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Extracorporeal Photopheresis (ECP)

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Related Policies (if applicable)
None

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Coverage

Organ Rejection after Solid Organ Transplant
Cardiac Allograft Rejection
Extracorporeal photopheresis (ECP) **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**.**

Lung Transplant Rejection
Extracorporeal photopheresis (ECP) **may be considered medically necessary** for treatment of bronchiolitis obliterans syndrome (BOS) or chronic lung allograft dysfunction (CLAD) when refractory to standard treatment.

Extracorporeal photopheresis **is considered experimental, investigational and/or unproven** in all other situations related to treatment or prevention of rejection in solid organ transplantation.

Graft-Versus-Host Disease

Acute

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 experimental, investigational and/or unproven** as a technique to treat acute GVHD that is either previously untreated or is responding to established therapies.

Chronic

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

Extracorporeal photopheresis **is considered experimental, investigational and/or unproven** as a technique to treat chronic GVHD that is either previously untreated or is responding to established therapies.

Autoimmune Diseases

Extracorporeal photopheresis **is considered experimental, investigational and/or unproven** as a technique to treat either 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's disease.

Cutaneous T-cell Lymphoma

Extracorporeal photopheresis **may be considered medically necessary** as a technique to treat:

- Late-stage (III/IV) cutaneous T-cell lymphoma (CTCL); or
- Early-stage (I/II) CTCL that is progressive and refractory to established non-systemic therapies.

Extracorporeal photopheresis **is considered experimental, investigational and/or unproven** as a technique to treat early-stage (I/II) CTCL that is either previously untreated or is responding to established non-systemic therapies.

Other

Extracorporeal photopheresis is **considered experimental, investigational and /or unproven** for all other indications.

Policy Guidelines

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 after standard immunosuppressive therapy.

There is no standard schedule for extracorporeal photopheresis (ECP), and reported schedules vary by the organ type. However, most reported cardiac and lung schedules initiate therapy with 2 consecutive days of ECP 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.

Graft-Versus-Host Disease
Methylprednisolone is considered first-line treatment of acute graft-versus-host disease (GVHD). For chronic GVHD, an alternating regimen of cyclosporine and prednisone is commonly used; other therapies include antithymocyte globulin, corticosteroid monotherapy, and cytotoxic immunosuppressive drugs such as procarbazine, cyclophosphamide, or azathioprine. Therefore, refractory disease is defined as GVHD that fails to respond adequately to a trial of any of these therapies.

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

Cutaneous T-Cell Lymphoma Staging
Cutaneous T-cell Lymphoma staging is based on the tumor, node, metastases (TNM) classification system (see Table 1).

Table 1. Cutaneous T-cell Lymphoma Staging

Stage	Tumor T, N, and M Categories
IA	T1N0M0
IB	T2N0M0
IIA	T1-2N1M1
IIB	T3N0-1M0
III	T4N0-1M0
IVA	T1-4N2-3M0
IVB	T1-4N0-3M1

Sézary Syndrome
According to the World Health Organization-European Organization for Research and Treatment of Cancer, Sézary syndrome is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in the skin, lymph nodes,

and peripheral blood. The International Society of Cutaneous Lymphomas recommends an absolute Sézary cell count of at least 1000 cells/mm3, in the presence of immunophenotypical abnormalities (CD4/CD8 ratio >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

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

1. The patient's 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-A (UVA) (320-400 nm wavelength) light at a dose of 1-2 J/cm^2; and
3. The light-sensitized lymphocytes are reinfused into the patient.

The use of ECP has been investigated for patients needing treatment for organ rejection after solid organ transplant, graft-versus-host disease (GVHD), autoimmune diseases, and T-cell lymphoma.

Organ Rejection Treatment After Solid Organ Transplant

The standard treatment for 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.

Although first approved for the treatment of cutaneous T-cell lymphoma, ECP has more recently been used as a supplement to conventional therapies in the area of solid organ transplantation. (1) Reports of the successful use of ECP in human cardiac transplant recipients were published in 1992 (3, 4) and use in other transplant patients followed. Although the specific mechanism of action of ECP is unknown, the reinfusion of treated leukocytes seems to specifically suppress the patient's immune response to the donor organ, although maintaining the body's ability to respond to other antigens. (5) 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. (6)

<u>Chronic Lung Allograft Dysfunction</u>

Chronic lung allograft dysfunction (CLAD) is an umbrella term that defines a significant decline in lung function following lung transplantation in the absence of other identifiable causes. CLAD is defined as a substantial and persistent decline (≥20 percent) in forced expiratory volume in one second (FEV_1) when compared with the posttransplant baseline, which is itself defined as the average of the two maximal posttransplant FEV_1 values that are at least three weeks apart. (2)

