyte or antilymphocyte globulin, OKT3, or IL-2 receptor antibodies), chronic postoperative calcineurin inhibitors (e.g., tacrolimus and cyclosporine), mycophenolate mofetil, sirolimus, and others.122,123 Because of the association between rejection, graft failure, and death, evidence of rejection should result in adjustment in the immunosuppressive regimen to initially resolve the episode of rejection. For unresponsive cardiac rejection or lung transplant BOS, ECP is an appropriate adjuvant; and these are listed by ASFA as Category II indications for ECP based on the evidence described below.1

Extracorporeal photochemotherapy in the treatment of cardiac allograft rejection
Studies in support of ECP for treatment of cardiac allograft rejection focus on the effects of ECP on endomyocardial biopsy findings, rather than on survival or graft function.120 Two pilot studies have shown evidence that the risk of acute cellular rejection episodes can be decreased by incorporating ECP into the prophylactic immuno-suppressive regimen of cardiac allograft recipients without increasing the risk of infection caused by immunosuppression.124,125 A prospective randomized pilot trial comparing 10 cases receiving ECP and 13 controls treated with only immunosuppression reported that development of panel-reactive antibodies (responsible for chronic antibody-mediated rejection) and coronary artery intimal hyperplasia (a pathogenic mechanism of graft failure in chronic rejection) are mitigated by the addition of ECP to the posttransplant immunosuppressive regimen for the first two years after transplant surgery.126 Dall’Amico and colleagues in Padua, Italy, reported a prospective pilot trial in eight patients, with recurrent acute rejection episodes despite immunosuppression, who were treated with two consecutive days of ECP every four weeks for six months.127 Seven benefited with a reduction in the number and severity of rejection episodes; reduction in daily prednisone, cyclosporine, or azathioprine doses; and improvement on endomyocardial biopsy specimens. Other small case series and case reports have presented corroborating data supporting ECP efficacy.128

Extracorporeal photochemotherapy in the treatment of lung allograft rejection
The use of ECP in lung transplant is a promising new avenue, although only retrospective studies have been reported thus far. The first reports of treatment were in 1995 and represented a handful of cases pointing to effective improvement in clinical lung function (FEV1) and histological improvement. A number of small studies followed that generally supported these findings.128 Only recently have larger studies examining ECP been reported encompassing a total 135 patients and supporting a role for ECP in stabilizing lung function (FEV1) with minimal procedural side effects. Although the lack of adequate controls leaves a larger question as to the benefit of ECP compared to regimens that do not include ECP, there is a decrease in donor-specific antibodies in patients treated with ECP compared to controls, akin to ECP for cardiac rejection.132

Graft-versus-host disease
GVHD occurs in hematopoietic progenitor cell transplant recipients when T cells of donor origin (either transplanted with, or that develop from, the graft) interact with tissue in the HLA-matched but genetically nonidentical host.133 Classical acute GVHD develops within 100 days of transplantation, with skin manifestations that vary from an erythematous morbilliform rash to epidermal necrolysis, mucosal inflammation causing diarrhea and abdominal cramping, and abnormalities of liver function tests.133 GVHD that develops beyond 100 days of transplantation, or persists more than three months, is traditionally referred to as chronic GVHD, and is characterized by an oral, ocular, and mucous membrane sicca syndrome; skin involvement; scleroderma; bronchiolitis obliterans; joint contractures; myofasciitis; esophageal stricture; or other fibrotic complications in various organ systems.133 The cumulative incidence of acute GVHD is approximately 12% to 75%, and the cumulative incidence of chronic GVHD is approximately 15% to 70% after hematopoietic progenitor cell transplantation, depending on whether the donor–recipient pair are related or unrelated and on whether a myeloablative or nonmyeloablative conditioning regimen was used.134,135 Accurate diagnosis and staging are important in that recurrent or late-onset acute GVHD may not require prolonged therapy as is required with chronic GVHD, whereas overlap syndromes may require shorter courses of typical treatments for chronic GVHD.136

