Name of Policy: Extracorporeal Photopheresis

Policy #: 028      Latest Review Date: June 2014
Category: Therapy      Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:
1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**

Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory procedure that involves the following steps:

1. Patient blood is collected into a centrifuge system that separates the leukocyte-rich portion (buffy coat) from the rest of the blood.
2. The photosensitizer agent 8-methoxypsoralen (8-MOP) is added to the lymphocyte fraction, which is then exposed to ultraviolet (UV) A (320-400 nm wavelength) light at a dose of 1-2 J per square cm.
3. The light-sensitized lymphocytes are reinfused into the patient.

ECP has been investigated for the treatment of patients with a variety of autoimmune diseases, graft-versus-host disease (GVHD), T-cell lymphoma (TCL), treatment for and prevention of organ rejection after solid-organ transplant and other miscellaneous conditions.

**Treatment and Prevention of Organ Rejection after Solid-Organ Transplant**

The standard of care for treatment of organ transplant rejection is immunosuppression, with the particular regimen dictated by the organ being transplanted. As organ transplantation success rates have improved more patients are facing the morbidity and mortality associated with immuno-suppressive therapies developed to prevent rejection of the transplanted organ. Immunosuppressive therapies are used to lower the responsiveness of the recipient’s immune system, decreasing the chance of rejection. Unfortunately, portions of the immune system responsible for the prevention of viral, fungal and bacterial infection are also affected. This can in turn lead to serious infections, including opportunistic infections.

Although first approved for the treatment of cutaneous T cell lymphoma (CTCL), ECP has more recently been used as a supplement to conventional therapies in the area of solid organ transplantation. Reports of the successful use of ECP in human cardiac transplant recipients were published in 1992 and use in other transplant patients followed. Although the specific mechanism of action of ECP is unknown, the reinfusion of treated leukocytes seems to specifically suppress the patient’s immune response to the donor organ, although maintaining the body’s ability to respond to other antigens. The specificity of ECP to target the immune response to the transplanted organ allows ECP to decrease organ rejection without an increased risk of infection, common with immunosuppressive drugs.

**Treatment of Graft-versus-Host Disease (GVHD)**

ECP as a treatment of graft-versus-host disease (GVHD) after a prior allogeneic stem-cell transplant is based on the fact that GVHD is an immunologically mediated disease. GVHD can be categorized into acute disease, occurring within the first 100 days after infusion of allogeneic cells, or chronic disease, which develops sometime after 100 days. Acute GVHD is commonly graded from I to IV, ranging from mild disease, which is characterized by a skin rash without involvement of the liver or gut, to Grades III and IV, which are characterized by generalized erythroderma, elevated bilirubin levels, or diarrhea. Grade III acute GVHD is considered severe, while Grade IV is considered life-threatening. Chronic GVHD typically presents with more diverse symptomatology resembling autoimmune diseases such as progressive systemic sclerosis, systemic lupus erythematosus, or rheumatoid arthritis. Chronic GVHD may affect the
mouth, eyes, respiratory tract, musculoskeletal system, and peripheral nerves, as well as the skin, liver, or gut—the usual sites of acute GVHD.

Treatment of Autoimmune Disease
The use of ECP as a treatment of autoimmune disease is based on the premise that pathogenic lymphocytes form an expanded clone of cells, which are damaged when exposed to UV light in the presence of 8-MOP. It is hypothesized that the resulting damage induces a population of circulating suppressor T cells targeted against the light-damaged cells. It is further hypothesized that these suppressor T cells are targeted at a component of the cell that is common to the entire clone of abnormal cells (i.e., not just the light-sensitized cells), thus inducing a systemic effect. However, although scleroderma and other autoimmune diseases are associated with the presence of circulating antibodies, it is not certain how these antibodies are related to the pathogenesis of the disease, and, as discussed in this policy, photopheresis is not associated with consistent changes in autoantibody levels.

Treatment T-Cell Lymphoma
Cutaneous T-Cell Lymphoma (CTCL)
According to the National Cancer Institute (NCI), cutaneous T-cell lymphoma (CTCL) is a neoplasia of malignant T lymphocytes that initially present as skin involvement. CTCL is extremely rare, with an estimated incidence of approximately 0.4 per 100,000 annually but, because most are low-grade malignancies with long survival, the overall prevalence is much higher. Two CTCL variants, mycosis fungoides and the Sézary syndrome, account for approximately 60% and 5% of new cases of CTCL, respectively.

CTCL is included in the Revised European-American Lymphoma classification as a group of low-grade T cell lymphomas, which should be distinguished from other T cell lymphomas that involve the skin, such as anaplastic large cell lymphoma, peripheral T cell lymphoma, adult T cell leukemia/lymphoma (usually with systemic involvement), or subcutaneous panniculitic T cell lymphoma. In addition, a number of benign or very indolent conditions can be confused with mycosis fungoides, further complicating diagnosis. See the Policy Guidelines for the current staging classification of CTCL using the tumor, node, metastasis (TNM) classification system.

Mycosis fungoides typically progress from an eczematous patch/plaque stage, covering less than 10% of the body surface (T1), to a plaque stage, covering 10% or more of the body surface (T2), and finally to tumors (T3) that frequently undergo necrotic ulceration. Sézary syndrome is an advanced form of mycosis fungoides with generalized erythroderma (T4) and peripheral blood involvement (B1) at presentation. Cytologic transformation from a low-grade lymphoma to a high-grade lymphoma sometimes occurs during the course of these diseases and is associated with a poor prognosis. A common cause of death during the tumor phase is sepsis from Pseudomonas aeruginosa or Staphylococcus aureus caused by chronic skin infection with staphylococcus species and subsequent systemic infections.

The natural history of mycosis fungoides is typically indolent. Symptoms may present for long periods (mean 2-10 years) as waxing and waning cutaneous eruptions before biopsy confirmation. The prognosis of patients with mycosis fungoides/Sézary syndrome is based on the extent of disease at presentation and its stage. Lymphadenopathy and involvement of peripheral
blood and viscera increase in likelihood with worsening cutaneous involvement and define poor prognostic groups. Median survival after diagnosis varies according to stage. Median survival in patients with stage IA disease exceeds 20 years, with most deaths in this group typically unrelated to mycosis fungoides. In contrast, median survival in patients with stage III through stage IV disease is less than five years; more than 50% of these patients die of their disease.

Appropriate therapy of CTCL depends on a variety of factors, including stage, the patient's overall health, and the presence of symptoms. In general, therapies can be categorized into topical and systemic treatments that include ECP. In contrast to more conventional lymphomas, CTCL, possibly excepting ones in the earliest stages, is not curable. Thus, systemic cytotoxic chemotherapy is avoided except for advanced-stage cases. Partial or complete remission is achievable, although the majority of patients require lifelong treatment and monitoring.

Peripheral T-Cell Lymphoma (PTCL)
PTCL is a group of rare and usually aggressive non-Hodgkin lymphomas that develop from mature T cells. PTCL comprises approximately 10-15% of all cases of non-Hodgkin lymphoma in the United States and generally occur in people 60 years of age and older. Standards of care are evolving, including the use of hematopoietic stem-cell transplantation.

Policy:

Extracorporeal photopheresis meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when used for treatment of:

- **Chronic graft versus host disease (GVHD)** refractory to medical therapy. (Cyclosporine and prednisone are considered first-line treatment. Other therapies are added as second line treatment. If there is no symptomatic improvement or a regression of the disease in two weeks, GVHD would be considered refractory).
- **Acute graft-versus-host disease (GVHD)** that is refractory to medical therapy. (Methylprednisolone is considered first-line treatment. Other therapies are added as second-line treatment. If there is no symptomatic improvement or a regression of the disease in two weeks, GVHD would be considered refractory). (Effective on or after 05/01/2014)
- Treatment of late stage (III/IV) **cutaneous T cell lymphoma (CTCL)**
- Treatment of early stage (I/II) **cutaneous T cell lymphoma (CTCL)** that is refractory to established nonsystemic treatments.
- **Cardiac allograft rejection**, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.