The International Society for Heart and Lung Transplantation (ISHLT) 2019 guidelines define four phenotypes of CLAD, which should be identified at the time of CLAD onset based on the observed physiologic and radiographic patterns. Measurements of FEV_1, forced vital capacity (FVC), total lung capacity (TLC), and a chest computed tomography (CT) are required for an adequate phenotype classification. (2)

Table 2. Chronic Lung Allograft Dysfunction (CLAD) Phenotypes (2)

ISHLT Classification	Spirometry[a]	Lung Volumes[a]	Chest CT Findings[b]
BOS	FEV_1 ≤80% baseline FEV_1/FVC <0.7	TLC >90% baseline	No persistent opacities or fibrotic changes
RAS	FEV_1 ≤80% baseline FEV_1/FVC >0.7	TLC <90% baseline	Persistent opacities or fibrotic changes
Mixed	FEV_1 ≤80% baseline FEV_1/FVC <0.7	TLC <90% baseline	Persistent opacities or fibrotic changes
Undefined or unclassified	FEV_1 ≤80% baseline and any other pattern		

BOS: bronchiolitis obliterans syndrome; CT: computed tomography; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ISHLT: International Society for Heart and Lung Transplantation; RAS: restrictive allograft syndrome; TLC: total lung capacity.

[a] Phenotypes of CLAD based on spirometry, lung volumes, and CT findings. Baseline refers to the posttransplant baseline spirometry and lung volumes; for FEV_1 this is defined as the average of the two maximal posttransplant FEV_1 values (performed at least three weeks apart). The TLC baseline should be the posttransplant TLC associated with baseline FEV_1.

[b] For the purposes of CLAD phenotyping, CT findings of concern are persistent (lasting greater than three months) reticulations, ground-glass opacities, or consolidations consistent with possible fibrosis. New persistent pleural thickening is also a qualifying feature.

Bronchiolitis Obliterans Syndrome (BOS)

Bronchiolitis obliterans syndrome (BOS) is the predominant phenotype of CLAD and presents clinically as obstructive lung disease detected as a decline in FEV_1 from the posttransplant baseline, associated with a FEV_1/FVC <70 percent, with no restriction and no persistent fibrotic-like opacities. The ISHLT registry reports that 50% of lung transplant recipients develop BOS by five years after transplant and 74% after ten years. (2)

Symptoms associated with the development of BOS are nonspecific and include dyspnea on exertion and a nonproductive cough. Individuals may present with symptoms resembling an

upper respiratory infection. Some may simply present with subtle increases in exertional dyspnea and a decline in spirometry. The more advanced stages of BOS are associated with dyspnea at rest and in some patients, symptoms, and signs of bronchiectasis, including a productive cough and an abnormal chest examination with end-inspiratory pops and squeaks. It is unusual for BOS to begin less than three months after transplant, and the onset is more indolent than that of acute rejection. (2)

Treatment for BOS may include a variety of therapies, however there are no well-established protocols to guide therapy. Potential treatments include adding long-term azithromycin (if not already used for prevention), changing the maintenance immunosuppressive medications, extracorporeal photopheresis, total lymphoid irradiation, plasmapheresis, and other therapies to target antibodies to the allograft (immune globulin, rituximab, proteasome inhibitors), and inhaled cyclosporine. (2)

Graft-Versus-Host Disease

Given that GVHD is an immune-mediated disease, ECP can be used to treat GVHD after a prior allogeneic cell transplant. In fact, GVHD can be categorized in 2 ways: 1) As an acute disease, occurring within the first 100 days after the infusion of allogeneic cells; or 2) as a chronic disease, which develops sometime after 100 days. Acute GVHD is commonly graded from I to IV, ranging from mild disease, which is characterized by a skin rash without involvement of the liver or gut, to grades III and IV, which are characterized by generalized erythroderma, elevated bilirubin levels, or diarrhea. Grade III acute GVHD is considered severe, and 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.

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 ultraviolet light in the presence of agent 8-methoxypsoralen. 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 autoantibodies, it is unknown how these antibodies are related to the pathogenesis of the disease. As discussed in this policy, photopheresis is not associated with consistent changes in autoantibody levels.

T-Cell Lymphoma

<u>Cutaneous T-Cell Lymphoma</u>

According to the National Cancer Institute (NCI), cutaneous T-cell lymphoma (CTCL) is a neoplasia of malignant T lymphocytes that initially presents as skin involvement. Cutaneous T-

cell lymphoma 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, 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.

