Extracorporeal photopheresis (ECP) may be considered medically necessary for any of the following indications:

- **Organ Rejection after Solid-Organ Transplant**: To treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.

- **Graft-Versus-Host Disease**: As a technique to treat chronic graft-versus-host disease that is refractory to medical therapy

- **Cutaneous T-cell Lymphoma**:
  - As a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies
  - As a technique to treat late-stage (III/IV) cutaneous T-cell lymphoma

ECP is considered investigational for any of the following indications, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure:

- **Organ Rejection after Solid-Organ Transplant**: In all other situations related to treatment or prevention of rejection in solid-organ transplantation, other than as stated in the policy criteria above.

- **Graft-Versus-Host Disease**: As a technique to treat acute or chronic graft-versus-host disease that is either previously untreated or is responding to established therapies
**Autoimmune Disease:** 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

**Cutaneous T-cell Lymphoma:** 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

- For all indications other than as stated in the medically necessary policy criteria above.

**Cross-reference:**
MP-2.239 Laboratory Tests for Heart Transplant Rejection
MP 2.046 Ultraviolet Light Therapies
MP-9.007 Heart Transplant
MP-9.014 Heart/Lung Transplant

**II. PRODUCT VARIATIONS**

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*Refer to FEP Medical Policy Manual MP-8.01.36. Extracorporeal Photopheresis The FEP Medical Policy manual can be found at: [www.fepblue.org](http://www.fepblue.org)

**Refer to Centers of Medicare and Medicaid (CMS) National Coverage Determination (NCD) 110.4 Extracorporeal Photopheresis for coverage indications.

**III. DESCRIPTION/BACKGROUND**
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), and cutaneous T-cell lymphoma (CTCL), as well as treatment for and prevention of organ rejection after solid-organ transplant.

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. 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, while 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 immunosuppressant drugs.

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 sometime 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 erythoderma, 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 of 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 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. 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, with a median survival of less than 5 years.

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.

**Regulatory Status**

In the U.S., the UVAR® XTS Photopheresis System was approved via premarket application (PMA) by the U.S. Food and Drug Administration (FDA) for use in the ultraviolet-A (UVA) irradiation (in the presence of the photoactive drug, methoxsalen) of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) in persons who have not been responsive to other therapy.

8-MOP (UVADEX®) is approved by the FDA for use in conjunction with UVAR XTS Photopheresis System for use in the UVA irradiation in the presence of the photoactive drug methoxsalen of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of CTCL in persons who have not been responsive to other therapy.
The use of the UVAR® XTS Photopheresis System or UVADEX® for other conditions is an off-label use of a FDA-approved device/drug.

IV. RATIONALE

This policy is updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period of January 2012 through December 2012. The following is a summary of the key literature to date.

Organ Rejection after Solid-Organ Transplant

Literature Review

A literature search using MEDLINE was performed for the period of 1992 through January 2010. The search identified one randomized controlled trial (RCT) for the use of extracorporeal photopheresis (ECP) in cardiac transplant recipients and one nonrandomized comparative trial in liver transplant recipients. Other published data come from small case series and/or case reports.

Cardiac

Acute Rejection

One randomized, controlled trial (RCT) was published in 1992 on the efficacy of extracorporeal photopheresis (ECP) versus corticosteroids in treating heart transplant rejection. (2) Costanzo-Nordin and colleagues 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, and 3B). Participants were excluded for leukopenia, hemodynamic compromise manifested clinically or by decrease in cardiac output equal to or greater than 25% and an increase in mean pulmonary artery wedge pressure equal to or greater than 25%, and/or an allergy or intolerance to psoralen. Corticosteroids were dosed at 100 mg/day oral prednisone for 3 days or 1g/day IV (intravenous) methylprednisolone for 3 days at the discretion of the managing physician. The treatment was repeated if EMB at day 7 showed no improvement in rejection grade. If the 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 were given one ECP treatment unless an inadequate number of cells were treated. In that case, an additional treatment was given 48 hours later. Of the 9 rejection episodes treated with ECP, all but 1 improved; all 7 of rejection episodes treated with corticosteroids resolved. Improvement was seen in a mean of 7 days (range: 5–20) for ECP and 8 days (range: 6–67 days) after corticosteroid treatment. Seven infections occurred during follow-up, 5 in the corticosteroid
groups and 2 among those receiving ECP. No other adverse events were observed with ECP. The authors noted the major limitations of the study included the small sample size and the wide range of time from transplant to study entry. They concluded that ECP and corticosteroids in this small group with short-term follow-up appear to have similar efficacies for the treatment of moderate heart transplant rejection. They also noted the lower number of infections with no other observed harms associated with ECP.