Extracorporeal photopheresis does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for all other indications, including, but not limited to:

- Acute graft versus host disease
- Progressive systemic sclerosis (scleroderma)
- Pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, or other autoimmune bullous (blistering) diseases
- Systemic lupus erythematosus
• Multiple sclerosis
• Psoriatic arthritis or psoriasis vulgaris
• Rheumatoid arthritis
• Type I diabetes
• Atopic dermatitis
• Juvenile dermatomyositis
• Scleromyxedema
• All other situations related to treatment or prevention of rejection in solid organ transplantation

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administer benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
Organ Rejection after Solid-Organ Transplant
Cardiac
Acute Rejections
A 1992 randomized, controlled trial (RCT) compared the efficacy of extracorporeal photopheresis (ECP) with corticosteroids for the treatment of heart transplant rejection. Costanzo-Nordin et al enrolled 16 heart transplant patients and randomly assigned them to either ECP (n=9) or corticosteroids (n=7). Recipients of orthotopic transplanted hearts were eligible if endomyocardial biopsy (EMB) showed moderate rejection (Grades 2, 3A, 3B). Participants were excluded for leukopenia; hemodynamic compromise, manifested clinically or by a minimum 25% decrease in cardiac output and a minimum 25% increase in mean pulmonary artery wedge pressure; and/or allergy or intolerance to psoralen. Corticosteroids were dosed at 100 mg/day oral prednisone for three days or 1g/day IV (intravenous) methylprednisolone for three days at the discretion of the managing physician. Treatment was repeated if EMB at day seven showed no improvement in rejection grade. If rejection grade persisted after retreatment, patients were given 10 mg oral methotrexate at weekly intervals for eight weeks. Participants were followed for a mean of 6.2 months, and all participants completed the study. ECP participants received one ECP treatment unless an inadequate number of cells were treated. In that case, an additional treatment was given 48 hours later. Eight of nine rejection episodes treated with ECP improved; all seven rejection episodes treated with corticosteroids resolved. Improvement was seen a mean of seven days (range, 5-20) after ECP and eight days (range, 6-67) after corticosteroid treatment. Seven infections occurred during follow-up, five in the corticosteroid group and two in the ECP group. No other adverse events were observed with ECP. The authors noted the major limitations of the study included a small sample size and wide range in time from transplant to study entry. They concluded that ECP and corticosteroid in this small group with short-term follow-up appeared to have similar efficacies for the treatment of moderate heart transplant rejection. They also noted the reduced number of infections and no other observed harms associated with ECP.
Recurrent, Multiple and/or Refractory Rejection

In 2006, Kirklin et al published a comparative study of 343 heart transplant recipients. Thirty-six patients were treated with ECP for rejection and formed the treatment group. Patients were 18 years of age or older, treated from 1990-1993, and followed to May 2004. Indications for ECP were episodes of rejection with hemodynamic compromise (HC rejection) (n=12); recurrent (n=9), or persistent (n=11) rejection; or prophylaxis in the presence of antidonor antibodies (n=4). ECP consisted of psoralen in a two-day treatment protocol every three to six weeks for 18 months; maintenance immunosuppression used cyclosporine- or tacrolimus-based therapy with prednisone for the first four to six months and azathioprine, which was replaced by mycophenolate mofetil during the later years of the study. The primary outcome was incidence of HC rejection or death from rejection (rejection death). Hazard functions were used for analysis. Patients with at least three months of ECP were considered to have effective photopheresis treatment; patients who received less than three months of treatment were considered untreated but were analyzed as part of the photopheresis group. The period after three months of ECP was associated with a reduction in risk of HC rejection or rejection death (risk reduction [RR]=0.29). A sustained decrease in the risk of HC rejection or HC death was observed for the photopheresis group through two years of follow-up. This study was not randomized; risk factor analysis showed that the ECP group had higher baseline risk of HC rejection or rejection death. Changes in maintenance immunotherapy over time may confound the results, as patients in the comparison group did not receive a consistent regimen. However, improvements in maintenance immunotherapy would tend to obscure any treatment effect of ECP compared with evolving immunotherapy regimens. This bias therefore strengthens the authors’ conclusion that ECP reduces the risk of subsequent HC rejection and/or death from rejection in patients at high risk of rejection.

In 2000, Dall’Amico et al reported on a case series of 11 heart transplant recipients with recurrent rejection. Participants were eligible if they had acute rejection and at least two rejection episodes after standard immunosuppressive therapies in the three months before ECP. ECP was administered with UVAR photopheresis instruments in two consecutive treatments at weekly intervals for one month, at two-week intervals for two months, and then monthly for three months. One patient with grade 3B rejection received pulse IV corticosteroids during the first ECP cycle. Patients were followed for 60 months. During follow-up, one patient died from hepatitis C virus and one patient dropped out due to rejection unresponsive to ECP and high-dose corticosteroids; all others completed the study. All acute rejection episodes were successfully reversed after a mean of 14.2 days (range, 7-32). In terms of rejection relapse, the fraction of EMBs with grade 0/1A rejection increased during ECP from 46% to 72%, and those showing 3A/3B rejection decreased from 42% to 18%. One of 78 EMBs during ECP showed 3B rejection compared with 13 of 110 during the pre-ECP period. Six rejection relapses were observed during follow-up, two during the tapering of oral corticosteroids. Four were reversed by ECP, one by IV corticosteroids, and one by methotrexate after failure of both ECP and IV corticosteroids. Mean dose of immunosuppressive drugs (corticosteroids, cyclosporine, azathioprine) was reduced after six months of ECP therapy. One patient with anemia and low body weight experienced symptomatic hypotension during treatment, and one patient had interstitial pneumonia. The authors concluded that ECP was a well-tolerated treatment that allowed for better recurrent
rejection control and reductions in immunosuppressive therapy. Follow-up time and patient population are adequate; the study is limited by its small size and lack of comparison group.

In 2001, Maccherini et al presented a case series of 12 patients treated with ECP for recurrent rejection. Inclusion criteria were recurrent rejection (n=5), recurrent infections associated with acute rejection (n=2), and a Grade 3A acute rejection two years after transplantation (n=5). Mean post-ECP follow-up was 23.3 months. ECP was performed as two treatments weekly for one month, once weekly for two months and then once monthly for two months. Total number of rejection episodes decreased from a mean of three per patient pre-ECP to 0.4 per patient post-ECP. All patients reduced immunosuppressive therapy. There were no adverse effects or infections reported during follow-up. The authors concluded that ECP was safe and effective for heart transplant patients with recurrent rejection and reduced both rejection episodes and immunosuppressive therapy.

Lehrer et al (2000) presented similar results in four patients treated with ECP for severe refractory (Grade 3A to 4) cardiac allograft rejection. All four patients experienced reversal of their rejection. Three patients improved following two consecutive days of treatment, and the fourth patient responded after three two-day treatments. Two patients subsequently died of acute rejection at nine weeks and ten weeks, respectively, after completing ECP. The other two patients had no signs of rejection, one at six years and the other at four months after completion of ECP. This small case series adds to the evidence provided by the previous two slightly larger studies.

Prevention of Rejection
A 1998 RCT by Barr et al investigated ECP for the prevention of rejection after cardiac transplant. Sixty consecutive adult cardiac transplant recipients at 12 clinical sites (9 U.S., 3 in Europe) were randomly assigned to both immunosuppressive therapy and ECP (n=33) or immunosuppressive therapy alone (n=27). Standard immunosuppressive therapy consisted of cyclosporine, azathioprine, and prednisone. Entry criteria were adequate peripheral venous access and residence less than 2 hours away from the transplant center. ECP treatment was delivered on days 1, 2, 5, 6, 10, 11, 17, 18, 27, and 28 in month 1; then for 2 consecutive days every 2 weeks in months 2 and 3; and then for 2 consecutive days every 4 weeks in months 4 to 6 for a total of 24 ECP procedures per patient. The primary end point was the number and frequency of histologic acute rejection episodes. Pathologists were blinded to treatment assignment. Follow-up for the primary end point was 6 months; an additional 6 months of follow-up was completed to assess safety and survival.

After six months of follow-up, the (mean±standard deviation [SD]) number of acute rejection episodes per patient was statistically greater in the standard therapy group (1.4±1.0) than in the ECP group (0.9±1.0). In the standard therapy group, five patients had no rejection episodes, nine had one, nine had two, and four had three or more. In the ECP group, 13 had none, 14 had one, three had two, and three had three or more. These differences were statistically significant. There were no differences in 6- or 12-month survival, number of infections, or time to first rejection between groups. During a subsequent six months of follow-up, there was no difference between groups in the number of acute rejection episodes; however, because of time management issues, institutions reverted to nonstandardized protocols during this time. The authors concluded that
ECP in addition to standard immunosuppressive therapy significantly reduced the risk of cardiac rejection without increasing the risk of infection. More long-term follow-up is necessary to see the effects of a reduction of acute rejection on long-term graft function, survival of the transplant recipient, and development of graft vasculopathy.

