Extracorporeal Photopheresis

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for extracorporeal photopheresis (ECP) when it is determined to be medically necessary because the criteria shown below are met.

Policy Topic Statements
Organ Rejection after Solid-Organ Transplant
Extracorporeal photopheresis may be considered medically necessary to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.

Extracorporeal photopheresis is considered investigational in all other situations related to treatment or prevention of rejection in solid-organ transplantation.

Acute GVHD
Extracorporeal photopheresis may be considered medically necessary as a technique to treat acute graft-versus-host disease (GVHD) that is refractory to medical therapy.

Extracorporeal photopheresis is considered investigational as a technique to treat acute GVHD that is either previously untreated or is responding to established therapies.

Chronic GVHD
Extracorporeal photopheresis may be considered medically necessary as a technique to treat chronic GVHD that is refractory to medical therapy.

Extracorporeal photopheresis is considered investigational as a technique to treat chronic GVHD that is either previously untreated or is responding to established therapies.

Autoimmune Diseases
Extracorporeal photopheresis is considered investigational as a technique to treat either the cutaneous or visceral manifestations of autoimmune diseases, including but not limited to scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, multiple sclerosis, diabetes, or autoimmune bullous disorders, severe atopic dermatitis, or Crohn disease.

Cutaneous T-cell lymphoma
Extracorporeal photopheresis may be considered medically necessary as a technique to treat latestage (III/IV) cutaneous T-cell lymphoma.

Extracorporeal photopheresis may be considered medically necessary as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies.
Extracorporeal photopheresis is considered investigational as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or is responding to established nonsystemic therapies.

**Other**
Extracorporeal photopheresis is considered investigational for all other indications.

**Considerations**

**Organ Rejection after Solid Organ Transplant**

A regimen of immunosuppressive therapy is standard of care for the treatment of solid-organ rejection. Therefore, refractory rejection is defined as rejection that fails to respond adequately to a standard regimen of immunosuppressive therapy.

Recurrent allograft rejection is defined as having at least 2 rejection episodes that recurred after standard immunosuppressive therapy.

There is no standard schedule for extracorporeal photopheresis, and reported schedules vary by the organ type. However, most reported cardiac and lung schedules initiate therapy with 2 consecutive days of extracorporeal photopheresis in month 1, followed by biweekly therapy on 2 consecutive days in months 2 and 3, then monthly on 2 consecutive days in months 4 through 6.

**GVHD**

An alternating regimen of cyclosporine and prednisone is commonly used to treat chronic graft-versus host disease. Other therapies include antithymocyte globulin, corticosteroid monotherapy, and cytotoxic immunosuppressive drugs such as procarbazine, cyclophosphamide, or azathioprine. Therefore, refractory disease is defined as chronic graft-versus-host disease that fails to respond adequately to a trial of any of the above therapies.

Treatment schedule and duration of ECP for GVHD have not been optimally defined. Guidelines and consensus statements generally recommend 1 cycle (ie, ECP on 2 consecutive days) weekly for acute GVHD and every 2 weeks for chronic GVHD. Treatment duration is based on clinical response (see Practice Guidelines and Position Statements); discontinuation is generally recommended for no or minimal response.

**CTCL Staging (based on the TNM classification system)**

IA: T1N0M0
IB: T2N0M0
I IA: T1-2N1M1
I IB: T3N0-1M0
III: T4N0-1M0
IVA: T1-4N2-3M0
IVB: T1-4N0-3M1

**Sézary Syndrome**

According to the World Health Organisation-European Organisation for Research and Treatment of Cancer (WHO-EORTC), Sézary syndrome is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in skin, lymph nodes, and peripheral blood. The International Society of Cutaneous Lymphomas recommends an absolute Sézary cell count of at least 1,000 cells per cubic mm, in the presence of immunophenotypical abnormalities (CD4/CD8 ratio greater than 10, loss of any or all of the T-cell antigens CD2, CD3, CD4, and CD5, or both), or the demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods.
**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.

**Background**

**Treatment for 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 immunosuppressive 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.