Recurrent, Multiple and/or Refractory Rejection

Kirklin and colleagues published a comparative study of 343 patients in 2006 who received heart transplants. (7) Thirty-six of those patients were treated with ECP for rejection and formed the treatment group. Patients were at least 18 years or older, treated from 1990-93, and followed to May 2004. Indications for ECP were episodes of rejection with hemodynamic compromise (HC) (n=12), recurrent (n=9) or persistent (n=11) rejection, or as prophylaxis in the presence of anti-donor antibodies. ECP consisted of psoralen in a 2-day treatment protocol every 3 to 6 weeks for 18 months; maintenance immunosuppression-utilized 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 hazard rate of subsequent HC rejection after at least 1 HC had already occurred. Hazard functions were used for analysis. Patients with at least 3 months of ECP were considered to have effective photopheresis treatment; if less than 3 months, they were considered to not have had treatment but were analyzed as part of the photopheresis group. Risk factor analysis showed those who received photopheresis were at high risk for HC rejection. 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; there was imbalance in the pretreatment risk of rejection or rejection death between the 2 groups. Changes in maintenance immunotherapy over time may confound the results, as patients in the comparison group did not receive a consistent regimen. However, these changes in maintenance immunotherapy would tend to make the identification of an effect of ECP created by the ever-evolving immunotherapy regimen more difficult. This only strengthens the authors’ conclusion that ECP reduces the risk of subsequent HC rejection and/or death from rejection when initiated for patients with high risk of rejection.

Dall’Amico et al. reported in 2000 on a case series of 11 patients with recurrent rejection after heart transplant. (8) Participants were eligible if they had acute rejection and at least 2 rejection episodes in the 3 months prior to ECP, which recurred after standard immunosuppressive therapies. ECP was performed with the UVAR photopheresis instruments, with 2 consecutive treatments at weekly intervals for 1 month, 2 treatments twice weekly during the second and third months, then monthly for 3 additional months. One patient, showing 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
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 days). In terms of rejection relapse, the fraction of EMB with a grade of 0/1A increased during ECP from 46% to 72%, and those showing 3A/3B rejection decreased from 42% to 18%. One of 78 EMB during ECP showed 3B rejection compared to 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 the last by methotrexate after failure of both ECP and IV corticosteroids. Mean dose of immunosuppressive drugs (corticosteroids, cyclosporine, and azathioprine) was reduced after 6 months of ECP therapy. One patient with anemia and low body weight experienced symptomatic hypotension episodes during treatment, and 1 patient had interstitial pneumonia. The authors concluded ECP to be a well-tolerated treatment, which allows for better recurrent rejection control and significant reductions in immunosuppressive therapy. The follow-up time and patient population are adequate; the study is limited by its small size and lack of a comparison group.

Maccherini and colleagues 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 3A acute rejection 2 years after transplantation (n=5). Mean post-ECP follow-up was 23.3 months. ECP was performed as 2 treatments per week for 1 month, once a week for 2 months, then once a month for 2 months, totaling 20 ECP treatments during 6 months. Total number of rejection episodes decreased from a mean of 3 per patient pre-ECP to 0.4 per patient post-ECP. Reduction in immunosuppressive therapy was achieved by all patients. 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, allowing for both a reduction in rejection episodes and immunosuppressive therapy.

Similar results were presented by Lehrer and colleagues describing the experience of 4 patients treated with ECP for severe refractory (grade IIIA to IV) 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 following three 2-day treatments. Two of these patients subsequently died of acute rejection at 9 weeks and 10 weeks, respectively, after completion of ECP. The other 2 were without signs of rejection, one for 6 years and the other’s last report was 4 months after ECP ended. This small case series adds to the evidence provided by the prior 2 slightly larger studies.

Prevention of Rejection

An RCT by Barr and colleagues 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. To be eligible, participants needed adequate peripheral venous access and had to reside 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 2 consecutive days every 2 weeks in months 2 and 3; and 2 successive days every 4 weeks for months 4 to 6 for a total of 24 ECP procedures per patient. Primary endpoint of the study was the number and frequency of histologic acute rejection episodes. Pathologists were blinded to treatment assignment. Follow-up for the primary endpoint was 6 months; an additional 6 months of follow-up was completed to assess safety and survival.