Lung

Acute rejection

In 2000, Villanueva et al reported on a retrospective review of 14 transplant recipients (seven bilateral lung, six single lung, one heart-lung) who received ECP for bronchiolitis obliterans syndrome (BOS). All patients were refractory to standard immunosuppressive therapy. ECP was administered every two weeks for two months and then monthly for two months for a total of six treatments. Four of eight patients with baseline Grade 0-1 BOS had improvement in BOS or stabilization after treatment. Mean (SD) survival after ECP was 14 months (SD=12). Three of four patients received ECP during a concurrent episode of acute rejection; all three patients had complete resolution of acute rejection after treatment. Another study published in 1999 by Salerno et al reported on two patients with histologic reversal of concurrent acute rejection after treatment with ECP. These two studies reported on only five cases of ECP used to treat acute rejection. Additional prospective trials are needed to determine the efficacy of ECP to treat acute rejection after lung transplantation.

In 2008, Benden et al published a single-center study of 24 patients treated with ECP, 12 for recurrent acute rejection and 12 for BOS (reviewed in the next section). The primary outcome measure was clinical stabilization of rejection after ECP. Twelve patients had biopsy-confirmed chronic acute rejection, defined as two or more biopsy-proven episodes of acute rejection before ECP. Of 11 patients who had follow-up biopsies during treatment, two patients had an episode of biopsy-proven acute rejection. All 12 patients experienced clinical stabilization after 12 ECP cycles; none experienced BOS. Treatment was well-tolerated with no ECP-related adverse events reported. Median patient survival was 7.0 years (range, 3.0-13.6); median patient survival post-ECP was 4.9 years (range, 0.5-8.4). However, these results are for all 24 patients (i.e., including the 12 patients with BOS).

Chronic rejection refractory to corticosteroid/Refractory Bronchiolitis Obliterans Syndrome (BOS)

In 2013, Greer et al reported a retrospective analysis of 65 patients treated at a single institution with ECP for chronic lung allograft dysfunction, defined as deteriorating FEV1 due to BOS, as well as reduced total lung capacity and broncho-alveolar lavage neutrophilia. Fifty-one patients (78%) had undergone double lung transplant, nine patients (14%) had undergone single-lung transplant, and five patients (8%) had undergone heart-lung transplant. Median time to CLAD diagnosis was three years (interquartile range [IQR]=2-5). Patients had progressed (10% or greater decline in FEV1) on first-line azithromycin. At ECP initiation, 35 patients (54%) were graded BOS Stage 3; 21 patients (32%) were BOS Stage 2; and nine patients (14%) were BOS Stage 1 or 0p (potential BOS). ECP was administered every two weeks for three months; subsequent treatments were administered not more than eight weeks apart to maintain stabilized graft function. Median follow-up was 17 months; 44 patients who continued treatment beyond three months received a median of 15 ECP treatments. Eight patients (12%) achieved a 10% or greater improvement in FEV1, considered treatment response; 27 patients (42%) experienced no
change in FEV1; and 30 patients (46%) experienced a 10% or greater decline in FEV1, considered progressive disease. Median progression-free survival was 13 months (IQR=10-19) among responders and four months (IQR=3-6) among those who did not respond. These data are retrospective and lack a control group.

Jaksch and colleagues reported on a series of 194 patients who developed BOS and received standard treatment and 51 of those received additional ECP. Patients who did not respond to standard immunosuppressive therapy and showed further decline of lung function received EPC when reaching BOS stage greater or equal to one. ECP was performed on two successive days every two weeks during the first three months and every four weeks after until the end of therapy. ECP was stopped after a minimum of three months of therapy when lung function decreased significantly. If improvement or stabilization of forced expiratory volume in one second (FEV1) occurred, ECP was continued for a minimum of six months. FEV1 values at three, six, and twelve months after EPC initiation were used as a surrogate for treatment response. The primary endpoint was change in lung function before and after ECP. Changes in lung function score was compared to patients with BOS who did not receive add on EPC. Eighteen percent of patients receiving ECP experienced an improvement in FEV1 for more than one year after initiation of ECP treatment and 12% showed improvement for only three to six months. FEV1 stabilized in 31% of patients and declined in 39%. Kaplan-Meier analysis showed a significant difference in responders and non-responders in survival and the need for a transplant. When compared to patients with BOS who did not receive EPC but with similar demographics and prior treatment, the ECP-treated groups had longer survival (p=0.046) and underwent fewer transplantations: 18 versus 21 (p=0.04). Time to transplant was also twice as long in the ECP group, 1,839 ± 1,090 days versus 947 ± 861 days. No adverse events were reported as a result of EPC. While this was not a randomized study, a group was available for comparison with similar demographics, and treatment history.

Jaksch et al (2012) reported on a prospective series of 194 patients who developed BOS and received either standard treatment (n=143) or standard treatment plus ECP (n=51). Patients who did not respond to standard immunosuppressive therapy and showed further decline of lung function received ECP when reaching BOS Stage 1 or higher. ECP was administered on two successive days every two weeks during the first three months and then every four weeks until the end of therapy. ECP was discontinued after a minimum of three months if lung function decreased significantly. If FEV1 improved or stabilized, ECP was continued for a minimum of six months. Change in FEV1 at three, six, and twelve months after EPC initiation was used as a surrogate for treatment response. The primary end point was change in lung function before and after ECP. Eighteen percent of patients receiving ECP experienced an improvement in FEV1 for more than one year after initiation of ECP, and 12% showed improvement for only three to six months. FEV1 stabilized in 31% of patients and declined in 39%. Kaplan-Meier method analysis showed a significant difference in responders and nonresponders in survival and the need for transplant. In comparison with patients with BOS who did not receive ECP but were similar in demographics and treatment history, the ECP group had longer survival (p=0.046) and underwent fewer transplantations (18 vs 21; p=0.04). Mean time to transplant (±SD) also was twice as long in the ECP group (1839±1090 days vs 947±861 days; p=0.006). No ECP-related adverse events were reported. Although this study was not randomized, a group with similar demographics and treatment history was available for comparison.
Lucid et al (2011) published a review of nine patients treated with ECP between July 2008 and August 2009. Median follow-up was 23 months post-transplant (range, 9-93), and median age was 38 years (range, 21-54). The primary indication for ECP was symptomatic progressive BOS that failed previous therapy. Patients were treated weekly with two sessions of ECP for three to four weeks. Treatment frequency then decreased to every two to three weeks, with the goal of reducing treatment to every four weeks. Clinical response was defined as symptomatic improvement, decreased dependency on supplemental oxygen, and improved pulmonary function tests. Six of nine patients (67%) responded to ECP after a median of 25 days. No ECP-related complications occurred in this series. As in several previous studies, this report has no control group for comparison.

Morrell et al (2010) published a retrospective case series of all lung transplant recipients (n=60) who received ECP for progressive BOS at Barnes-Jewish Hospital-Washington University. Ninety-five percent of patients had received a bilateral lung transplant, and 58% had Grade 3 BOS. The indication for ECP was progressive decline in lung function that was refractory to standard immunosuppressive therapy. The primary end point was the rate of change in lung function before and after the initiation of ECP. ECP was delivered as two cycles on days 1, 2, 5, 6, 10, 11, 17, 18, 27, and 28 during the first month (ten treatments); biweekly for the next two months (eight treatments); and then monthly for the following three months (six treatments), for a total of 24 treatments. Sixty patients were followed from the time of lung transplantation to death or the end of the study (July 1, 2008). Median follow-up was 5.4 years (range, 1.0-16.6). At the end of the study, 33 patients were still alive; four deaths occurred early in the study. Most deaths were due to progression of respiratory failure, except for one death due to sepsis and one to graft failure. In the six months before ECP, the mean rate of decline in FEV1 was -116.0 mL per month; after ECP, the mean rate of decline was -28.9 mL per month (mean difference 87.1 mL [95% confidence interval (CI), 57.3 to 116.9]). The rate of decline in lung function decreased in 44 patients (79%), and lung function improved (increase in FEV1 above pretreatment values) in 14 patients (25%). Through 12 months of follow-up, mean improvement in FEV1 was 145.2 mL. Ten of 60 patients (17%) experienced adverse events. Eight were hospitalized for catheter-related bacteremia; one case resulted in death. All cases resulted from indwelling pheresis catheters. The authors concluded that ECP was associated with a significant reduction in the rate of decline in lung function. This reduction was sustained through 12 months of follow-up. The major limitations of this study are its retrospective nature and lack of a control group. Most patients had Grade 3 BOS, and therefore, may differ from patients with other grades. Statistical analyses were robust.

As mentioned earlier, Benden et al (2008) published a single-center study of 24 patients treated with ECP (12 for BOS and 12 for recurrent acute rejection, reviewed in a previous section). ECP was delivered when BOS grade worsened despite standard therapy. At the start of therapy, five patients had BOS Grade 1; two patients had BOS Grade 2; and five patients had BOS Grade 3. Before ECP, the rate of decline in FEV1 was 112 mL per month compared with 12 mL per month after ECP (mean difference, 100 mL per month [range, 28-171]). However, ECP did not seem to affect absolute FEV1. Treatment was well-tolerated with no ECP-related adverse events reported. Median patient survival was 7.0 years (range, 3.0-13.6); median patient survival post-
ECP was 4.9 years (range, 0.5-8.4). However, these results are for all 24 patients (i.e., including the 12 patients with BOS).