While first approved for the treatment of CTCL, ECP has more recently been used as a supplement to conventional therapies in the area of transplantation. (1) Reports of the successful use of ECP in human cardiac transplant recipients were published in 1992 (2, 3) 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, while maintaining the body’s ability to respond to other antigens. (4) 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 immunosuppressant drugs. (5)

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

ECP as a treatment of 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 some time after 100 days. Acute GVHD is commonly graded from I–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), 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 Sezary 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 Considerations 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. Sezary 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, an average of 2 to 10 years, as waxing and waning cutaneous eruptions prior to biopsy confirmation. The prognosis of patients with mycosis fungoides/Sezary 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. The median survival following diagnosis varies according to stage. Patients with stage IA disease have a median survival of 20 or more years, with the majority of deaths for this group typically unrelated to mycosis fungoides. In contrast, more than 50% of patients with stage III through stage IV disease 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. (6)

**Regulatory Status**
The U.S. Food and Drug Administration (FDA) has approved via premarket application for 2 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 2 systems are:

- 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 the UVAR® XTS Photopheresis System or UVADEX® for other conditions is an off-label use of a FDA-approved device/drug.

Rationale
This policy was originally created in 1992 and was updated regularly with searches of the MEDLINE database. The most recent literature review was performed on April 16, 2014. The following is a summary of the key literature to date.

Organ Rejection after Solid Organ Transplant

Cardiac

Acute Rejection
A 1992 randomized, controlled trial (RCT) compared the efficacy of extracorporeal photopheresis (ECP) with corticosteroids for the treatment of heart transplant rejection. (2) 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 3 days or 1 g/day IV (intravenous) methylprednisolone for 3 days at the discretion of the managing physician. Treatment was repeated if EMB at day 7 showed no improvement in rejection grade. If rejection grade persisted after retreatment, patients were given 10 mg oral methotrexate at weekly intervals for 8 weeks. Participants were followed for a mean of 6.2 months, and all participants completed the study. ECP participants received 1 ECP treatment unless an inadequate number of cells were treated. In that case, an additional treatment was given 48 hours later. Eight of 9 rejection episodes treated with ECP improved; all 7 rejection episodes treated with corticosteroids resolved. Improvement was seen a mean of 7 days (range, 5-20) after ECP and 8 days (range, 6-67) after corticosteroid treatment. Seven infections occurred during follow-up, 5 in the corticosteroid group and 2 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. (7) 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 2-day treatment protocol every 3 to 6 weeks for 18 months; maintenance immunosuppression used cyclosporine- or tacrolimus-based therapy with prednisone for the first 4 to 6 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 3 months of ECP were considered to have effective photopheresis treatment; patients who received less than 3 months of treatment were considered untreated but were analyzed as part of the photopheresis group. The period after 3 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 2 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. (8) Participants were eligible if they had acute rejection and at least 2 rejection episodes after standard immunosuppressive therapies in the 3 months before ECP. ECP was administered with UVAR photopheresis instruments in 2 consecutive treatments at weekly intervals for 1 month, at 2-week intervals for 2 months, and then monthly for 3 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, 1 patient died from hepatitis C virus and 1 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, 2 during the tapering of oral corticosteroids. Four were reversed by ECP, 1 by IV corticosteroids, and 1 by methotrexate after failure of both ECP and IV corticosteroids. Mean dose of immunosuppressive drugs (corticosteroids, cyclosporine, azathioprine) was reduced after 6 months of ECP therapy. One patient with anemia and low body weight experienced symptomatic hypotension during treatment, and 1 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. (9) Inclusion criteria were recurrent rejection (n=5), recurrent infections associated with acute rejection (n=2), and a grade 3A acute rejection 2 years after transplantation (n=5). Mean post-ECP follow-up was 23.3 months. ECP was performed as 2 treatments weekly for 1 month, once weekly for 2 months, and then once monthly for 2 months. Total number of rejection episodes decreased from a mean of 3 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 4 patients treated with ECP for severe refractory (grade 3A to 4) cardiac allograft rejection. (10) All 4 patients experienced reversal of their rejection. Three patients improved following 2 consecutive days of treatment, and the fourth patient responded after three 2-day treatments. Two patients subsequently died of acute rejection at 9 weeks and 10 weeks, respectively, after completing ECP. The other 2 patients had no signs of rejection, one at 6 years and
the other at 4 months after completion of ECP. This small case series adds to the evidence provided by
the previous 2 slightly larger studies.