Extracorporeal photochemotherapy in the treatment of GVHD
The application of ECP to the treatment of GVHD has been extensively reviewed.126,137 Among the larger prospective reports is one from a London group that treated 28 patients who had developed steroid-refractory chronic GVHD following HLA-matched allogeneic marrow or peripheral blood progenitor cell transplant.138 Among the patients, 27 were classified as having extensive chronic GVHD and 20 had involvement of more than 50% of their skin surface. Patients were given ECP on two consecutive days every two weeks for the first four months, and monthly thereafter. ECP was initiated a median of 34 months (range 10–167) after transplantation and 23 months (range 2–164) from the onset of chronic GVHD. Of the 21 patients with cutaneous involvement who were evaluable, a 25% reduction in skin involvement was noted in eight (38%) after three months and in 10 (48%) after six months, and a statistically nonsignificant improvement in liver function tests was noted.138 There is only one randomized control study that failed to show significant improvement in the primary outcome, decrease in skin involvement (14.5% for ECP arm vs. 8.5% in control); however, there was significant decrease in steroid usage compared to the control arm.139 Given the lack of large randomized prospective studies, a meta-analysis was performed combining 18 prospective and retrospective studies of steroid-refractory GVHD with sufficient comparable cases.137 This meta-analysis found significant efficacy with a complete response rate of 29% (CI 19–42%) along with particularly strong response rates of 74% (CI 60–85%) and 68%
Specialized therapeutic plasma processing

In its 2013 evidence-based review of apheresis therapies, ASFA lists 14 Category I, II, or III indications for therapeutic immunoadsorption, LDL apheresis, or hemoeresis (a form of double-membrane filtration plasmapheresis, or DFPP). The physiology of non-selective TPE and its indications are addressed in Chapter 33. The following discussion focuses on therapeutic procedures that are designed to remove a specified fraction of the plasma. A pathogenic plasma substance (e.g., a specific autoantibody) is usually present at relatively low levels in the circulation. Thus, selective extraction of pathologic plasma constituents in a way that minimizes the sacrifice of healthy plasma proteins has been proposed as a more efficient treatment of disorders that might otherwise be treated using TPE.

Immunoadsorption systems apheresis

Immunoadsorption systems employ the principle of affinity chromatography and make use of immobilized sorbents or ligands that have enhanced or specific binding affinity for a specific antigen, antibody, immune complex, or other substance in the patient’s circulation. Examples include (1) staphylococcal protein A or sheep antihuman immunoglobulin (IgG) for extraction of IgG and immune complexes from the circulation, (2) sheep antihuman low-density lipoprotein (LDL) or apolipoprotein B antibody for extraction of LDL, (3) synthetic blood group substances for removal of ABO isoagglutinins, and (4) DNA for removal of DNA antibody. Although no longer commercially distributed in the United States, two immunoadsorption systems that have received approval from the FDA are the staphylococcal protein A-agarose column (Immonosorba, Fresenius Hemocare, Redmond, WA), and the staphylococcal protein A silica column (Prosorba, Prosorba HemoCare). Protein A is a cell-wall constituent of the Cowan I strain of Staphylococcus aureus. Mammalian IgG binds to five homologous regions at its amino terminus, but interaction of protein A with other plasma proteins is insignificant. Processing of 2.5 plasma volumes using a protein A-agarose column resulted in a 97% reduction in IgG1, a 98% reduction in IgG2, a 40% reduction in IgG3, a 77% reduction in IgG4, a 56% reduction in IgM, and a 55% reduction in IgA, whereas plasma levels of albumin, fibrinogen, and antithrombin were reduced by less than 20%. Thus, in principle, plasma adsorption with protein A affinity columns permits the processing of more plasma than does TPE without unacceptable loss of other essential plasma constituents. The use of these devices in a variety of clinical conditions in Europe and Japan has been extensively reviewed.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) describes a cardiac disorder in which the left ventricle is dilated and exhibits impaired contraction. It may be idiopathic, familial, postviral, alcohol- or drug-induced, or related to other cardiac disease. Both ventricles may be affected. It presents with heart failure, is often progressive, and may be complicated by arrhythmias, thromboembolic events, and sudden death. It is the most frequent antecedent cause of heart transplantation throughout the world. Approximately 60% to 80% of patients with DCM harbor autoantibodies directed against cardiac myosin heavy chain, myocardial β1-adrenergic receptors, or other cardiac tissue with a predominance of antibodies of the IgG 3 subclass. Immunoadsorption in the treatment of dilated cardiomyopathy