Cutaneous T-cell lymphoma 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 panniculitis T-cell lymphoma. In addition, a number of benign or very indolent conditions can be confused with mycosis fungoides, further complicating diagnosis.

Mycosis fungoides typically progresses from an eczematous patch/plaque stage, covering less than 10% of the body surface (T1), to a plaque stage, covering 10% or more of the body surface (T2), and finally to tumors (T3) that frequently undergo necrotic ulceration. Sézary syndrome is an advanced form of mycosis fungoides with generalized erythroderma (T4) and peripheral blood involvement (B1) at presentation. The cytologic transformation from a low-grade lymphoma to a high-grade lymphoma sometimes occurs during the course of these diseases and is associated with 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 of time (mean, 2-10 years) as waxing and waning cutaneous eruptions. The prognosis of patients with mycosis fungoides or Sézary syndrome is based on the extent of disease at presentation and its stage. Lymphadenopathy and involvement of peripheral blood and viscera increase in likelihood with worsening cutaneous involvement and define poor prognostic groups. Median survival after diagnosis varies according to stage. Median survival in patients with stage IA disease exceeds 20 years, with most deaths in this group typically unrelated to mycosis fungoides. In contrast, median survival in patients with stage III through stage IV disease is less than 5 years; more than 50% of these patients die of their disease.

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

Regulatory Status

Two photopheresis systems (Therakos; now Mallinckrodt) were approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. Both systems are approved for use in UVA irradiation treatment, in the presence of the photoactive drug 8-methoxypsoralen, 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:

- UVAR® XTS Photopheresis System (FDA approved in 1987).
- CELLEX® (FDA approved in 2009).

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

The use of either photopheresis system or UVADEX® for other conditions is off-label. FDA product code: LNR.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical uses of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

GRAFT REJECTION AFTER SOLID ORGAN TRANSPLANT

Clinical Context and Therapy Purpose

The purpose of administering extracorporeal photopheresis (ECP) in individuals who are heart, lung, liver, or kidney transplant recipients who experience graft rejection (acute or recurrent) refractory to medical therapy or who require prophylaxis to avoid graft rejection is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations
The relevant populations of interest include the following:
- Heart transplant recipients who experience acute or recurrent graft rejection or receive preventive measure to avoid graft rejection;
- Lung transplant recipients who experience acute graft rejection or have bronchiolitis obliterans syndrome (BOS);
- Liver transplant recipients who experience graft rejection; and
- Kidney transplant recipients who experience graft rejection.

Interventions
The therapy being considered is ECP.

The number of treatments varies by medical condition and treatment response. Each procedure can take between 2 and 4 hours.

Comparators
The following practices are currently being used to treat transplant recipients: medical management, immunosuppression, and dialysis (for kidney only).

Outcomes
The general outcomes of interest are overall survival (OS), recurrence of graft failure, reduction in immunosuppressive agents, and treatment-related adverse events (e.g., infections).

Follow-up varies by treatment response and medical condition. The clinical follow-up to assess treatment response may take up to 6 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Heart Transplant
Acute Graft Rejection
An RCT compared the efficacy of ECP with corticosteroids for the treatment of heart transplant rejection. (3) Costanzo-Nordin et al. (1992) enrolled 16 heart transplant patients and randomly assigned them to ECP (n=9) or corticosteroids (n=7). Recipients of orthotopic transplanted hearts were eligible if an 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 milligrams/day (mg/d) oral prednisone for 3 days or 1 gram/day (1 g/d) IV (intravenous) methylprednisolone for 3 days at the discretion of the managing physician. If on the seventh day EMB had not demonstrated improvement in rejection grade, treatment was repeated. If rejection grade persisted after retreatment, patients were given oral methotrexate 10-mg at weekly intervals for 8 weeks. Participants were followed for a mean of 6.2 months, and all participants completed the trial. Those who participated in ECP treatment generally only received the treatment once. The only reason for multiple treatments was if an inadequate number of cells had been treated; in those cases, 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 at a mean of 7 days (range, 5-20 days) after ECP and 8 days (range, 6-67 days) 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 that major trial limitations included a small sample size and a wide range in time from transplant to study entry. They concluded that ECP and corticosteroids 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 and/or Refractory Graft Rejection

Carlo et al. (2014) reported their experience with ECP in 20 pediatric heart transplant recipients between 1990 and 2012 at a U.S. University. (7) Patients who had transplants at a median age of 12.7 years (range, 0.3-18.5 years) and received their first ECP treatment at a median age of 15.3 years (range, 7.3-31 years) were included. Indications for ECP included rejection with hemodynamic compromise (i.e., HC rejection), rejection without HC, and prophylaxis. One- and 3-year survival rates after ECP were 84% and 53%, respectively. Survival outcomes were worse in noncompliant patients compared with compliant patients.