Prevention of Rejection
A 1998 RCT by Barr et al investigated ECP for the prevention of rejection after cardiac transplant. (11)
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 6 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, 5 patients had no rejection episodes, 9 had one, 9 had two,
and 4 had three or more. In the ECP group, 13 had none, 14 had one, 3 had two, and 3 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 6 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 (7 bilateral lung,
6 single lung, 1 heart-lung) who received ECP for bronchiolitis obliterans syndrome (BOS). (12) All
patients were refractory to standard immunosuppressive therapy. ECP was administered every 2
weeks for 2 months and then monthly for 2 months for a total of 6 treatments. Four of 8 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 4 patients received ECP during a concurrent episode of
acute rejection; all 3 patients had complete resolution of acute rejection after treatment. Another study
published in 1999 by Salerno et al reported on 2 patients with histologic reversal of concurrent acute
rejection after treatment with ECP. (13) These 2 studies reported on only 5 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). (14) The primary outcome measure was
clinical stabilization of rejection after ECP. Twelve patients had biopsy-confirmed chronic acute
rejection, defined as 2 or more biopsy-proven episodes of acute rejection before ECP. Of 11 patients
who had follow-up biopsies during treatment, 2 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 (ie, including the 12 patients with BOS).

Chronic Rejection Refractory to Corticosteroid/Refractory 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. (15) Fifty-one patients (78%) had undergone double lung transplant, 9 patients (14%) had undergone single-lung transplant, and 5 patients (8%) had undergone heart-lung transplant. Median time to CLAD diagnosis was 3 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 9 patients (14%) were BOS stage 1 or 0p (potential BOS). ECP was administered every 2 weeks for 3 months; subsequent treatments were administered not more than 8 weeks apart to maintain stabilized graft function. Median follow-up was 17 months; 44 patients who continued treatment beyond 3 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 4 months (IQR=3-6) among those who did not respond. These data are retrospective and lack a control group.

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). (16) 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 2 successive days every 2 weeks during the first 3 months and then every 4 weeks until the end of therapy. ECP was discontinued after a minimum of 3 months if lung function decreased significantly. If FEV1 improved or stabilized, ECP was continued for a minimum of 6 months. Change in FEV1 at 3, 6, and 12 months after ECP 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 1 year after initiation of ECP, and 12% showed improvement for only 3 to 6 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 9 patients treated with ECP between July 2008 and August 2009. (17) 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 2 sessions of ECP for 3 to 4 weeks. Treatment frequency then decreased to every 2 to 3 weeks, with the goal of reducing treatment to every 4 weeks. Clinical response was defined as symptomatic improvement, decreased dependency on supplemental oxygen, and improved pulmonary function tests. Six of 9 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. (18) 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 2 cycles on days 1, 2, 5, 6, 10, 11, 17, 18, 27, and 28 during the first month (10 treatments); biweekly for the next 2 months (8 treatments); and then monthly for the following 3 months (6 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
At the end of the study, 33 patients were still alive; 4 deaths occurred early in the study. Most deaths were due to progression of respiratory failure, except for 1 death due to sepsis and 1 to graft failure. In the 6 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; 1 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). (14) ECP was delivered when BOS grade worsened despite standard therapy. At the start of therapy, 5 patients had BOS grade 1; 2 patients had BOS grade 2; and 5 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 (ie, including the 12 patients with BOS).