Also as previously noted, Villanueva et al (2000) retrospectively reviewed outcomes of 14 transplant recipients (seven bilateral lung, six single lung, and one heart-lung) who received ECP for BOS. All patients were refractory to standard immunosuppressive therapy. ECP was administered every two weeks for two months and then once monthly for two months, for a total of six treatments. In four of eight patients with Grade 0 or 1 BOS, BOS improved or stabilized after treatment. Mean (SD) survival after ECP was 14 months (SD=12). Six patients with initial BOS Grade 2 or higher suffered progression of their BOS after ECP. Mean (SD) survival after ECP was 14 months (SD=10). Four of these patients died of chronic rejection, and one died of lung cancer. The remaining patient survived to retransplantation. Two of the 14 patients developed line-related sepsis, which cleared with antibiotic therapy and catheter removal.

In 1999, O’Hagan et al published a case series of six patients at the Cleveland Clinic who received ECP for BOS refractory to standard immunosuppressive therapy and various other strategies including antithymocyte globulin, methotrexate, monomurine anti-C3 antibody, and tacrolimus. ECP was performed on two consecutive days twice a month until FEV1 stabilization. Treatment was then repeated every four to six weeks. Four of the six patients had temporary stabilization of their airflow obstruction with minimal adverse effects. BOS grade was not reported. The study is limited by the lack of a control group. In this case, the comparison of interest would be between those receiving immunosuppressive therapies alone versus those being treated with immunosuppressive therapy plus ECP. Larger prospective randomized trials are necessary to examine the comparative effects of ECP for patients with BOS stratified by BOS grade.

**Prevention of BOS and/or Rejection**

There are no studies addressing the prophylactic effects of ECP for lung transplant recipients.

**Liver**

The published evidence on the use of ECP in liver recipients is from one group in Italy. Urbani et al have published a series of papers on various potential applications of ECP for liver transplant patients. The first paper is a retrospective review of five patients who received liver transplants and ECP for biopsy-proven allograft rejection, where the indications for ECP were recalcitrant ductopenic rejection with Hepatitis C virus recurrence, corticosteroid-resistant acute rejection in two patients, severe acute rejection in a major ABO-incompatible liver graft, and severe acute rejection in a patient with a proven corticosteroid allergy. ECP was performed twice a week for four weeks, then every two weeks for two months and once a month, thereafter. ECP was stopped when indicated by biopsy-proven rejection reversal or the absence of clinically evident rejection relapse. Liver function tests improved to baseline in all but one patient, and no procedure-related complications were reported. At a median follow-up of 7.9 months, three patients were off ECP with normal liver tests and low level immunosuppressive therapy. Two were receiving continued ECP treatments with full dose immunosuppressive therapy.

The second paper from 2007 was a nonrandomized comparative study of 36 patients (18 treatment and 18 historic matched controls) who were treated with ECP to delay the introduction
of calcineurin inhibitors (CNI) with the goal of preventing toxicity. Patients were included if they were at risk of post-liver transplant renal impairment and neurological complications, defined as having at least one of the following risk factors: a calculated glomerular filtration rate <50 mL/min at transplantation; severe ascites; history of more than one hospitalization for encephalopathy within one year of transplant and/or one hospitalization within one month of transplantation; or age 65 years or greater. Outcome measures were treatment success rate, defined as the ratio of patients with full CNI-sparing or delayed immunosuppression, interval from liver transplant to CNI introduction, safety of ECP, and need for biopsy. ECP was initiated in the first week post-transplant; two different systems (Therakos and PIT) for photopheresis were used and treatment was given according to a common schedule for the system used. All 18 patients completed the scheduled course and tolerated the ECP. CNI was introduced at a mean number of eight days for 17 patients, while one patient remained CNI free for 22 months. Acute rejection was higher but not significantly higher in ECP group (5/18) vs. controls (3/18). One, six, and twelve month survival rates were 94.4, 88.1, and 88.1%, respectively, for ECP recipients vs. 94.4, 77.7, and 72.2%, respectively, among controls. The authors concluded that the addition of ECP offers better management of liver transplant patients in the early transplant phase, delayed CNI introduction and lower CNI-related mortality. This study was not randomized and had a small number of patients.

The third paper (2008) was a report on three fields of interest for ECP as prophylaxis of allograft rejection in liver transplant patients. The three fields include:

- Use of ECP to delay CNI among high-risk liver transplant recipients to avoid toxicity (discussed above),
- Use of ECP for prophylaxis of acute cellular rejection among ABO-incompatible liver transplant recipients where 11 consecutive patients underwent ECP with immunosuppression with no evidence of acute rejection through 568 days of follow-up,
- Use of ECP in hepatitis C virus-positive patients (the use of ECP for the prevention of Hepatitis C virus recurrence is beyond the scope of this policy).

Except for the first area, these studies were small and had no comparison group. Randomized, clinical trials are needed for the proper assessment of outcomes.

Renal

Recurrent, Multiple and/or Refractory Rejection

The largest reported group of renal patients to receive ECP was at the Royal Prince Alfred Hospital, Sydney, Australia. In 2009, Jardine et al published a prospective case series of 10 patients treated with ECP for recurrent and/or refractory rejection after renal transplant at this center. ECP was delivered weekly for four weeks, then every two weeks. Total treatment range was two to twelve treatments for more than five to 20 weeks. Median follow-up time was 66.7 months following transplant and 65.0 months from commencement of ECP. Indication for ECP was acute resistant/recurrent rejection in nine patients and the need to avoid high dose corticosteroids in another. Refractory rejection was resolved in all patients through the stabilization of renal function. The authors concluded that ECP may have a role as an adjunct to current therapies in patients with refractory rejection. While this is the largest series of renal patients, it is small and there is no comparison group. It also suffers from the fact that renal biopsies were not used to document therapeutic response.
The remainder of the evidence in renal transplant recipients comes from case reports on 32 patients. Twenty-six of these patients had refractory rejection. After ECP, renal function improved in 19 of 26 patients, three patients were stable and four patients returned to dialysis due to deteriorating function. Reports of long-term outcomes varied. Among the 22 patients who showed initial improvement and or stabilization of renal function, five had improved function at one year, one was stable at 25 months, five were stable at one year, seven were rejection free at two to five years, and one graft was lost. Three patients did not have long-term outcome reports.

Section Summary
Evidence for the use of extracorporeal photopheresis (ECP) in cardiac transplant patients relates to three indications: acute rejection; recurrent, multiple and/or refractory rejection; and prevention of rejection. For acute rejection, a 1992 randomized trial enrolled 16 heart transplant recipients. ECP in combination with immunosuppressive therapy had similar efficacy compared with immunosuppressive therapy alone, with fewer infections in the ECP group. This study was small, and time from transplantation to study entry varied. For prevention of rejection, one randomized trial from 12 clinical sites randomized 33 patients to immunosuppressive therapy plus ECP and 27 patients to immunosuppressive therapy alone. Differences between numbers of acute rejection episodes were statistically significant; however, there was no difference in survival at six months. Thus, evidence to date is insufficient to permit conclusions concerning the effect of ECP on net health outcome for the treatment and prevention of acute cardiac rejection. Therefore, ECP is considered investigational for the treatment and prevention of acute rejection in cardiac transplant recipients. Studies with more patients and longer follow-up are needed.

ECP for recurrent, multiple and/or refractory cardiac allograft rejection has been the focus of most of the research on ECP. Although data are from nonrandomized studies, a comparative study of 343 cardiac transplant recipients in which 36 patients received ECP has been completed. The authors showed that at three months, ECP was related to a risk reduction of hemodynamic compromise (HC) rejection or rejection death (risk ratio [RR]=0.29). A reduction in HC rejection or rejection death was observed through two years of follow-up. Although results of this trial may be confounded by improvements in immunosuppressive therapy regimens over time, they are consistent with the remainder of the literature for this indication, which indicates a benefit of ECP in patients with recurrent or refractory cardiac rejection. Thus, the evidence to date, comprising one nonrandomized comparative study, two case series, and a case report of four patients, provides consistent evidence for a beneficial effect of ECP for cardiac transplant patients with rejection refractory to standard therapy. Therefore, ECP is considered medically necessary for the treatment of recurrent, multiple and/or refractory cardiac rejection.