A variety of immunoadsorption (IA) columns, including antihuman polyclonoglobulin, staphylococcal protein A agarose, β1-adrenoreceptor antibody peptides, and tryptophan polyvinyl alcohol, have all shown potential efficacy but still await formal comparisons to other therapies. Initially, the potential relevance of heart antibodies to clinical DCM was explored in a pilot study of eight patients with DCM and advanced congestive heart failure who were subjected to a series of four or five IA procedures per week over two weeks using the Therasorb-Ig system. β1-adrenoreceptor autoantibody levels decreased by an order of magnitude and heart failure symptoms improved in seven of the subjects, but the effect was transient: autoantibodies and symptoms returned to baseline 75 days after completion of IA. In a companion pilot trial, nine patients were subjected to daily IA treatments for five days using Therexorbs-Ig. Patients received 35 g of IVIG after the final procedure. Once again, plasma levels of β1-adrenoreceptor autoantibody were substantially reduced, and significant improvement in hemodynamic parameters (including cardiac output, mean arterial pressure, mean pulmonary arterial pressure, left ventricular filling pressure, and systemic vascular resistance) was demonstrated, thus providing objective preliminary evidence of the clinical benefit of antibody removal by IA. In another randomized trial, 18 patients with DCM and advanced heart failure were randomly assigned to either best medical therapy (control group) or best medical therapy with the addition of IA. During the first course of IA, procedures were performed on three consecutive days, and patients received 0.5 g/kg of IVIG by intravenous infusion. Three subsequent courses of IA, performed on two consecutive days at four-week intervals, were also followed by infusions of IVIG at the same dose. IA was performed using the Therasorb-Ig column. After the first course of IA/IVIG, left ventricular ejection fraction, cardiac index, stroke volume index, and systemic vascular resistance improved significantly in the treatment group, and these changes remained evident after the final series. Improvement in symptoms and functional status paralleled the hemodynamic changes. The control group demonstrated no hemodynamic improvement at the end of the three-month study. β1-adrenoreceptor antibodies decreased by >80% after the first course of IA but tended to rise between monthly courses of treatment. There have now been multiple trials, case reports, and case series generally supporting improvement.

The vast majority of studies infused intravenous IgG (IVIG), which might solely, or in concert with IA, account for clinical improvement. Unfortunately, trials of treatment with IVIG alone have been equivocal. One trial, in which patients initially received a total of 2 g/kg followed by 0.4 g/kg monthly for five months, demonstrated significant improvement in left ventricular ejection fraction in the treatment group but not the placebo group. A second trial, in which patients received a single course totaling 2 g/kg, demonstrated no effect of IVIG on left ventricular ejection fraction after six or 12 months (although both the treatment and placebo groups showed improvement). One prospective case-control trial was important in that no IVIG replacement was
performed for 17 cases receiving IA compared to controls matched for age, body surface area (BSA), duration of symptoms, cardiac function, and New York Heart Association (NYHA) functional class. Specifically, at one year, the IA-treated patients demonstrated significant improvement in NYHA functional class and left ventricular status with 67% improvement in ejection fraction and 14% decrease in the ventricular diameter compared to pretreatment. Controls demonstrated no improvement, and the treated cases demonstrated improved survival at five years compared to controls (82% vs. 42%). Although a single study, it supports the possibility that IA has significant effects irrespective of IVIG. The role for the removal of antibodies is also supported in that patients that respond to IA have stronger negative inotropic antibody activity in vitro. Overall, ASFA does not recommend a singular adsorption modality, and designates DCM a Category II indication for immunoadsorption apheresis.