Also as previously noted, Villanueva et al (2000) retrospectively reviewed outcomes of 14 transplant recipients (7 bilateral lung, 6 single lung, and 1 heart-lung) who received ECP for BOS. (12) All patients were refractory to standard immunosuppressive therapy. ECP was administered every 2 weeks for 2 months and then once monthly for 2 months, for a total of 6 treatments. In 4 of 8 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 1 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 6 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. (19) ECP was performed on 2 consecutive days twice a month until FEV1 stabilization. Treatment was then repeated every 4 to 6 weeks. Four of the 6 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 published a series of articles on various potential applications of ECP for liver transplant recipients. (20-22) The first article from 2004 was a retrospective review of 5 patients who received liver transplantation and ECP for biopsy-proven allograft rejection. Indications for ECP were recalcitrant ductopenic rejection with hepatitis C virus recurrence; corticosteroid-resistant acute rejection (2
patients); severe acute rejection in a major ABO-incompatible liver graft; and severe acute rejection in a patient with a proven corticosteroid allergy. (20) ECP was performed twice weekly for 4 weeks, then every 2 weeks for 2 months, and then once monthly. ECP was discontinued when indicated by biopsy-proven reversal of rejection or the absence of clinically evident rejection relapse. Liver function tests improved to baseline in all but 1 patient, and no procedure-related complications were reported. At a median follow-up of 7.9 months, 3 patients were off ECP with normal liver function tests and low-level immunosuppressive therapy, and 2 patients 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 historical matched controls) who received ECP to delay the introduction of calcineurin inhibitors (CNI) to avoid CNI toxicity. (22) Patients were included if they were at risk of postliver transplant renal impairment and neurologic complications, defined as having at least 1 of the following risk factors: a calculated glomerular filtration rate of 50 mL/min or less at transplantation; severe ascites; history of more than 1 hospitalization for encephalopathy within 1 year of transplant and/or one hospitalization within 1 month of transplantation; or age 65 years or older. Outcome measures were treatment success rate, defined as the ratio of patients with full CNI-sparing or delayed immunosuppression; interval from liver transplantation to CNI introduction; safety of ECP; and need for biopsy. ECP was initiated during the first week post-transplant; 2 different systems (Therakos and PIT) for photopheresis were used, and treatment was given as scheduled for the system used. All 18 patients tolerated and completed ECP therapy. For 17 patients, CNI was introduced at a mean of 8 days; 1 patient remained CNI-free for 22 months. Acute rejection occurred in 5 (28%) of 18 patients in the ECP group and in 3 (17%) of 18 historical controls. One-, 6-, and 12-month survival was 94.4%, 88.1%, and 88.1%, respectively, for ECP recipients versus 94.4%, 77.7%, and 72.2%, respectively, for 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 3 fields of interest for ECP as prophylaxis of allograft rejection in liver transplant patients. (21) The 3 fields are:

- Use of ECP to delay CNI among high-risk liver transplant recipients to avoid toxicity (previously discussed);
- Use of ECP for prophylaxis of acute cellular rejection among ABO-incompatible liver transplant recipients (11 consecutive patients received ECP plus immunosuppressive therapy with no evidence of acute rejection through 568 days of follow-up); and
- 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 lacked comparison groups. RCTs 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 transplantation at this center. (23) ECP was delivered weekly for 4 weeks, then every 2 weeks. Total treatment range was 2 to 12 treatments for more than 5 to 20 weeks. Median follow-up was 66.7 months after transplant and 65.0 months from initiation of ECP. Indication for ECP was acute resistant/recurrent rejection in 9 patients and the need to avoid high-dose corticosteroids in another. Refractory rejection 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. Although this is the largest series of renal patients, it is small and there is no comparison group. 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 (73%) of 26 patients, 3 patients were stable, and 4 patients returned to dialysis because of deteriorating function. Reports of long-term outcomes varied. Among 22 patients who showed initial improvement and/or stabilization of renal function, 5 had improved function at 1 year, (24) 1 was stable at 25 months, (25) 5 were stable at 1 year, (24, 26) 7 were rejection-free at 2 to 5 years, (25) and 1 graft was lost. (26) Long-term outcomes were not reported for 3 patients. (27, 28)

**Ongoing Clinical Trials**

A search of online site ClinicalTrials.gov in January 2014 found 1 registered clinical study seeking to assess ECP for acute rejection of liver transplantation (NCT01824368). This is a single-arm, Phase 2 study of 10 patients. The study is conducted in Spain, and results are expected April 2014.

**Section Summary**

Evidence for the use of extracorporeal photopheresis (ECP) in cardiac transplant patients relates to 3 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, 1 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 6 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 3 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 2 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 1 nonrandomized comparative study, 2 case series, and a case report of 4 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 2 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 1 group in Italy. Although there is 1 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 1 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 does not have any policies related to ECP in the treatment or prevention of any form of rejection following solid organ transplant.

**Medicare National Coverage**

Based on a 2006 evidence review, the Centers for Medicare and Medicaid Services concluded that extracorporeal photopheresis is reasonable and necessary for persons with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment.