Evidence on the use of ECP in lung transplant recipients relates to two indications: acute rejection and chronic rejection refractory to corticosteroids/refractory BOS. Data for acute rejection are very limited and do not permit any conclusions. Patients were subgroups of larger studies who received ECP during periods of acute rejection. This area needs a prospective, randomized, clinical trial focused specifically on the treatment of patients in acute rejection.
The bulk of the evidence for ECP in lung transplantation focuses on treatment of refractory BOS. The primary limitations of these data are that they are nonrandomized and uncontrolled. Further, the evidence is not entirely consistent, with some studies reporting ECP to be beneficial in those with early refractory BOS but not in those with Grade 2 or higher BOS, which contrasts with a retrospective series of 60 patients who responded well to ECP (nearly 60% of these patients were BOS Grade 3). Prospective, RCTs are necessary, and analyses should be stratified by BOS grade, as there is some preliminary evidence that ECP efficacy may vary by BOS grade at the start of therapy.

Evidence to date consists of small case series and is insufficient to permit conclusions concerning the effect of this procedure on health outcomes in lung transplantation. Studies with larger numbers of subjects and longer follow-up are needed. Therefore, ECP is considered investigational when used in lung transplantation.

In liver transplantation, evidence for the use of ECP is limited, and research to date has been generated by one group in Italy. Although there is one comparative (nonrandomized) study, it involved only 18 cases and 18 historical controls. There is a need for RCTs. The focus in liver transplantation has been on prevention of rejection with ECP. This question lends itself well to a RCT comparing immunosuppressive therapy alone to immunosuppressive therapy with ECP. The evidence to date, which consists of small case series and one comparative study, is insufficient to permit conclusions concerning the effect of ECP on net health outcome for liver transplant patients. Therefore, ECP is considered investigational in liver transplant patients for any indication.

For renal transplant recipients, evidence for the use of ECP is sparse. A total of 42 ECP-treated patients have been reported in the literature. Studies consistently report evidence of benefit from ECP for those with refractory rejection. However, there are no comparative studies and current numbers are too small to permit conclusions. A prospective, randomized trial, with histologic confirmation of treatment response is needed. This trial would randomize patients to immunosuppressive therapy or immunosuppressive therapy with ECP with the primary aim of addressing the question of whether there is an additional benefit from ECP for patients with refractory rejection after renal transplantation. Evidence to date, which consists of small case series, is insufficient to permit conclusions concerning the effect of ECP on net health outcome for renal transplant patients. Therefore, ECP is considered investigational in renal transplant patients for any indication.

**Practice Guidelines and Position Statements**
United Network of Organ Sharing (UNOS) does not have any policies related to ECP in the treatment or prevention of any form of rejection following solid organ transplant.

**Graft-versus-Host Disease**
ECP for the treatment of acute and chronic graft-versus-host disease (GVHD) was initially addressed by a 2001 TEC Assessment that offered the following observations and conclusions: For acute GVHD or chronic GVHD in previously untreated patients or in those responding to conventional therapy, no studies met selection criteria and reported results of ECP, alone or in combination with other therapies. Therefore, photopheresis for these indications failed to meet
TEC criteria. Studies focusing on patients with chronic GVHD unresponsive to other therapies reported resolution or marked improvement of lesions in approximately 50% of patients. Finally, studies of patients with acute GVHD also reported successful outcomes in 67% to 84% of patients with Grade 3 disease, but patients with Grade 4 disease rarely responded.

**Treatment of GVHD in Pediatrics**

The most recent and largest series was a 2010 retrospective review of 73 pediatric patients (age <18 years) with acute or chronic GVHD after an allogeneic stem-cell transplant unresponsive to one week of steroid treatment. Patients received ECP for a minimum of 10 treatments. ECP was administered two to three times weekly on alternating days until clinical improvement. Treatment was then reduced to two procedures per week for two weeks, then two procedures every other week for three weeks, ending with two procedures per month until maximum response as clinically indicated. ECP was discontinued if no improvement (50% or greater clinical and laboratory response) was seen after four weeks. Of 47 patients with acute GVHD, 39 (83%) of 47 patients with skin involvement improved, and seven (87.5%) of eight patients with mucosal involvement improved. Among patients with chronic GVHD, all four patients (100%) with liver involvement improved, and 22 (95.6%) of 23 patients with skin involvement improved.

The literature also includes, but is not limited to, two small studies that focused on photopheresis for treatment of GVHD in children and one larger retrospective case series. This case series (published in 2007) reported results of ECP for steroid-resistant GVHD in pediatric patients (aged 6-18 years) who had undergone hematopoietic stem-cell transplantation for a variety of cancers. Patients had acute GVHD (aGVHD, n=15, stages 2-4) or chronic GVHD (cGVHD, n=10, 7 deemed extensive) that did not respond to at least seven days of methylprednisolone therapy. Patients received ECP on two consecutive days at weekly intervals for the first month, every two weeks for two months, and then monthly for three months. ECP was progressively tapered and discontinued based on individual patient response. Response to ECP was assessed three months after ECP ended or after six months if the ECP protocol was prolonged. Among patients with aGVHD, complete response (CR) occurred in seven (100%) of seven patients with Grade 2 and two (50%) of four patients with Grade 3 disease; none of four patients with Grade 4 disease responded to ECP. In the group with cGVHD, CR occurred in three (100%) of three patients with limited disease and one (14%) of seven patients with extensive disease. Five (71%) of seven patients with extensive cGVHD had no response to ECP. Adverse effects of ECP were generally mild in all cases. These results are similar to those summarized in the 2001 TEC Assessment cited previously and thus do not alter the current policy statements.

One of the two smaller studies reported on eight children (aged 5-15 years) with refractory extensive cGVHD who received ECP and either oral 8-methoxypsoralen (8-MOP) or infusion of an 8-MOP solution into the pheresed lymphocytes. Cutaneous status reportedly improved in seven patients. Five patients stopped treatment, and three decreased doses of immunosuppressive therapy. In addition, gut involvement resolved in all patients, and liver involvement resolved in four of six patients. Two years after discontinuation of photopheresis, five patients remained in remission without immunosuppressive therapy. Salvaneshci et al reported on ECP in refractory GVHD in 23 pediatric patients (aged 5.4-11.2 years). Seven (78%) of nine patients with acute...
GVHD experienced either partial response (PR) or CR. Nine (64%) of 14 patients with cGVHD experienced PR or CR. These findings also are consistent with the current policy statements.

In 2014, the Cochrane Collaboration childhood cancer group published two systematic reviews on aGVHD and cGVHD in pediatric patients. Literature searches were performed in September 2012, and no RCTs were found. The authors cited the need for RCTs but stated that “performing RCTs in this patient population will be challenging because of the limited number of patients, the variable disease presentation, and the lack of well-defined response criteria.” International collaboration and establishment of patient registries was encouraged.

Treatment of GVHD in Adults
Chronic GVHD (cGVHD)
In addition to the 2001 TEC Assessment referenced above, several additional publications report on the use of ECP for the treatment of GVHD. In 2006, the Ontario Health Technology Advisory Committee (OHTAC) published results of a systematic review of ECP for the treatment of refractory chronic GVHD. In summary, OHTAC reported that there is low-quality evidence that ECP improves response rates and survival in patients with chronic GVHD who are unresponsive to other forms of therapy. Limitations in the literature related to ECP for the treatment of refractory GVHD mostly pertained to the quality, size, and heterogeneity in treatment regimens and diagnostic criteria of available clinical studies. The committee did, however, recommend a two-year duration field evaluation of ECP for chronic GVHD, using standardized inclusion criteria and definitions to measure disease outcomes including response rates, quality of life, and morbidity. As of January 2014, this evaluation is not listed on the OHTAC website.

Foss et al (2005) reported results of a prospective (nonrandomized) study of ECP in 25 patients who had extensive corticosteroid-refractory or corticosteroid-resistant cGVHD after allogeneic stem-cell transplantation. ECP was administered for two consecutive days every two weeks in 17 patients and once weekly in eight patients until best response or stable disease was achieved. With a nine-month median ECP duration (range, 3-24 months), 20 patients had improvement in cutaneous GVHD, and six had healing of oral ulcerations. 80% of patients reduced or discontinued immunosuppressive therapies. Overall, improvement was reported in 71% of cases with skin and/or visceral GVHD and 61% of those deemed to be high-risk patients.