Kirklin et al. (2006) conducted a comparative study of 343 heart transplant recipients. (8) 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 anti-donor 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 the incidence of HC rejection or death from rejection (rejection death). 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 (relative risk reduction, 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 a higher baseline risk of HC rejection or rejection death. Changes in maintenance immunotherapy over time might have confounded the results because 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.

Maccherini et al. (2001) 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 events 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.

Dall'Amico et al. (2000) reported on a case series of 11 heart transplant recipients with recurrent rejection. (10) 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 ultraviolet-A radiation 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 intravenous pulse of 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 days). 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 the failure of both ECP and IV corticosteroids. The 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 were adequate; however, the study was small and lacked a comparison group.

Prophylaxis to Prevent Graft Rejection

A small, international, non-comparative pilot study by Gökler et al. (2022) investigated ECP for the prevention of rejection after cardiac transplant in high-risk patients. (11) The study included 28 patients (13 with high risk of infection due to infection at the time of transplant, 7 bridging to transplant via extracorporeal membrane oxygenation, and 8 with a high risk of malignancy). Six months of prophylactic ECP was initiated immediately postoperatively, along with a reduced-intensity immunosuppressive protocol. Results demonstrated a 1-year survival of 88.5% (25 of 28 patients). The causes of death were infectious complications in 3 patients and recurrence of malignancy in 1 patient. After a median follow up of 23.7 months, the OS was 84% (n=24). While patients who received ECP were not directly compared to patients who did not, a non-ECP cohort transplanted during the study period (n=172) had an estimated 1-year survival rate of 93%.

An RCT by Barr et al. (1998) investigated ECP for the prevention of rejection after cardiac transplant. (12) Sixty consecutive adult cardiac transplant recipients at 12 clinical sites (9 in U.S., 3 in Europe) were randomly assigned to both immunosuppressive therapy plus ECP (n=33) or immunosuppressive therapy alone (n=27). Standard immunosuppressive therapy consisted of cyclosporine, azathioprine, and prednisone. Entry criteria included 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 endpoint was 6 months; an additional 6 months of follow-up was completed to assess safety and survival.

After 6 months, the mean number of acute rejection episodes per patient was statistically greater in the standard therapy group (1.4) than in the ECP group (0.9) (p=.04). 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 patients had none, 14 had one, 3 had two, and 3 had three or more. These differences were statistically significant (p=.02). There were no differences in 6- or 12-month survival rates, 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 non-standardized protocols during this interval. The authors concluded that ECP plus standard immunosuppressive therapy significantly reduced the risk of cardiac rejection without increasing the risk of infection. More long-term follow-up is necessary to assess the effects of a reduction of acute rejection on long-term graft function, the survival of the transplant recipient, and the development of graft vasculopathy.

Section Summary: Graft Rejection after Heart Transplant

Acute Graft Rejection

For acute rejection, a 1992 randomized trial enrolled 16 heart transplant recipients. The use of ECP in combination with immunosuppressive therapy had efficacy similar to immunosuppressive therapy alone, with fewer infections in the ECP group. This trial was small, and time from transplantation to study entry varied.

Recurrent and/or Refractory Graft Rejection
The use of ECP for recurrent 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 HC rejection or rejection death (relative risk reduction, 0.29). A reduction in HC rejection or rejection death was observed through 2 years of follow-up. Although trial results might have been confounded by improvements in immunosuppressive therapy regimens over time, they are consistent with case series for this indication, which have suggested a benefit of ECP in patients with recurrent or refractory cardiac rejection. Thus, the evidence to date provides consistent evidence for a beneficial effect of ECP for cardiac transplant patients with rejection refractory to standard therapy.

Prophylaxis to Prevent Graft Rejection
For prevention of rejection, a single RCT from 12 clinical sites randomized 33 patients to immunosuppressive therapy plus ECP and 27 patients to immunosuppressive therapy alone. Differences between the numbers of acute rejection episodes were statistically significant; however, there was no difference in survival at 6 months. A non-comparative prospective pilot study found 1-year and OS rates of 88.5% and 84%, respectively, among 28 high-risk cardiac transplant patients who received prophylactic ECP immediately postoperatively along with a reduced-intensity immunosuppressive protocol. Overall, the current evidence does not permit conclusions on the utility of ECP for the prevention of acute cardiac graft rejection. Studies with more patients and longer follow-up are needed.