Effective April 30, 2012, Medicare also provides coverage for ECP for the treatment of BOS following lung allograft transplantation only when ECP is provided under a clinical research study that meets certain conditions. (29)

**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 1 week of steroid treatment. Patients received ECP for a minimum of 10 treatments. ECP was administered 2 to 3 times weekly on alternating days until clinical improvement. Treatment was then reduced to 2 procedures per week for 2 weeks, then 2 procedures every other week for 3 weeks, ending with 2 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 4 weeks. Of 47 patients with acute GVHD, 39 (83%) of 47 patients with skin involvement improved, and 7 (87.5%) of 8 patients with mucosal involvement improved. Among patients with chronic GVHD, all 4 patients (100%) with liver involvement improved, and 22 (95.6%) of 23 patients with skin involvement improved. (31)

The literature also includes, but is not limited to, 2 small studies that focused on photopheresis for treatment of GVHD in children (32, 33) and 1 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. (34) 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 7 days of methylprednisolone therapy. Patients received ECP on 2 consecutive days at weekly intervals for the first month, every 2 weeks for 2 months, and then monthly for 3 months. ECP was progressively tapered and discontinued based on individual patient response. Response to ECP was assessed 3 months after ECP ended or after 6 months if the ECP protocol was prolonged. Among patients with aGVHD, complete response (CR) occurred in 7 (100%) of 7 patients with grade 2 and 2 (50%) of 4 patients with grade 3 disease; none of 4 patients with grade 4 disease responded to ECP. In the group with cGVHD, CR occurred in 3 (100%) of 3 patients with limited disease and 1 (14%) of 7 patients with extensive disease. Five (71%) of 7 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 2 smaller studies reported on 8 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. (32) Cutaneous status reportedly improved in 7 patients. Five patients stopped treatment, and 3 decreased doses of immunosuppressive therapy. In addition, gut involvement resolved in all patients, and liver involvement resolved in 4 of 6 patients. Two years after discontinuation of photopheresis, 5 patients remained in remission without immunosuppressive therapy. Salvaneschi et al reported on ECP in refractory GVHD in 23 pediatric patients (aged 5.4-11.2 years). (33) Seven (78%) of 9 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 2 systematic reviews on aGVHD (35) and cGVHD (36) 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.” (36) International collaboration and establishment of patient registries was encouraged.

Treatment of GVHD in Adults

Chronic GVHD

In addition to the 2001 TEC Assessment previously referenced, several additional publications reported 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 cGVHD. (37) In summary, OHTAC reported that there is low-quality evidence that ECP improves
response rates and survival in patients with cGVHD who are unresponsive to other forms of therapy. Limitations in the literature related to ECP for the treatment of refractory GVHD mostly pertained to study quality and size and heterogeneity in both treatment regimens and diagnostic criteria. The committee did, however, recommend a 2-year duration field evaluation of ECP for cGVHD, 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. (38) ECP was administered for 2 consecutive days every 2 weeks in 17 patients and once weekly in 8 patients until best response or stable disease was achieved. With a 9-month median ECP duration (range, 3-24 months), 20 patients had improvement in cutaneous GVHD, and 6 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. (39) 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 2 consecutive days every 2 weeks until PR (defined as minimum 50% improvement from baseline in 1 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 6 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 6 months of ECP. Of 25 patients receiving immunosuppressive therapy who completed 6 months of ECP, 20 (80%) reduced immunosuppressive dose; 5 patients discontinued steroids, and 8 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 6 months. Five patients developed indwelling catheter-related infections, 1 patient had a catheter-related thrombosis, and 1 patient had an increase in red cell transfusion requirements, which was considered due to ECP alone.

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). (41) Median duration of ECP was 7 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 2 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. (42) 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 1 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. (43) ECP was initiated at 2 to 3 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 9 patients with grade 2 to 3 steroid-refractory aGVHD at a single institution in Italy. (44) ECP was administered on 2 consecutive days weekly until improvement and then every 2 weeks; treatment was then tapered as tolerated. At 3 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 6 patients with liver and gastrointestinal tract involvement had CRs. All patients developed cGVHD, 7 (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. (45) For aGVHD, ECP was administered 2 or 3 times weekly on consecutive days until clinical improvement, then 2 treatments on consecutive days biweekly, reducing to monthly, if tolerated. At 3 months, 15 patients (50%) achieved CR or PR (9 [30%] complete). Ten (83%) of 12 patients who continued ECP beyond 3 months and had data available decreased steroid dose by 50% or more. For cGVHD, ECP was administered on 2 consecutive days weekly until improvement, then biweekly for 3 to 4 weeks, and then monthly. At 3 months, 14 patients (44%) achieved CR or PR (2 [6%] complete). Five (29%) of 17 patients who continued ECP beyond 3 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. (46) For aGVHD, ECP was administered on 2 consecutive days weekly for up to 4 weeks. Although clinical response was noted in 3 patients (37.5%), there were no long-term (more than 18 months after ECP) survivors. For cGVHD, ECP was administered on 2 consecutive days every 2 weeks for 14 weeks and then monthly for up to 8 weeks. Four-year OS was 67.7%.