In 2014, Dignan et al reported on a series of 38 consecutive adults who received ECP for cGVHD. Median patient age was 47 years (range, 18-73). Patients had steroid-refractory or steroid-dependent disease or were intolerant of corticosteroids. Thirty-six patients (95%) were receiving immunosuppressive therapy. ECP was administered on two consecutive days every two weeks until PR (defined as minimum 50% improvement from baseline in one organ and no evidence of GVHD progression in other organs) was achieved and was then reduced to monthly treatments. Median time from transplant to first ECP was 1.7 years (range, 0.25-7.25). Response was assessed after six months. Nineteen patients (50%) had a CR (n=2; defined as complete resolution of all signs and symptoms of GVHD) or PR (n=17); all 19 had completed six months of ECP. Of 25 patients receiving immunosuppressive therapy who completed six months of ECP, 20 (80%) reduced immunosuppressive dose; five patients discontinued steroids, and eight patients had a 50% or greater reduction in steroid dose. Mean improvements in validated quality-of-life (QOL) measures (Lee chronic GVHD symptom scale and dermatology QOL index) were
clinically and statistically significant in 17 (94%) of 18 patients who completed the questionnaires at six months. Five patients developed indwelling catheter-related infections, one patient had a catheter-related thrombosis, and one patient had an increase in red cell transfusion requirements, which was considered due to ECP alone.

**Acute GVHD (aGVHD)**

Greinix et al (2006) reported findings from a Phase 2 (nonrandomized) study of intensified ECP as second-line therapy in 59 patients with poststem cell transplant, steroid-refractory, acute GVHD (Grade 2 to 4). ECP was initially administered on two consecutive days (one cycle) at one- to two-week intervals until improvement was noted and thereafter every two to four weeks until maximal response. At the start of ECP, all patients had been receiving immunosuppressive therapy with prednisone and cyclosporine A. Complete resolution of GVHD was documented in 82% of patients with cutaneous manifestations, 61% with hepatic involvement, and 61% with gut involvement. CR occurred in 87% and 62% of patients with exclusively skin or skin and liver involvement, respectively; only 25% with GVHD of skin, liver, and gut involvement and 40% with skin and gut involvement obtained a CR of GVHD with ECP therapy. The probability of survival was 59% among patients with CR to ECP, compared with 11% of those who did not achieve CR. Although these results suggest ECP may be beneficial in the treatment of acute GVHD, the small size, few study details in the report, and lack of a standard treatment comparator group limit inferences as to the clinical efficacy of ECP for aGVHD.

In 2008, Perfetti et al reported on a retrospective review of 23 patients with corticosteroid-refractory aGVHD (n=10 Grade 2; n=7 Grade 3; and n=6 Grade 4). Median duration of ECP was seven months (range, 1-33) and median number of cycles per patient was 10. CRs were seen in 70%, 42%, and 0% of patients with GVHD Grades 2, 3, and 4, respectively. Eleven patients (48%) survived, and 12 (52%) died (10 of GVHD and two of relapse of leukemia). Eighty-three percent of patients treated within 35 days from onset of GVHD responded compared with 47% of patients treated after 35 days (p=0.1). Although these findings suggest that ECP may provide benefit for patients with refractory aGVHD, they are limited by a small sample size and the noncomparative study design.

Shaughnessy et al (2010) studied ECP to prevent aGVHD in patients undergoing standard myeloablative conditioning and allogeneic transplant. ECP was administered before a standard conditioning regimen. Results were compared with historical controls from the Center for International Blood and Marrow Transplant Research database. Multivariate analysis indicated a lower incidence of Grade 2 to 4 acute GVHD among patients who received ECP. Adjusted overall survival (OS) at one year was 83% in the ECP group and 67% among historical controls (RR=0.44; 95% CI=0.24-0.80). Additional prospective RCTs are necessary to confirm these findings.

Jagasia et al (2013) reported an international, retrospective comparative analysis of nonconcurrent cohorts who received ECP (n=57) or anticytokine therapy (inolimomab or etanercept; n=41) for Grade 2 or higher steroid-refractory aGVHD. ECP was initiated at two to three treatments weekly or biweekly until maximal response and then discontinued (European sites) or tapered (U.S. sites). More patients in the ECP group than in the anticytokine group experienced overall response (CR plus PR; 66% vs 32%, p=0.001) and CR (54% vs 20%).
p=0.001). Two-year OS was 59% in the ECP group and 12% in the anticytokine group (p value not reported).

Rubegni et al (2013) reported on a cohort of nine patients with Grade 2 to 3 steroid-refractory aGVHD at a single institution in Italy. ECP was administered on two consecutive days weekly until improvement and then every two weeks; treatment was then tapered as tolerated. At three months, mean dose of methylprednisolone decreased from 2.22 mg/kg to 0.27 mg/kg, and mean dose of cyclosporine decreased from 2.46 mg/kg to 0.77 mg/kg. Six patients (67%) showed a complete skin response. Five (83%) of six patients with liver and gastrointestinal tract involvement had CRs. All patients developed cGVHD, seven (78%) while still receiving ECP.

aGVHD and cGVHD

Hautmann et al (2013) reported on a cohort of 62 patients with aGVHD (n=30) or cGVHD (n=32) at a single institution in Germany. For aGVHD, ECP was administered two or three times weekly on consecutive days until clinical improvement, then two treatments on consecutive days biweekly, reducing to monthly, if tolerated. At three months, 15 patients (50%) achieved CR or PR (nine [30%] complete). Ten (83%) of 12 patients who continued ECP beyond three months and had data available decreased steroid dose by 50% or more. For cGVHD, ECP was administered on two consecutive days weekly until improvement, then biweekly for three to four weeks, and then monthly. At three months, 14 patients (44%) achieved CR or PR (two [6%] complete). Five (29%) of 17 patients who continued ECP beyond three months had data available and were taking steroids at baseline, decreased steroid dose by 50% or more.

Ussowicz et al (2013) reported on 21 patients with steroid-refractory or steroid-dependent, Grade 3 or 4 acute (n=8) or extensive chronic (n=13) GVHD in Poland. For aGVHD, ECP was administered on two consecutive days weekly for up to four weeks. Although clinical response was noted in three patients (37.5%), there were no long-term (more than 18 months after ECP) survivors. For cGVHD, ECP was administered on two consecutive days every two weeks for 14 weeks and then monthly for up to eight weeks. Four-year OS was 67.7%.

Section Summary

Evidence for the use of extracorporeal photopheresis (ECP) for the treatment of graft-versus-host disease (GVHD) relates to both acute GVHD (aGVHD) and chronic GVHD (cGVHD) in pediatric and adult populations. The published literature lacks randomized trials. Evidence comprises retrospective reviews and nonrandomized comparisons. These data consistently show improvement in GVHD that is unresponsive to standard therapy and are consistent with conclusions from the 2001 TEC Assessment. Additionally, there is a lack of other treatment options for these patients, with the added benefit of minimal side effects from ECP, as well as the possibility of reduction and often cessation of treatment with corticosteroids and other immunosuppressive agents if there is a response to ECP. Clinical input unanimously supported the use of ECP in patients with refractory aGVHD. Therefore, treatment of refractory aGVHD or cGVHD with ECP is considered medically necessary.

For patients with untreated disease or those who are showing improvement on standard therapy, there is no data to support the use of ECP; therefore, ECP is considered investigational in these settings.
Practice Guidelines and Position Statements

**aGVHD**
Evidence-based recommendations from the American Society of Blood and Marrow Transplantation (2012) advise that ECP cannot be considered superior to horse antithymocyte globulin for treatment of aGVHD. This conclusion was based on older studies.

**aGVHD and cGVHD**
Evidence-based guidelines from the British Committee for Standards in Haematology and the British Society for Bone Marrow Transplantation (2012) recommend ECP in aGVHD as second-line treatment for steroid-refractory disease and in cGVHD as second-line treatment for skin, oral, or liver involvement.

**Treatment schedule**
- For aGVHD, no recommendation is provided.
- For cGVHD, one cycle (i.e., ECP on two consecutive days) every two weeks; no benefit has been associated with more regular treatments. Responders may taper to monthly treatments.

**Treatment duration**
- For aGVHD, guideline authors observed that optimal treatment duration “has yet to be established” and cited a case series of 19 patients (published as an abstract who received at least eight weekly cycles, continued until maximal response (undefined) or CR (defined as “resolution of features of acute GVHD with reduction of prednisolone dose to 20 mg/day or less”).
- For cGVHD, no specific treatment duration was recommended, but an earlier evidence-based consensus statement was cited. This statement included recommendations for baseline, monthly, and every three-monthly assessments and criteria for discontinuation based on response and ability to taper concomitant immunosuppressive therapy. Typical treatment duration of three or four months was noted.

In 2013, a 9-member panel representing the Italian Society of Hemapheresis and Cell Manipulation and the Italian Group for Bone Marrow Transplantation published consensus recommendations for ECP in adults and children with aGVHD or cGVHD. The panel recommended ECP: for treatment of aGVHD in adults and children who are nonresponsive to steroids or calcineurin inhibitors or have contraindications to immunosuppressive therapy because of viral reactivation or other infectious complication (“better results are expected in patients with isolated skin involvement”); and for treatment of cGVHD in adults and children who are steroid-resistant or steroid-dependent.