Familial hypercholesterolemia (FH), an autosomal dominant disorder, is a major cause of death or early disability resulting from premature atherosclerotic heart and peripheral vascular disease. It is caused by mutations in the LDL receptor, with frequencies of 1:500 for heterozygotes and 1:1,000,000 for homozygotes. Clinical features including xanthomas, xanthelasmans, corneal arcs, and the occurrence of coronary heart disease, stroke, and death are common in the fourth or fifth decade of life. A serum LDL cholesterol level below 100 mg/dL (achieved through diet, lifestyle modification, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibiting drugs or statins) can lower cardiovascular morbidity and mortality in high-risk patients, but a sizable minority of high-risk patients fail to achieve LDL-cholesterol-lowering goals by this approach.

LDL apheresis

Manual, then automated, plasma exchange was successfully employed as an adjunct to lipid-lowering therapy beginning over 40 years ago. However, the kinetics of restoration of plasma lipid levels and the unwanted lowering of essential plasma proteins (e.g., fibrinogen and albumin) rendered this approach challenging for long-term therapy. The development of apheresis devices that permit a more selective removal of plasma LDL cholesterol and related substances has provided a practical approach to managing statin-resistant patients in conjunction with statins and other medical therapies.

Two apheresis systems for selective removal of LDL cholesterol are FDA-approved for use in the United States. The Liposorber LA-15 system (Kaneka Pharma America, New York, NY) uses dextran sulfate bound to cellulose to selectively extract LDL cholesterol from plasma. In this system, plasma is initially separated from the cellular components of blood by filtration through a disposable semipermeable polysulfone hollow fiber column, and the separated plasma is then perfused over a disposable adsorption column that contains 150 mL of dextran sulfate. Dextran sulfate has strong affinity for lipoproteins and adsorbs these from the plasma.

The H.E.L.P. system (B. Braun Medical, Bethlehem, PA) employs a 0.55-micron hollow fiber column to separate the plasma from the cellular elements of the blood. The plasma is acidified with 0.3 M sodium acetate buffer, and heparin is added to precipitate LDL cholesterol. The LDL cholesterol–heparin precipitate is filtered from the plasma using a 0.45-micron polycarbonate filter, excess heparin is adsorbed from the filtered plasma with a DEAE cellulose membrane filter, and the filtered plasma is then restored to physiologic pH by bicarbonate hemodialysis.

ASFA has designated FH a Category I indication for LDL apheresis in homozygotes and a Category II indication for LDL apheresis in heterozygotes. The FDA-approved indications include homozygotes with plasma LDL cholesterol >500 mg/dL, and heterozygotes with LDL cholesterol >300 mg/dL (or >200 with known coronary artery disease). A regimen that combines medical therapy with LDL apheresis on a biweekly schedule can effectively lower LDL cholesterol by 60% to 80% in otherwise treatment-resistant patients, improve the physical stigmata of hypercholesterolemia such as xanthomas and xanthelasmas, improve myocardial perfusion and coronary artery patency, and favorably affect other markers of cardiovascular risk (e.g., triglycerides, fibrinogen, homocysteine, C-reactive protein, and adhesion molecules). More recently, LDL apheresis has been found effective in ameliorating drug-refractory coronary artery disease in patients with Lp(a)-hyperlipoproteinemia.

Conclusion

The continued growth of therapeutic apheresis as a treatment option in diverse clinical conditions depends on an understanding of the pathophysiology of the disorders in question and the acquisition of evidence, from properly conducted clinical studies, of the efficacy of apheresis therapies in their management.

Disclaimer

The authors have disclosed no conflicts of interest.

Key References

A full reference list for this chapter is available at: http://www.wiley.com/go/simon/transfusion