Lung Transplant
Acute Graft Rejection – Retrospective Studies
Villanueva et al. (2000) retrospectively assessed 14 transplant recipients (7 bilateral lung, 6 single lungs, 1 heart-lung) who received ECP for bronchiolitis obliterans syndrome (BOS). (13) All patients were refractory to standard immunosuppressive therapy. Extracorporeal photopheresis 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 of 0 or 1 BOS had an improvement in BOS or stabilization after treatment. The mean survival after ECP was 14 months. Three of 4 patients received ECP during a concurrent episode of acute rejection; all 3 patients had complete resolution of acute rejection after treatment.

Case Series
Benden et al. (2008) 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. Pooled median patient survival post-ECP treatment was 4.9 years (range, 0.5-8.4 years); however, these data were not specific to the group being treated for acute rejection.

Another series published by Salerno et al. (1999) reported on 2 patients with histologic reversal of concurrent acute rejection after treatment with ECP. (15)

Bronchiolitis Obliterans Syndrome (BOS) Refractory to Corticosteroids

Systematic Review

Benden et al. (2017) conducted a systematic review of studies (randomized, nonrandomized, or observational) that evaluated second-line/salvage treatment of chronic lung allograft dysfunction. (16) Eleven studies of ECP were included (8 publications, 3 meeting abstracts), but only 2 studies had a comparator group (Jaksch et al. 2012 and Del Fante et al. 2015) consisting of individuals with less severe bronchiolitis obliterans syndrome. (18, 17) The systematic review concluded that ECP improved mean survival time and survival rates up to 5 years compared to pulsed high-dose methylprednisolone and tacrolimus-based immunosuppression. However, the low quality of evidence (Level C; consensus of expert opinion or small studies, retrospective studies, and/or registries) supporting this conclusion limits the strength of recommendation for ECP to IIb (usefulness/efficacy is less well-established by evidence/opinion). Well-conducted randomized trials would be needed to support a stronger recommendation.

Prospective Studies

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). (18) 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. Extracorporeal photopheresis was administered on 2 successive days every 2 weeks during the first 3 months and then every 4 weeks until the end of therapy. The use of ECP was discontinued after a minimum of 3 months if lung function decreased significantly. If forced expiratory volume in 1 second (FEV_1) improved or stabilized, ECP was continued for a minimum of 6 months. Change in FEV_1 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 FEV_1 for more than 1 year after initiation of ECP, and 12% showed improvement for only 3 to 6 months. The FEV_1 stabilized in 31% of patients and declined in 39%. Kaplan-Meier method analysis showed a significant difference in responders and non-responders in survival and the need for transplant. Compared with patients with BOS and 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 also was twice as long in the ECP group (1839 days versus 947 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.

Retrospective Studies

Leroux et al. (2022) retrospectively analyzed 25 lung transplant recipients at a single institution with mild to moderate refractory BOS after standard treatment; of these patients, 12 were treated with ECP. (19) In the ECP group, double-lung transplant, single-lung transplant, and heart and lung transplant were received by 9, 2, and 1 patient, respectively. At ECP initiation, 11 patients were graded BOS stage 1 and 1 patient was graded BOS stage 2. Extracorporeal photopheresis was performed on 2 consecutive days every 2 weeks during the first 6 months, and was progressively extended to every 4, 6, and 8 weeks thereafter, depending on both FEV_1 variations and patient treatment tolerance. Within the first year of ECP initiation, 75% of patients demonstrated an improvement in FEV_1. Within 24 months of ECP initiation, 5 patients displayed an increase in FEV_1 compared with ECP onset (62.5%), 2 remained stable, and 1 experienced a decrease in FEV_1. Among non-ECP-treated control patients who were still alive at the time of analysis (n=13), 6 experienced a persistent decline and 7 remained stable over time. When comparing ECP-treated patients versus control decliners and control non-decliners separately, the risk of an additional drop in FEV_1 of at least 20% significantly differed among the groups (p=.003), with a trend toward a lower risk in the ECP-treated group when compared with control decliners only (p=.05).

Del Fante et al. (2015) retrospectively evaluated 48 patients who received ECP for chronic lung allograft dysfunction and lack of response to conventional therapy. (17) The cohort that received ECP was compared to 58 controls who did not receive ECP. Up to 9 years of data were available. The ECP group had statistically lower mortality (41.7% vs. 72.4%; p=.002) and failures over time (66.7% vs. 93.1%; p=.001) compared to controls. In a univariate analysis, experiencing fast decline in the 6 months before ECP initiation was associated with a higher failure rate (HR, 4.9; 95% CI, 2.03 to 11.82; p<.001).