**Treatment schedule**
- “For either acute or chronic GVHD, in the absence of controlled trials, the most frequently applied schedule is two ECP sessions weekly.”

**Treatment duration**
- For aGVHD or cGVHD, treatments continue until maximum response.
- Clinical response should be assessed weekly in aGVHD and every eight to 12 weeks in cGVHD.
- ECP should be discontinued in the case of no response or minimal response.

In its guideline on childhood hematopoietic cell transplantation, the National Cancer Institute lists ECP as a second-line treatment for patients with aGVHD who are resistant to first-line methylprednisolone. For cGVHD therapy, the guideline states that steroids are first-line therapy, but steroid-sparing approaches, including ECP, are being developed. In this setting, ECP shows “some efficacy in a percentage of patients.”

**Autoimmune Disease**

ECP for the treatment of autoimmune diseases was initially addressed by a 2001 TEC Assessment that considered a variety of autoimmune diseases: systemic sclerosis, pemphigoid, systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, rheumatoid arthritis, and Type 1 diabetes mellitus. The Assessment concluded that for all of these indications, available evidence was insufficient to permit conclusions on outcomes. At the time, photopheresis had been most thoroughly studied as a treatment for scleroderma. However, data on this indication include one single-blind RCT and three small, uncontrolled series. Although the RCT reported positive outcomes in terms of skin manifestations, a number of methodologic flaws have been discussed in the literature, including inadequate treatment duration and follow-up, excessive dropouts, a midstudy change of primary outcome, and inadequate washout of prior penicillamine therapy. Results reported from other small case series regarding systemic sclerosis conflict with each other and do not resolve the difficulties in interpreting the randomized trial.

**Type 1 Diabetes Mellitus**

A subsequent clinical trial on diabetes was published by Ludvigsson et al in 2001. This was a randomized double-blind controlled trial on photopheresis in 49 children with newly diagnosed Type 1 diabetes. Forty children (aged 10-18 years) completed the study and were followed for three years. All patients received standard treatment with insulin therapy and diet, exercise, and self-management education. Of these patients, 19 received active photopheresis treatment with oral 8-MOP, and 21 received placebo tablets and sham pheresis. Hemoglobin A1C did not differ statistically between groups.

**Multiple Sclerosis**

Cavaletti et al (2007) published a small case series of five patients with immunorefractory relapsing-remitting multiple sclerosis who received ECP. ECP appeared safe and tolerable in these patients, with some evidence for a reduction in the relapse rate and symptom stabilization. However, data are insufficient to alter the policy statement for this use of ECP.

**Bullous Disorders**

In 2010, Sanli et al published a retrospective report on 11 patients with drug-resistant autoimmune bullous diseases. ECP was performed between January 2005 and January 2010. Patients were treated on two consecutive days at four-week intervals. Of 8 patients with pemphigus vulgaris (PV), 7 (87.5%) experienced CR after two to six cycles. Of three patients with epidermolysis bullosa acquisita (EBA), two (67%) had CR and one (33%) had PR. All patients with PV reduced corticosteroid dose. Decrease in the frequency of ECP resulted in progression of lesions for three patients with PV and two patients with EBA. No adverse effects
were observed. RCTs are necessary to adequately assess the efficacy of ECP for patients with drug-resistant autoimmune bullous diseases.

Scleroderma (Systemic Sclerosis)
In addition to the RCT previously discussed, a 2012 cohort study by Papp et al enrolled 16 patients from a single institution in Hungary who had diffuse cutaneous systemic sclerosis. ECP was administered on two consecutive days every six weeks for six cycles. At the end of the treatment period, statistically significant reductions from baseline dermal thickness (by echography) were observed at four extensor surfaces (upper arm, forearm, hand, finger). Lung diffusing capacity did not decrease more than 5% in any of nine patients with pulmonary fibrosis at baseline.

Severe Atopic Dermatitis
Some patients with atopic dermatitis do not respond to standard treatments and require immunosuppression with traditional (e.g., systemic corticosteroids, azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, rituximab, intravenous immunoglobulin, infliximab, omalizumab) or biologic (e.g., alefacept, rituximab, intravenous immunoglobulin, infliximab, omalizumab) agents for chronic disease. In 2013, Rubegni et al reported on seven patients and summarized previous case series and case reports of patients with varying disease severity who were treated with ECP. Of 81 total patients, 69 (85%) were considered responders to ECP. Wolf et al subsequently published a case series of 10 adults with severe, refractory atopic dermatitis of at least one-year duration. ECP was administered for two consecutive days biweekly for 12 weeks and then monthly for two months. Only concomitant topical treatments and antihistamine were allowed. Mean (SD) baseline SCORAD (Scoring of Atopic Dermatitis) was 64.8 (18.9) on a 0 to 103-point scale, indicating moderate to severe disease. At week 20, mean (SD) SCORAD was 54.5 (22.8), a statistically significant improvement (p=0.015) of uncertain clinical significance. Improvements in QOL measures did not reach statistical significance. This evidence is insufficient to support the use of ECP in patients with severe atopic dermatitis.

Crohn Disease
Patients with steroid-dependent Crohn disease may respond to double immunosuppression with azathioprine and infliximab, but these treatments are associated with significant adverse events, particularly with long-term use. Reinisch et al (2013) assessed the steroid-sparing effect of ECP in 31 patients with steroid-dependent Crohn disease in clinical remission (Crohn Disease Activity Index [CDAI] <150). Other immunosuppressive treatments were tapered and discontinued before ECP initiation and steroid tapering. ECP was administered on two consecutive days every two weeks for 24 weeks. Steroids were tapered as tolerated during this 24-week period. Nineteen patients (61%) completed 24 weeks of treatment; seven patients (23%) achieved steroid-free remission at week 24 (the primary end point), and 20 patients (65%) maintained remission with a 50% or greater reduction in steroid dose from baseline. Three patients (10%) maintained steroid-free remission after 48 weeks of ECP (frequency decreased to monthly after week 24), and three other patients who discontinued steroids experienced mild disease (CDAI<220) at 48 weeks of ECP. One catheter-related complication was reported. This evidence is insufficient to support the use of ECP in patients with steroid-dependent Crohn disease.
Section Summary
Evidence for the use of extracorporeal photopheresis (ECP) for the treatment of autoimmune diseases including cutaneous or visceral manifestations of autoimmune diseases, including but not limited to scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, multiple sclerosis, diabetes, autoimmune bullous disorders, severe atopic dermatitis, and Crohn disease, is sparse and insufficient to permit conclusions. There are randomized trials for two indications: scleroderma and Type 1 diabetes. Methodologic flaws in the scleroderma trial limit applicability of the data. In the Type 1 diabetes trial, no difference in hemoglobin A1C was observed between those treated with and without ECP. Therefore, treatment of autoimmune diseases with ECP is considered investigational.

Practice Guidelines and Position Statements
Evidence-based consensus guidelines from the European Dermatology Forum (2013) recommend ECP for:

- Second-line or adjuvant therapy for skin manifestations of systemic sclerosis but not for organ involvement
- Second-line therapy for atopic dermatitis that is: more than 12 months’ duration; SCORAD (Scoring Atopic Dermatitis) score greater than 45%; and refractory in the previous year to all first-line therapies (topical steroids, calcineurin inhibitors, phototherapy or to one second-line therapy (systemic steroids, cyclosporine)
- Moderate to severe steroid-dependent Crohn disease that is refractory or intolerant to immunosuppressive agents including tumor necrosis factor inhibitors
- Other dermatologic diseases, such as pemphigus, epidermolysis bullosa acquisita, and erosive oral lichen planus, that are refractory to conventional systemic therapies

T-Cell Lymphoma
Cutaneous T-cell Lymphoma
Stage III/IV Mycosis Fungoides and Sézary Syndrome
The initial report on the use of ECP as therapy for cutaneous T cell lymphoma (CTCL) was published by Edelson et al in 1987. Twenty-seven (73%) of 37 patients with otherwise resistant CTCL responded, with a mean 64% decrease in cutaneous involvement after a mean (SD) of 22 weeks. Responders included 8 (80%) of 10 patients with lymph node involvement, 24 (83%) of 29 with exfoliative erythroderma, and 20 (71%) of 28 whose disease was resistant to standard chemotherapy. Adverse effects of standard chemotherapy, such as bone marrow suppression, gastrointestinal erosions, and hair loss, did not occur. In 2012, Knobler et al reanalyzed these data using current response criteria and reported no change in overall response rate. Response was defined as 90% or greater (near CR) or 50% or greater (PR) improvement in skin score for four weeks; in the original study, response was defined as 25% or greater improvement for four weeks. With seven years of follow-up, median OS was nine years from diagnosis and seven years from the start of ECP. (Mean age at study entry was 57 years [range, 24-80]). These results showed that ECP is safe and effective in advanced, resistant CTCL.