Average number of acute rejection episodes per patient was statistically different, with 1.44 in the standard therapy group and 0.91 in the ECP group. 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 survival at 6 months or number of infections between the 2 groups. Time to a first rejection also did not differ between the groups. During the second 6 months of follow-up, there were no differences between the numbers of acute rejection episodes between the 2 groups; however, due to time management issues, institutions reverted to nonstandardized protocols during this time. The authors concluded that using ECP in addition to standard immunosuppressive therapy significantly reduced the risk of cardiac rejection without increasing the rate of infections. More long-term follow-up will be necessary to see the effects of a reduction of acute rejection on long-term graft function, the survival over time of the transplant recipient, and the development of graft vasculopathy.

**Lung**

**Acute Rejection**

Villanueva and colleagues reported in 2000 on a retrospective review of data on 14 transplants (7 bilateral lung, 6 single lung, 1 heart-lung) recipients 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 followed by once a month for the next 2 months for a total of 6 treatments. Four of 8 patients with initial BOS grade of 0 or 1 had improvement in BOS or stabilization of BOS after treatment. Mean survival after ECP was 14 +/- 12 months. Three of these patients received ECP during a concurrent episode of acute rejection. All 3 of these patients had complete resolution of the acute rejection following therapy. Another study published in 1999 completed 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 and colleagues published a single-center experience with ECP, which included 24 patients treated with ECP, 12 for recurrent acute rejection and 12 for BOS (see review in the next section). (14) Patients had biopsy-confirmed chronic acute rejection, defined as 2 or more biopsy-proven episodes of acute rejection prior to the start of ECP. The primary outcome measure was clinical stabilization of rejection after ECP. All but one patient had follow-up biopsies during treatment; 2 patients had an episode of biopsy-proven acute rejection. All patients with recurrent acute rejection experienced clinical stabilization after 12 cycles of ECP; none experienced BOS. Treatment was well-tolerated with no adverse events related to ECP reported. Median patient survival was 7.0 years (range: 3.0–13.6 years), the median patient survival post-ECP was 4.9 years (range: 0.5–8.4 years). However, these rates are for the 24 patients as a whole, not broken down by indication for ECP.

**Chronic Rejection Refractory to Corticosteroid/Refractory Bronchiolitis Obliterans Syndrome (BOS)**

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 ECP when reaching BOS stage greater or equal to 1. (15) ECP was performed on 2 successive days every 2 weeks during the first 3 months and every 4 weeks after until the end of therapy. ECP was stopped after a minimum of 3 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 6 months. FEV1 values at 3, 6, and 12 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 3 to 6 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.

Lucid and colleagues published a review of 9 patients treated with ECP between July 2008 and August 2009. Median follow-up was 23 months post-transplant (range: 9-93 months), and the median age was 38 years (range: 21-54 years). The primary indication for ECP was symptomatic progressive BOS, which failed prior therapy. (16) Patients were treated weekly with 2 sessions of pheresis for 3-4 weeks. Treatment then decreased in frequency to every 2 to
3 weeks, with the goal of getting treatment to every 4 weeks. Clinical response was defined as symptomatic improvement, decreased dependency on supplemental oxygen, and improvement in pulmonary function tests (PFTs). Sixty-seven percent (6 of 9) of patients responded to ECP after a median of 25 days. No ECP-related complications occurred in this series. As with prior studies, this report has no control group for comparison.

Morrell et al. published a retrospective case series of all lung transplant recipients treated with ECP for progressive BOS at Barnes-Jewish Hospital-Washington University. (17) Ninety-five percent of the patients had received a bilateral lung transplant and were BOS grade 3. The indication for ECP was progressive decline in lung function that was refractory to standard immunosuppressive therapy. Primary endpoint of the study 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 (6 treatments); and then monthly for the following 3 months (6 treatments, for a total of 24 treatments. Patients were followed from the time of lung transplantation to death or the end of the study (July 1, 2008). Median follow-up time was 5.4 years (range: 1.0–16.6 years). Sixty patients were followed; at the end of the study, 33 patients were still alive, with 4 deaths occurring early in the study. The majority of deaths were due to progression of respiratory failure, except for 1 death due to sepsis and 1 to graft failure. The mean rate of decline in forced expiratory volume in the first second of expiration (FEV1) in the 6 months prior to ECP was -116.0 mL per month; after ECP, the mean rate of decline decreased to -28.9 mL per month. The mean difference in the rate of decline was 87.1 mL (95% confidence interval [CI]: 57.3–116.9 mL per month). The rate of decline in lung function was reduced in 44 patients (78.6%), and lung function improved for 14 (25%) of these patients, with an increase in the FEV1 above pretreatment values. Through 12 months of follow-up, the mean improvement in FEV1 was 145.2 mL. Ten of 60 patients 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 limitation of this study is its retrospective nature and the lack of a control group for comparison. A majority of these patients had BOS grade 3, and therefore, may be different than patients with other grades. The statistical analysis was well-done, with robust methods to analyze the available data.