Greer et al. (2013) retrospectively analyzed 65 patients treated at a single institution with ECP for chronic lung allograft dysfunction, defined as deteriorating FEV_1 due to BOS, as well as reduced total lung capacity and broncho-alveolar lavage neutrophilia. (20) Fifty-one patients (78%) had undergone double lung transplant, 9 patients (14%) had undergone a single-lung transplant, and 5 (8%) patients had undergone heart-lung transplant. The median time to chronic lung allograft dysfunction (CLAD) diagnosis was 3 years (interquartile range [IQR], 2-5 years). Patients had progressed (≥10% decline in FEV_1) on first-line azithromycin. At ECP initiation, 35 (54%) patients were graded BOS stage 3; 21 patients (32%) were BOS stage 2; and 9 patients (14%) were BOS stage 1 or 0p (potential BOS). Extracorporeal photopheresis was administered every 2 weeks for 3 months; subsequent treatments were administered not more than 8 weeks apart to maintain stabilized graft function. The 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 FEV_1, considered treatment response; 27 patients (42%) experienced no change in FEV_1; and 30 patients (46%) experienced a 10% or greater decline in FEV_1, considered progressive disease. Median

progression-free survival was 13 months (interquartile range, 10-19 months) among responders and 4 months (interquartile range, 3-6 months) among those who did not respond. This study was retrospective and lacked a control group.

Lucid et al. (2011) retrospectively evaluated 9 patients treated with ECP between July 2008 and August 2009. (21) Median follow-up was 23 months post-transplant (range, 9-93 months), and median age was 38 years (range, 21-54 years). 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 lacked a 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 a University based hospital. (22) 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. Extracorporeal photopheresis 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 2008). Median follow-up was 5.4 years (range, 1.0-16.6 years). At the end of the study, 33 patients were still alive; 4 deaths occurred early in the study. Most deaths were due to the progression of respiratory failure, except for one death due to sepsis and another to graft failure. In the 6 months before ECP, the mean rate of decline in FEV_1 was -116.0 mL/mo.; after ECP, the mean rate of decline was -28.9 mL/mo. (mean difference, 87.1 mL; 95% confidence interval [CI], 57.3 to 116.9 mL). The rate of decline in lung function slowed in 44 patients (79%), and lung function improved (increase in FEV_1 above pretreatment values) in 14 patients (25%). Through 12 months of follow-up, mean improvement in FEV_1 was 145.2 ml. Ten (17%) 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 limitations of this study were its retrospective design and the 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 noted, Benden et al. (2008) published a single-center study of 24 patients treated with ECP (12 for BOS and 12 for recurrent acute rejection). (14) Extracorporeal photopheresis 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 FEV_1 was 112 mL/month compared with 12 mL/month after ECP (mean difference, 100 mL/month; range, 28-171 ml/month). However, ECP did not seem to affect absolute FEV_1. Treatment was well-tolerated with no ECP-related adverse events reported. Median patient survival was 7.0 years (range, 3.0-13.6 years); median patient survival post-ECP was 4.9 years (range, 0.5 to 8.4 years). However, results were pooled and not specific to the 12 patients with BOS.

Also as noted, Villanueva et al. (2000) retrospectively reviewed outcomes of 14 transplant recipients (7 bilateral lung, 6 single lung, 1 heart-lung) who received extracorporeal photopheresis for BOS. (13) All patients were refractory to standard immunosuppressive therapy. Extracorporeal photopheresis 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. Six patients with initial BOS grade 2 or higher suffered progression of their BOS after ECP. Four of these patients died of chronic rejection, and 1 died of lung cancer. The remaining patient survived to re-transplantation. Two of the 14 patients developed line-related sepsis, which cleared with antibiotic therapy and catheter removal.

Section Summary: Organ Rejection After Lung Transplant

Acute Graft Rejection

Data on acute graft rejection are very limited and do not permit any conclusions on the utility of ECP for this indication. Use of ECP in this population needs a prospective, randomized trial focused specifically on the treatment for acute rejection.

Bronchiolitis Obliterans Syndrome Refractory to Corticosteroids

The bulk of the evidence for ECP in lung transplantation focuses on the treatment of refractory BOS. The primary limitations of these data are they derive from nonrandomized and uncontrolled studies. Further, the evidence is inconsistent, 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 because there is some evidence that ECP efficacy may vary by BOS grade.