**Ongoing Clinical Trials**

A search of online site, ClinicalTrials.gov in January 2014 found 3 ongoing randomized trials and 1 prospective case-only observational study:
- A Randomized Controlled Study of Extracorporeal Photopheresis (ECP) Therapy With UVADEX for the Treatment of Patients With Moderate to Severe Chronic Graft-versus-Host Disease (cGvHD) trial (NCT01380535) is a Phase II randomized trial evaluating the safety and effectiveness of ECP when added to standard drug therapies and given to adult patients with moderate-to-severe cGVHD. Primary outcome is overall response. They aim to enroll 60 participants and follow them for 28 weeks.
A Randomized Phase II Study for the Evaluation of Extracorporeal Photopheresis (ECP) in Combination With Corticosteroids for the Initial Treatment of Acute Graft-Versus-Host Disease (GVHD) trial (NCT00609609) is a Phase II randomized trial evaluating whether the addition of ECP to standard drug therapies for acute GVHD improves response to treatment, length of treatment, and survival. Primary outcome is overall response. They aim to enroll 80 participants and follow them for 6 months after treatment completion. Final data collection for the primary end points will be January 2014.

Randomized trial NCT00402714 is registered, but its status was unknown and has not been updated since April 2009.

The Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis trial (NCT01460914). This is a prospective observational case-only study looking to measure response rates. In addition, a prospective database will be maintained so that new patient data can be collected.

Clinical Input Received through Physician Specialty Societies, Academic Medical Centers, and Blue Distinction Centers for Transplant

In response to requests, input was received through 2 academic medical centers and 5 Blue Distinction Centers for Transplant when this policy was under review in 2014. While the various physician specialty societies, academic medical centers, and Blue Distinction Centers for Transplant may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies, academic medical centers, or Blue Distinction Centers for Transplant unless otherwise noted. Respondents agreed unanimously that ECP should not be medically necessary in previously untreated aGVHD but should be medically necessary in aGVHD that is refractory to medical therapy.

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. (25, 47, 48) 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. (49) This conclusion was based on older studies. (41, 50)

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 (51) and in cGVHD as second-line treatment for skin, oral, or liver involvement. (52)

Treatment schedule
For aGVHD, no recommendation is provided. For cGVHD, 1 cycle (ie, ECP on 2 consecutive days) every 2 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 8 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 3-monthly assessments and criteria for discontinuation based on response and ability to taper concomitant immunosuppressive therapy. Typical treatment duration of 3 or 4 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 2 ECP sessions weekly.”

**Treatment duration**
- For aGVHD or cGVHD, treatments continue until maximum response.
- Clinical response should be assessed weekly in aGVHD and every 8 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.”

**Medicare National Coverage**

Effective December 19, 2006, Medicare provides coverage of ECP for patients with cGVHD whose disease is refractory to standard immunosuppressive drug treatment.