As noted above, Villanueva and colleagues retrospectively reviewed data on 14 transplant patients (7 bilateral lung, 6 single lung, one heart-lung) recipients who received ECP for BOS. (12) All patients were refractory to standard immunosuppressive therapy. ECP was administered every 2 weeks for 2 months, followed by once monthly therapy for the next 2 months, for a total of 6 treatments. Four of 8 patients with initial BOS grade of 0 or 1 had improvement in BOS or stabilization of BOS after treatment. Mean survival after ECP was 14 +/- 12 months. The 6 patients with initial BOS grade 2 or higher suffered progression of their
BOS after ECP. Mean survival after ECP was 14 +/- 10 months. Four of these patients died of chronic rejection, one of lung cancer. The remaining patient survived to retransplantation. Two of the 14 patients developed line-related sepsis, which was cleared with antibiotics and the removal of the vascular catheter.

Also as mentioned earlier, Benden and colleagues published a single-center experience with ECP, which accounted for 24 patients treated with ECP (12 for BOS and 12 for recurrent acute rejection, see previous section). (14) ECP was delivered once the BOS grade worsened, despite standard therapy. At the start of therapy, the distribution of BOS was as follows: BOS grade 1 (n=5), BOS grade 2 (n=2), BOS grade 3 (n=5). Before ECP, the decline in FEV1 was 112 mL per month, compared to 12 mL per month post-ECP, mean change in rate of decline of FEV1 of 100 (range: 28–171); however, ECP did not seem to have an effect on absolute FEV1 among this subgroup. Treatment was well-tolerated with no adverse events related to ECP reported. Median patient survival was 7.0 years (range: 3.0–13.6 years), the median patient survival post-ECP was 4.9 years (range: 0.5–8.4 years). However, these are for the 24 patients as a whole, not broken down by indication for ECP.

O’Hagan and colleagues published in 1999, case reports 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. (18) ECP was performed on 2 consecutive days twice a month until stabilization of the FEV1. 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. Grade of BOS was not reported. Case report data suffer from the lack of a control group, which allows for a measurement of the difference in outcomes between two treatments. In this case, that would be the difference in FEV1 between those receiving immunosuppressive therapies alone versus those being treated with immunosuppressive therapy combined with 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 and colleagues have published a series of papers on various potential applications of ECP for liver transplant patients. (19-21) The first paper is a retrospective review of 5 patients who
received liver transplants and ECP for biopsy-proven allograft rejection, in which the indications for ECP were recalcitrant ductopenic rejection with hepatitis C virus recurrence, corticosteroid-resistant acute rejection in 2 patients, severe acute rejection in a major ABO-incompatible liver graft, and severe acute rejection in a patient with a proven corticosteroid allergy. (19) ECP was performed twice a week for 4 weeks, then every 2 weeks for 2 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 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 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. (21) Patients were included if they were at risk of post-liver transplant renal impairment and neurologic complications, defined as having at least 1 of the following risk factors: a calculated glomerular filtration rate equal to or less than 50 mL/min at transplantation; severe ascites; history of more than one 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 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 8 days for 17 patients, while one patient remained CNI-free for 22 months. Acute rejection was higher but not significantly higher in the ECP group (5/18) versus in controls (3/18). One-, 6-, and 12-month survival rates were 94.4, 88.1, and 88.1%, respectively, for ECP recipients versus 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. (20) 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. (22) ECP was delivered weekly for 4 weeks, then every 2 weeks. Total treatment range was 2 to 12 treatments for more than 5-20 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 9 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, 3 patients were stable, and 4 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, 5 had improved function at 1 year, (23) 1 was stable at 25 months, (24) 5 were stable at 1 year, (23, 25) 7 were rejection-free at 2 to 5 years, (24) and one graft was lost. (25) Three patients did not have long-term outcome reports. (26, 27)

**Ongoing Clinical Trials**

A search of online site ClinicalTrials.gov in January 2012 found no registered clinical trials seeking to assess ECP as a treatment of solid-organ transplant rejection in any organ.

**Summary**
The 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 randomized trial was published in 1992 which enrolled 16 heart transplant patients. ECP in combination with immunosuppressive therapy had similar efficacy compared to immunosuppressive therapy alone, with fewer infections in the ECP group. This study was of a small size, and there was heterogeneity in the time from transplant to study entry. For prevention of rejection, there is a randomized trial from 12 clinical sites in which 33 patients were randomly assigned to immunosuppressive therapy and ECP and compared to 27 on immunosuppressive therapy alone. Differences between numbers of acute rejection episodes were statistically significant; however, there were no differences in survival at 6 months. Thus, the 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. While the data are from nonrandomized studies, a comparative study of 343 cardiac transplant patients in which 36 received ECP has been completed. The authors present data showing 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. While the results of this trial may be confounded by alterations in the immunosuppressive therapy regimen over time, they are consistent with the remainder of the literature for this indication showing a benefit of ECP in patients with recurrent or refractory cardiac rejection. Thus, the evidence to date, which consists of 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.