Liver Transplant

The published evidence on the use of ECP in liver recipients is from one group in Italy. Urbani et al. (2004-2008) published a series of articles on various potential applications of ECP for liver transplant recipients. (23-25) The first, from 2004, retrospectively reviewed 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. (23) Extracorporeal photopheresis was performed twice weekly for 4 weeks, then every 2 weeks for 2 months, and then once monthly. Extracorporeal photopheresis 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 study, from 2007, was a nonrandomized comparative assessment of 36 patients (18 active treatment, 18 historical matched controls) who received ECP to delay the introduction of calcineurin inhibitors (CNI) to avoid CNI toxicity. (24) 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 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. Extracorporeal photopheresis was initiated during the first week post-transplant; 2 different systems (Therakos, 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 rates were 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 improved management of liver transplant patients in the early transplant phase, delayed CNI introduction, and lowered CNI-related mortality. This study was not randomized and assessed a small number of patients.

The third case series (2008) was a report on 3 fields of interest for ECP as prophylaxis of allograft rejection in liver transplant patients: (25)

- 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 (which 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.

Section Summary: Organ Rejection after Liver Transplant

In liver transplantation, evidence for the use of ECP is limited, and research to date has been generated by a single group. Although there is a comparative (nonrandomized) study, it involved only 18 cases and 18 historical controls. The focus in liver transplantation has been on prevention of rejection with ECP; this would be best addressed by an RCT comparing

immunosuppressive therapy alone with immunosuppressive therapy plus ECP. Current evidence does not permit conclusions on the utility of ECP for liver transplant patients experience graft rejection.

Kidney Transplant

The largest reported group of renal patients to receive ECP was at a hospital Australia. Jardine et al. (2009) published a prospective case series of 10 patients treated with ECP for recurrent and/or refractory rejection after renal transplantation. (26) Extracorporeal photopheresis was delivered weekly for 4 weeks, then every 2 weeks. The total number of treatments ranged from 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 or 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 lacked a comparison group. Renal biopsies were not used to document therapeutic response.

Additional evidence comes from case reports on 32 patients with renal transplants. 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, (27) 1 was stable at 25 months, (28) 5 were stable at 1 year, (27, 29) 7 were rejection-free at 2 to 5 years, (28) and 1 graft was lost. (29) Long-term outcomes were not reported for 3 patients. (30, 31)

Section Summary: Graft Rejection after Kidney Transplant

For renal transplant recipients, the evidence base on the use of ECP to treat graft rejection is sparse. While studies have consistently reported evidence of benefit from ECP for those with refractory graft rejection, 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 plus ECP to address whether there is an additional benefit from ECP for patients with refractory graft rejection after renal transplantation.

GRAFT-VERSUS-HOST DISEASE

Clinical Context and Therapy Purpose

The purpose of administering ECP in individuals who have acute or chronic GVHD refractory to medical therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are adults and children with acute or chronic GVHD refractory to medical therapy.

Interventions
The therapy being considered is ECP.

The number of treatments varies by medical condition and treatment response. Each procedure can take between 2 and 4 hours.

Comparators
The following practices are currently being used to treat GVHD: medical management and immunosuppression.

Outcomes
The general outcomes of interest are overall survival (OS), recurrence of GVHD, reduction in immunosuppressive agents, and treatment-related adverse events (e.g., infections).

Follow-up varies by treatment response and medical condition. Clinical follow-up to assess treatment response may take up to 6 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Acute Graft-Versus-Host Disease and Chronic Graft-Versus-Host Disease
Systematic Reviews
Abu-Dalle et al. (2014) published a systematic review of prospective studies in patients with steroid-refractory acute or chronic GVHD. (32) Relevant literature was searched through February 2013, and the following items were identified: 1 RCT in patients with chronic GVHD, (33) and 8 cohort studies in patients with acute and/or chronic GVHD (N=323). In meta-analyses, the overall response rates for acute and chronic GVHD treated with ECP were 69% and 64%, respectively. In both acute GVHD and chronic GVHD, the overall response rates were highest in cutaneous disease (84% and 71%, respectively) followed by gastrointestinal disease (65% and 62%, respectively). Rates of immunosuppression discontinuation were 55% and 23% for acute GVHD and chronic GVHD, respectively. Statistical heterogeneity for most meta-analyses was high (I^2>60%).

Case Series

Hautmann et al. (2013) reported on a cohort of 62 patients with acute GVHD (n=30) or chronic GVHD (n=32) at a single institution in Germany. (34) For acute GVHD, 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 (50%) patients achieved complete response (CR) or partial response (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 chronic GVHD, ECP was administered on 2 consecutive days weekly until improvement, then biweekly for 3 to 4 weeks, and then monthly. At 3 months, 14 (44%) patients achieved CR or PR (2 [6%] complete). Five (29%) of 17 patients who continued ECP beyond 3 months had data available and decreased steroid dose by 50% or more from baseline.