Subsequent results from numerous small, nonrandomized studies generally have been consistent with the initial conclusion that ECP treatment can produce clinical improvement and may prolong survival in a substantial proportion of patients with advanced stage CTCL. Together, these data provide the basis for several evidence-based guideline or consensus statements on the
use of ECP in CTCL, as well as the position of the (NCI. NCI consistently recommends ECP as first-line treatment for patients with stage III/IV CTCL.

In 2006, OHTAC published results of a systematic review of ECP for the treatment of erythrodermic CTCL. In summary, OHTAC reported that there was low-quality evidence that ECP improves response rates and survival in patients with CTCL who are unresponsive to other forms of therapy. Limitations in the literature related to ECP for the treatment of refractory erythrodermic CTCL mostly pertained to study quality and size and heterogeneity in both treatment regimens and diagnostic criteria. The committee did, however, recommend a two-year duration field evaluation of ECP for refractory erythrodermic CTCL, using standardized inclusion criteria and definitions to measure disease outcomes including response rates, quality of life, and morbidity. As of April 2014, this evaluation is not listed on the OHTAC website.

Early Stage (I/II) CTCL
Between 1987 and 2007, data were reported from at least 16 studies including 124 patients with CTCL in early stages IA, IB, or II who were treated with ECP alone (n=79) or in combination with other agents (e.g., retinoids and interferon-alfa) (n=45). Many of these patients were refractory to numerous other therapies, including topical corticosteroids, interferon alfa, or whole skin irradiation. Response rates (PR plus CR) in these studies ranged from 33% to 88% with monotherapy and 50% to 60% with ECP plus adjuvant therapies. Although these findings suggest that ECP may provide benefit in early stage CTCL, none of the studies was randomized or comparative. Furthermore, many of the studies preceded universal acceptance of standardized elements of classification and diagnosis of CTCL, such as those proposed by the WHO and WHO-EORTC. Thus, the actual disease spectrum and burden represented in the available database likely vary between studies, and this complicates conclusions about the efficacy of ECP in this setting. Nonetheless, given the unfavorable prognosis for patients with early stage CTCL that progresses on nonsystemic therapies, the relative lack of adverse events with ECP compared with other systemic treatments, and the good response rates often observed with ECP, ECP may provide outcome benefit as a technique for the treatment of patients with refractory or progressive early stage CTCL. In contrast, because early stage CTCL typically responds to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience near-normal life expectancy.

Section Summary
Evidence from small case series has shown a response to extracorporeal photopheresis (ECP) in patients with advanced stage cutaneous T cell lymphoma (CTCL), as well as prolongation of survival in a proportion of patients. Therefore, in this policy, ECP may be considered medically necessary as a technique for the treatment of patients with stages III/IV CTCL.

Given the unfavorable prognosis for patients with early stage CTCL that progresses on nonsystemic therapies, the relative lack of adverse events with ECP compared with other systemic treatments, and the good response rates often observed with ECP, ECP may be considered medically necessary as a technique for the treatment of patients with refractory or progressive early stage CTCL.
In contrast, when early stage CTCL does respond to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience near-normal life expectancy. As a consequence ECP is considered investigational as a technique for the treatment of patients with Stage I/II CTCL that is either previously untreated or is responding to established therapies.

**Non-cutaneous T-Cell Lymphoma/Leukemia**

Between 1997 and 2005, Garben and colleagues treated 12 patients with refractory/relapsed disease with ECP. Ultraviolet-A (UVA) irradiation-induced apoptosis of the malignant T-cell clone is a mechanism of action of ECP that has been described in CTCL. Based on this observation, these patients were chosen for therapy based on a peripheral clone detected by flow cytometry. One patient had a T-lymphoblastic lymphoma, six had peripheral T-cell lymphoma (PTCL) (two with angioimmunoblastic type, four with PTCL-NOS [not otherwise specified]), and five had large granular lymphocytic leukemia (LGL). At the time of EPC, the median age of the patients was 49 years (37-82). All patients had failed at least one line of therapy. Patients were treated according to the Vilbert-Lourmat procedure. Six courses were given over three weeks, followed by one course per week for ten weeks. If at least a partial response was observed, treatment continued with one course per month until complete response, progression or disappearance of the peripheral clone for patients having a complete response. Response was evaluated after six induction courses, then after ten courses and every three months until relapse. Of the 12 patients, six were in PR after induction (four PTCL and two LGL), and six never responded. Of the six showing PR after induction, four reached CR at ten courses (two PTCL and two LGL), and two PTCL had a sustained PR. While these findings suggest ECP may provide benefit for patients with non-cutaneous T-cell lymphomas and LGL, studies with larger numbers are necessary to determine the role of this type of therapy in the treatment of these diseases.

**Section Summary**

Data from one small case series showed at least a partial response to ECP in some patients with refractory non-cutaneous T-cell malignancies. More data from larger studies are needed to determine the role of this type of therapy in the treatment of these diseases.

**Practice Guidelines and Position Statements**

National Comprehensive Cancer Network 2014 guidelines for the treatment of CTCL recommend the use of ECP alone or in combination with other agents (retinoids, interferon alfa, denileukin diftitox) as first-line systemic therapy for advanced (Stages II/IV) disease, as well as for patients with either earlier stage mycosis fungoides with Sézary syndrome involvement or disease that has failed multiple courses of topical skin-directed treatments. For patients with mycosis fungoides or Sézary syndrome, “photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 [<1000/mm3 Sézary cells or <20% atypical T-cells on peripheral smears] or B2 [leukemic]).” The guidelines do not address the use of ECP for peripheral T cell lymphoma.
**Key Words:**
Photopheresis, graft vs host disease, GVHD, GvHD, extracorporeal, cutaneous t-cell lymphoma, CTCL

**Approved by Governing Bodies:**
The U.S. Food and Drug Administration (FDA) has approved via premarket application for two photopheresis systems manufactured by Therakos™, Inc. (West Chester, PA). Both systems are approved for use in ultraviolet A (UVA) irradiation treatment, in the presence of the photoactive drug 8-MOP, of extracorporeally circulating leukocyte-enriched blood, in the palliative treatment of skin manifestations of CTCL, in persons who have not been responsive to other forms of treatment. The two systems are:
- **UVAR® XTS Photopheresis System**, FDA-approved in 1987
- **CELLEX®, FDA approved in 2009**

8-MOP (UVADEX®) is FDA-approved for extracorporeal administration with the UVAR XTS or CELLEX Photopheresis System in the palliative treatment of the skin manifestations of CTCL that is unresponsive to other forms of treatment.

The use of either Therakos Photopheresis System or UVADEX® for other conditions is an off-label use of an FDA-approved device/drug.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity. Special benefit consideration may apply. Refer to member’s benefit plan.
Pre-certification/Pre-determination requirements: Not applicable

**Current Coding:**
CPT code: 36522 Photopheresis, extracorporeal

**References:**


38. Leukemia & Lymphoma Society. Peripheral T-Cell Lymphoma Facts. 2012. Available online at:
www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/lymphoma/pdf/p
eripheralcellymphomafacts.pdf.


Policy History:
Medical Policy Group, 1991
Medical Policy Group, 1996
Medical Policy Group, July 2001
Medical Review Committee, September 26, 2001
Medical Policy Administration Team, November 8, 2001
Medical Policy Group, October 2003 (1)
Medical Policy Group, October 2004 (1)
Medical Policy Group, October 2005 (1)
Medical Policy Group, October 2006 (1)
Medical Policy Group, June 2007 (1)
Medical Policy Group, April, 2010 (1): Added new coverage statement, Key Points, References,
Medical Policy Administration Committee, April 2010
Available for comment April 8-May 23, 2010
Medical Policy Group, November 2012 (1): Update to Key Points and References related to
MPP update; no change in policy statement
Medical Policy Panel, February 2013
Medical Policy Group, September 2013 (1): Added verbiage to noncoverage statement for
clarification purposes, ECP is investigational for “all other indications, including, but not limited
to:”, no change in coverage; update to Description, Key Points, Governing Bodies and
References
Medical Policy Administration Committee, September 2013
Medical Policy Panel, May 2014
Medical Policy Group, June 2014 (1): Update to Policy statement, Key Points, Governing Bodies
and References related to addition of coverage criteria for refractory acute GVHD; no other
changes to policy
Medical Policy Administration Committee, July 2014
Available for comment June 30 through August 13, 2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-
by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i)
research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date
hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and
levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure
review) in Blue Cross and Blue Shield’s administration of plan contracts.