The evidence on the use of ECP in lung transplant recipients falls under two indications: acute rejection and chronic rejection refractory to corticosteroids/refractory bronchiolitis obliterans syndrome (BOS). The data for acute rejection are very limited and do not permit any conclusions. These are subsets of patients who have been pulled from a larger group because they were treated with ECP during a period 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 ECP in lung transplant literature focuses on treatment of refractory BOS. The primary limitations in these data are that they are nonrandomized with no control group. Further, the evidence is not entirely consistent, with some studies reporting ECP to be beneficial in those with early refractory BOS but not those with grade 2 or higher, which is in
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contrast to the largest series of 60 patients who responded well to ECP (nearly 60% of these patients were BOS grade 3). Prospective, randomized, controlled studies are necessary, and analyses should be stratified by BOS grade, as there is some preliminary evidence that ECP may work differently based on BOS grade at the start of therapy.

The evidence to date, which consists of small case series, is insufficient to permit conclusions concerning the effect of this procedure on health outcomes in lung transplant. 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, the evidence for the use of ECP is limited, and the research to date has been generated by one group in Italy. While there is one comparative (nonrandomized) study, this trial involves only 18 cases and 18 controls. There is a need for randomized, controlled trials. The effort in liver transplant patients has been on prevention of rejection with ECP. This question lends itself well to a randomized, controlled trial 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, the evidence for the use of ECP is sparse. There are a total of 42 patients whose treatment has been reported in the literature. The available evidence appears to 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 transplant. The 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
Extracorporeal photopheresis (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 (29): 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 a successful outcome in 67–84% of patients with grade III disease, but patients with grade IV disease rarely responded.

Treatment of GVHD in Pediatrics

The most recent and largest series was a retrospective review of 50 pediatric patients (age <18 years) with acute or chronic GVHD after an allogeneic stem-cell transplant unresponsive to 1-week steroid treatment. These patients were given ECP for a minimum of 10 treatments. ECP was administered 2-3 procedures per week 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 was seen after 4 weeks. Eighty-three percent (39/47) of patients had improvement in cutaneous acute GVHD, and 87.5% (7/8) saw improvement in the oral mucosa. Among patients with chronic GVHD, the greatest improvement was seen in the liver, with 100% (4/4) seeing improvement, followed by 95.6% (22/23) showing improvement of skin lesions. (30)

The literature also includes, but is not limited to, 2 small studies that focused on photopheresis for treatment of GVHD in children (31, 32) and one larger retrospective case series. The case series published in 2007 reported results of ECP for steroid-resistant GVHD in pediatric (aged 6–18 years) patients who had undergone hematopoietic stem-cell transplantation to treat a variety of cancers. (33) Patients had acute GVHD (aGVHD, n=15, stages II-IV) 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 during the second and third months, and then at monthly intervals for a further 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, a complete response (CR) was observed in 7 of 7 (100%) with grade II and 2 of 4 (50%) with grade III illness, whereas none with grade IV responded to ECP. In the group with cGVHD, 3 of 3 (100%) with limited disease had CR, compared to 1 of 7 (14%) with extensive disease who had CR; 5 of 7 (71%) of 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.

In the 2 smaller studies, 1 study, 8 children (aged 5–15 years) with refractory extensive chronic GVHD were treated with ECP and either oral 8-methoxypsoralen (8-MOP) or infusion of an 8-MOP solution into the pheresed lymphocytes. (31) Cutaneous status reportedly improved in 7 patients. Five patients stopped treatment, and 3 others decreased doses of immunosuppressive therapy. In addition, gut involvement resolved in all patients, and liver involvement resolved in 4 of 6 patients. Two years following discontinuation of photopheresis, 5 patients remained in remission without immunosuppressive therapy. Salvaneschi and colleagues reported on photopheresis results in refractory GVHD in 9 acute pediatric cases and in 14 chronic pediatric cases (aged 5.4–11.2 years). (32) In the acute GVHD cases, 7 of 9 experienced either partial response (PR) or complete response (CR), while in the chronic GVHD patients, 9 of 14 experienced either partial or complete remission.

These findings are also consistent with the current policy statements.