**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 1 single-blind RCT and 3 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. (62) Forty children (aged 10-18 years) completed the study and were followed for 3 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 5 patients with immunorefractory relapsing-remitting multiple sclerosis who received ECP. (63) 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. (64) ECP was performed between January 2005 and January 2010. Patients were treated on 2 consecutive days at 4-week intervals. Of 8 patients with pemphigus vulgaris (PV), 7 (87.5%) experienced CR after 2 to 6 cycles. Of 3 patients with epidermolysis bullosa acquisita (EBA), 2 (67%) had CR and 1 (33%) had PR. All patients with PV reduced corticosteroid dose. Decrease in the frequency of ECP resulted in progression of lesions for 3 patients with PV and 2 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, (58) a 2012 cohort study by Papp et al enrolled 16 patients from a single institution in Hungary who had diffuse cutaneous systemic sclerosis. (65) ECP was administered on 2 consecutive days every 6 weeks for 6 cycles. At the end of the treatment period, statistically significant reductions from baseline dermal thickness (by echography) were observed at 4 extensor surfaces (upper arm, forearm, hand, finger). Lung diffusing capacity did not decrease more than 5% in any of 9 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 (eg, systemic corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate) or biologic (eg, alefacept, rituximab, intravenous immunoglobulin, infliximab, omalizumab) agents for chronic disease. In 2013, Rubegni et al (66) reported on 7 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 (67) subsequently published a case series of 10 adults with severe, refractory atopic dermatitis of at least 1-year duration. ECP was administered for 2 consecutive days biweekly for 12 weeks and then monthly for 2 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 2 consecutive days every 2 weeks for 24 weeks. Steroids were tapered as tolerated during this 24-week period. Nineteen patients (61%) completed 24 weeks of treatment; 7 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 3 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 2 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 (68):

- 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 1 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

**Medicare National Coverage**

There are no national coverage decisions regarding the use of ECP for the treatment of autoimmune disease.

**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. (69) 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 (10) 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. (70) Response was defined as 90% or greater (near CR) or 50% or greater (PR) improvement in skin score for 4 weeks; in the original study, response was defined as 25% or greater improvement for 4 weeks. With 7 years of follow-up, median OS was 9 years from diagnosis and 7 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 (summarized in (71-75)). Together, these data provide the basis for several evidence-based guideline or consensus statements on the use of ECP in CTCL, (53, 76, 77) as well as the position of the (NCI. (78) 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. (37) 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 2-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 (eg, retinoids and interferon-alfa) (n=45) (summarized in (79)). 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. (80) 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.

Ongoing Clinical Trials
A search of online site, ClinicalTrials.gov in January 2014 did not find any ongoing randomized trials. One prospective, observational, case-only study includes response rates among its outcomes (Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis trial [NCT01460914]). Additionally, a prospective database will be maintained for the collection of new patient data.
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.

Noncutaneous T Cell Lymphoma/Leukemia

Garben et al (2012) used ECP to treat 12 patients with refractory/relapsed disease between 1997 and 2005. (81) Based on the observation that ultraviolet-A (UVA) irradiation-induced apoptosis of the malignant T cell clone may be a mechanism of action of ECP in CTCL (82), patients were chosen for therapy based on a peripheral clone detected by flow cytometry. One patient had T lymphoblastic lymphoma; 6 had peripheral T cell lymphoma (PTCL) (2 with angioimmunoblastic type and 4 with PTCL-NOS [not otherwise specified]); and 5 had large granular lymphocytic leukemia (LGL). At the time of ECP, median age was 49 years (range, 37-82). All patients had failed at least 1 line of therapy. Patients were treated according to the Vilbert-Lourmat procedure. (83) Six courses were given over 3 weeks, followed by 1 course per week for 10 weeks. If at least a PR was observed, treatment continued with 1 course per month until progression or CR with disappearance of the peripheral clone. Response was evaluated after 6 induction courses, then after 10 courses, and then every 3 months until relapse. Of the 12 patients, 6 were in PR after induction (4 PTCL and 2 LGL), and 6 never responded. Of the 6 showing PR after induction, 4 reached CR at 10 courses (2 PTCL and 2 LGL), and 2 patients (with PTCL) had a sustained PR. Although these findings suggest that ECP may provide benefit for patients with noncutaneous T cell lymphomas and LGL, studies with larger samples are necessary to determine the role of ECP in the treatment of these diseases.

Section Summary
Data from one small case series showed at least a partial response to extracorporeal photopheresis in some patients with refractory noncutaneous T cell malignancies. More data from larger studies are needed to determine the role of ECP 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 III/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. (84)

Medicare National Coverage
Based upon a 1988 evidence review, the Centers for Medicare and Medicaid Services concluded that extracorporeal photopheresis is reasonable and necessary for palliative treatment of skin manifestations of CTCL that has not responded to other therapy.

References


Billing Coding/Physician Documentation Information
### Additional Policy Key Words

N/A

### Policy Implementation/Update Information

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