Treatment of GVHD in Adults

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. (34) 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 2-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.

Foss and colleagues reported results of a prospective (non-randomized) study of ECP in 25 patients who had extensive corticosteroid-refractory or corticosteroid-resistant chronic GVHD secondary to allogeneic stem-cell transplantation. (35) ECP was administered for 2 consecutive days every 2 weeks in 17 patients and once weekly in 8 until best response or stable disease was achieved. With a 9-month median duration (range 3–24 months) of ECP, 20 patients had improvement in cutaneous GVHD, and 6 had healing of oral ulcerations. ECP allowed cessation or reduction of immunosuppressive medication treatment in 80% of patients. Overall, improvement was reported in 71% of cases with skin and/or visceral GVHD and 61% of those deemed to be high-risk patients.
Greinix and coworkers reported findings from a Phase II (nonrandomized) study to evaluate the efficacy of intensified ECP as second-line therapy in 59 patients with post-stem cell transplant acute (grades II-IV), steroid-refractory GVHD. (36) ECP was initially administered on 2 consecutive days (1 cycle) at 1- to 2-week intervals until improvement was noted and thereafter every 2 to 4 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 cases with cutaneous manifestations, 61% with hepatic involvement, and 61% with gut involvement. A CR was noted 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 to 11% of those who did not respond completely. While 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 acute GVHD.

In 2008, Perfetti and colleagues reported on a retrospective review of 23 patients with corticosteroid-refractory acute GVHD, 10 grade II, 7 grade III, and 6 grade IV. (37) Median duration of ECP was 7 months (1–33 months) and median number of cycles per patient was 10. Complete responses were seen in 70%, 42%, and 0% of patients with GVHD grades II, III, and IV, respectively. Eleven patients (48%) survived and 12 died: 10 of GVHD and 2 of relapse of leukemia. Patients treated within 35 days from onset of GVHD had a higher but not statistically significant different response (83 vs. 47%, respectively; p=0.1). While these findings suggest that ECP may provide benefit for patients with refractory acute GVHD, they are limited by the small sample size and non-comparative nature of the study.

One study was published in 2010 by Shaughnessy and colleagues using ECP to prevent acute GVHD in patients undergoing standard myeloablative conditioning and allogeneic transplant. (38) ECP was administered prior to a standard conditioning regimen. Results were compared to historical controls from the Center for International Blood and Marrow Transplant Research (CIBMTR) database. Multivariate analysis indicated a lower rate of grade II-IV acute GVHD in patients receiving ECP. Adjusted overall survival at 1 year was 83% in the ECP group and 67% among historical controls (relative risk [RR]: 0.44; 95% confidence interval [CI]: 0.24-0.80). Additional prospective randomized trials are necessary to confirm these findings.

**Ongoing Clinical Trials**

A search of online site ClinicalTrials.gov in January 2012 found three ongoing randomized trials and one 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 endpoints 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.

Summary

The evidence for the use of extracorporeal photopheresis (ECP) for the treatment of graft-versus-host disease (GVHD) relates to both chronic and acute GVHD in pediatric and adult populations. The published literature is lacking randomized trials. The evidence consists of retrospective reviews and non-randomized comparisons. These data consistently show improvement in GVHD that is unresponsive to standard therapy and are consistent with the conclusions from the 2001 TEC Assessment. Additionally, there are 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 a cessation of treatment with corticosteroids and other immunosuppressive agents if there is a response to ECP. (24, 39, 40) Therefore, treatment of refractory chronic GVHD 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, this is considered investigational.

Practice Guidelines and Position Statements

There are no practice guidelines or position statements
### Autoimmune Disease

**Literature Review**

ECP for the treatment of autoimmune diseases was initially addressed by a 2001 TEC Assessment, which offered the following observations and conclusions. (41) A variety of autoimmune diseases were considered, including systemic sclerosis, pemphigoid, systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, rheumatoid arthritis, and type I diabetes. For all of these indications, the available evidence was insufficient to permit conclusions on outcomes. At the time, photopheresis had been most thoroughly studied as a treatment of scleroderma. However, the data on this indication include 1 single-blind randomized controlled trial (RCT) (42) and 3 small, uncontrolled series. While the randomized study reported positive outcomes in terms of skin manifestations, a number of methodologic flaws have been discussed in the literature, (43-45) including inadequate treatment duration and follow-up, excessive dropouts, a mid-study 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.

One clinical trial on diabetes was found for a subsequent update of the original policy through 2003. No clinical trials were found on photopheresis for other autoimmune diseases. For diabetes, Ludvigsson and colleagues reported a randomized, double-blind, controlled trial on photopheresis in 49 children with newly diagnosed type 1 diabetes. (46) A total of 40 children aged 10–18 years completed the study and were followed up 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 in the control group. Hemoglobin A1C results, a key clinical outcome in diabetes control, were not statistically different in the 2 groups.

In 2007, one small series was identified in which ECP was administered to treat immunorefractory relapsing-remitting multiple sclerosis in 5 patients. (47) ECP appeared safe and tolerable in these patients, with some evidence for a reduction in the relapse rate and symptom stabilization. However, the data are insufficient to alter the policy statement for this use of ECP.

In 2010, Sanli and colleagues published a retrospective report on 11 patients with drug-resistant autoimmune bullous diseases. (48) ECP was performed between January 2005 and January 2010. Eight of these patients had pemphigus vulgaris (PV), while the others had epidermolysis bullosa acquisita (EBA). Patients were treated on 2 consecutive days at 4-week intervals. Among the patients with PV, all experienced complete remission after 2-6 cycles, except one. Two patients with EBA had complete remission, while one patient had partial remission. Corticosteroids were reduced in all patients with PV. Decrease in the frequency of ECP resulted in progression of lesions for 3 patients with PV and in 2 of the patients with...
EBA. No adverse effects were observed. Randomized controlled trials are necessary to adequately assess the efficacy of ECP for patients with drug-resistant autoimmune bullous diseases.

Summary

The 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, or autoimmune bullous disorders 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 have limited the use of the data and for type 1 diabetes, no differences in hemoglobin A1C were observed between those treated with and without ECP. Therefore, treatment of autoimmune diseases with ECP is considered investigational.

Practice Guidelines and Position Statements

There are no practice guidelines or position statements.

T-Cell Lymphoma

Cutaneous T-Cell Lymphoma

Literature Review

Stage III/IV MF and Sezary Syndrome

The initial report on the use of ECP as therapy for cutaneous T-cell lymphoma (CTCL) was published by Edelson and colleagues. (49) Twenty-seven of 37 (73%) patients with otherwise resistant CTCL responded to the treatment, with an average 64% decrease in cutaneous involvement after 22 ± 10 weeks (mean ± SD). The responding group included 8 of 10 (80%) patients with lymph-node involvement, 24 of 29 (83%) with exfoliative erythroderma and 20 of 28 (71%) whose disease was resistant to standard chemotherapy. Side effects that often occur with standard chemotherapy, such as bone marrow suppression, gastrointestinal erosions, and hair loss, did not occur. These results showed that ECP is safe and effective in advanced, resistant CTCL. Subsequent results from numerous small, nonrandomized studies have been generally 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 (50-54)).

Together, these data provide the basis for several evidence-based guideline or consensus statements on the use of ECP in CTCL, (55-57) as well as the position of the National Cancer Institute (NCI) (Available online at: http://www.cancer.gov/cancertopics/pdq/treatment/mycosisfungoides/HealthProfessional/page
2). They consistently recommend 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. (34) In summary, OHTAC reported that there is 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 the quality, size, and heterogeneity in treatment regimens and diagnostic criteria of available clinical studies. 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.

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 (n=45) including retinoids and interferon-alpha (summarized in (58)). Many of these patients were refractory to numerous other therapies, including topical corticosteroids, interferon alfa, or whole-skin irradiation. Response rates (partial plus complete) in these studies ranged from 33% to 88% with monotherapy and 50% to 60% with ECP and adjuvant therapies. While these findings suggest 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 World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC). (59) 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 CTLC that progresses while receiving nonsystemic therapies, the relative lack of adverse events with ECP compared to other systemic treatments, and the good response rates often associated with ECP, ECP may provide outcome benefit as a technique for the treatment of patients with refractory or progressive early-stage CTCL. By contrast, because early-stage CTCL typically responds to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience a near-normal life expectancy.

Ongoing Clinical Trials

A search of online site clinicaltrials.gov in January 2012 did not find any ongoing randomized trials but did find a registered study 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.

**Summary**

The 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 while receiving nonsystemic therapies, the relative lack of adverse events with ECP compared to other systemic treatments, and the good response rates often associated with ECP, ECP may be considered medically necessary as a technique for the treatment of patients with refractory or progressive early-stage CTCL. By contrast, when early-stage CTCL does respond to less-invasive, topical therapies; patients whose disease remains quiescent under such treatments usually experience a 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**

**Literature review**

Between 1997 and 2005, Garben and colleagues treated 12 patients with refractory/relapsed disease with ECP. (60) 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. (61) 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, 6 had peripheral T-cell lymphoma (PTCL) (2 with angioimmunoblastic type, 4 with PTCL-NOS [not otherwise specified]), and 5 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. (62) Six courses were given over 3 weeks, followed by 1 course per week for 10 weeks. If at least a partial response was observed, treatment continued with 1 course per month until complete response, progression or disappearance of the peripheral clone for patients having a complete response. Response was evaluated after 6 induction courses, then after 10 courses and 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 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.

**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**

The National Comprehensive Cancer Network (NCCN) 2013 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 either with earlier stage mycosis fungoides with Sézary syndrome involvement or with disease that has failed multiple courses of topical skin-directed treatments (Available online at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf). NCCN does not address the use of EPC for peripheral T-cell lymphoma.

**V. Definitions**

**Autoimmune Disease** is a disease produced when the body's normal tolerance of the antigens on its own cells is disrupted.

**Graft-versus-host disease (GVHD)** refers to immunological injury suffered by an immunosuppressed recipient of a bone marrow transplant. The donated lymphoid cells (the "graft") attack the recipient (the "host"), causing damage to the skin, liver, and gastrointestinal tract.

**Lymphocyte** is a white blood cell responsible for much of the body's immune protection.

**Pheresis** refers to the removal of blood or other body fluids from a patient, separating certain elements (e.g., immunoglobulins, platelets, or red blood cells) and reinfusing the remaining elements into the patient.

**Psoralen** is one of a group of plant-derived chemicals that sensitize the skin to damage by ultraviolet light.
VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2014:

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<tr>
<td>C84.10 – C84.19</td>
<td>Sezary’s disease; code range</td>
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<tr>
<td>D89.810 – D89.813</td>
<td>Graft-versus-host disease; code range</td>
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<tr>
<td>T86.00 – T86.09</td>
<td>Complications of bone marrow transplant; code range</td>
</tr>
<tr>
<td>T86.20 - T86.298</td>
<td>Complication of heart transplant code range</td>
</tr>
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</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES


<table>
<thead>
<tr>
<th><strong>Policy Title</strong></th>
<th><strong>Extracorporeal Photopheresis (Formerly Extracorporeal Photopheresis After Solid-Organ Transplant and for Graft-versus-host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma)</strong></th>
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MEDICAL POLICY

<table>
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<tr>
<th>POLICY TITLE</th>
<th>EXTRACORPOREAL PHOTOPHERESIS (FORMERLY EXTRACORPOREAL PHOTOPHERESIS AFTER SOLID-ORGAN TRANSPLANT AND FOR GRAFT-VERSUS-HOST DISEASE, AUTOIMMUNE DISEASE, AND CUTANEOUS T-CELL LYMPHOMA)</th>
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Other sources

Centers for Medicare and Medicaid Services (CMS) CMS Manual System. Pub 100-03
Medicare National Coverage Determinations Transmittal 143, May 18, 2012. CMS
Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD) 110.4, Extracorporeal Photopheresis. Effective 4/30/12 CMS [Website]:

X. POLICY HISTORY

<table>
<thead>
<tr>
<th>MP 2.068</th>
<th>CAC 7/27/04</th>
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<tr>
<td></td>
<td>CAC 7/26/05</td>
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<tr>
<td></td>
<td>CAC 7/25/06</td>
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<td>CAC 7/31/07</td>
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<td></td>
<td>CAC 7/29/08</td>
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<tr>
<td></td>
<td>CAC 1/26/10 Added medical necessity indications to policy statement to include treating late-stage (III/IV) and early-stage (I/II) cutaneous T-cell lymphoma. References updated.</td>
</tr>
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<td></td>
<td>CAC 7/26/11 Added treatment of autoimmune bullous disorders and psoriasis to the investigational statement as per BCBSA policy. Revised policy title to match BCBSA policy title. Remainder of current CBC MP criteria already matched BCBSA policy.</td>
</tr>
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<td></td>
<td>Medicare variation added 5/22/12. Effective for claims with dates of service on or after April 30, 2012, CMS will cover extracorporeal photopheresis for the treatment of bronchiolitis obliterans syndrome (BOS) following lung allograft transplantation only when extracorporeal photopheresis is provided under a clinical research study that meets specific requirements to assess the effect of extracorporeal photopheresis for the treatment of BOS following lung allograft transplantation.</td>
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</tbody>
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**CAC 6/26/12** Consensus. No change to policy statement. References updated.

**CAC 3/26/13** Consensus review. References updated but no changes to the policy statements. FEP variation revised to refer to the FEP manual. (Coding reviewed-skb)

**CAC 1/28/14** Consensus review. Added statement indicating ECP is investigational for any other indications. Added rationale section. References updated.

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