Ussowicz et al. (2013) reported on 21 patients with steroid-refractory or steroid-dependent, grade 3 or 4 acute (n=8) or chronic (n=13) GVHD in Poland. (35) For acute GVHD, 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 chronic GVHD, ECP was administered on 2 consecutive days every 2 weeks for 14 weeks and then monthly for up to 8 weeks. The four-year overall survival rate was 67.7%.

Treatment in Pediatrics - Acute and Chronic Graft-Versus-Host Disease

Systematic Reviews

Three Cochrane reviews, two by Weitz et al. (2014) and one by Buder et al. (2022), assessed acute GVHD (36) and chronic GVHD (37, 38) in pediatric patients. Literature searches were performed in September 2012 and January 2021, and no RCTs were found. Reviewers 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." (37, 38)

Prospective Studies

Kitko et al. (2022) evaluated the efficacy and safety of a single-device ECP (Therakos CellEx Photopheresis System) in 29 children with steroid-refractory acute GVHD. (39) This was a prospective, single-arm, open-label, multicenter study conducted at 14 study centers in the U.S. and Europe. During the treatment period, patients received ECP with methoxsalen in conjunction with the Therakos CellEx Photopheresis System 3 times per week for weeks 1 to 4, followed by twice weekly for weeks 5 to 12. Sixteen of the 29 patients achieved an overall response by the end of week 4 without the need for next-line systemic treatment (primary endpoint) (odds ratio, 55.2%; 95% CI, 35.7 to 73.6). Similar trends were seen in 2 additional sensitivity analysis that excluded patients with incomplete organ system assessment data at baseline (n=18 remaining) and incomplete organ system assessment data at baseline or week 4 (n=11 remaining). The most common treatment-related adverse event was nausea (8 occurrences among 4 children).

Retrospective Studies

A retrospective review by Perotti et al. (2010) assessed 73 pediatric patients (age, <18 years) with acute or chronic GVHD after an allogeneic cell transplant unresponsive to 1 week of

steroid treatment. (40) Patients received ECP for a minimum of 10 treatments. Extracorporeal photopheresis 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. Extracorporeal photopheresis was discontinued if no improvement (≥50% clinical and laboratory response) was seen after 4 weeks. Of 47 patients with acute GVHD, 39 (83%) of 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.

The literature also includes small studies that focused on ECP for treatment of acute and chronic GVHD in children (41, 42) and a larger retrospective study. The retrospective study by Berger et al. (2007) reported results of ECP for steroid-resistant GVHD in pediatric patients (age, 6-18 years) who had undergone hematopoietic cell transplantation for a variety of cancers. (43) Patients had acute GVHD (n=15, stages 2 to 4) or chronic GVHD (n=10, 7 deemed extensive) that had not responded 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. The use of 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 acute GVHD, complete response (CR) occurred in all 7 (100%) 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 chronic GVHD, CR occurred in all 3 (100%) of patients with limited disease and 1 (14%) of 7 patients with extensive disease. Five (71%) of 7 patients with extensive chronic GVHD had no response to ECP. Adverse effects of ECP were generally mild in all cases.

One of the 2 smaller studies reported on 8 children (age, 5 to 15 years) with refractory chronic GVHD who received ECP and either oral 8-methoxypsoralen or infusion of an 8-methoxypsoralen solution into the apheresed lymphocytes. (41) Cutaneous status improved in 7 patients. Five patients stopped treatment; 3 patients 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 ECP, 5 patients remained in remission without immunosuppressive therapy. Salvaneschi et al. (2001) reported on the use of ECP for refractory GVHD in 23 pediatric patients (age, 5.4-11.2 years). (42) Seven (78%) of 9 patients with acute GVHD experienced either PR or CR. Nine (64%) of 14 patients with chronic GVHD experienced PR or CR.

Kozlov et al. (2021) also performed a retrospective analysis of pediatric patients with steroid-refractory chronic GVHD (n=42). (44) Patients received ECP for 2 consecutive days bimonthly, with a reduction in frequency according to response. Complete and partial response rates were 17% and 57%, respectively. Overall response rates by organ involvement were 75% for skin (n=24), 73% for mucous membranes (n=16), 80% for liver (n=8), 80% for gut (n=4), 22% for lungs (n=2), and 67% for joints (n=2). After a median follow-up of 774 days, 5-year OS and

progression-free survival were 57% (95% CI, 39% to 72%) and 56% (95% CI, 37% to 72%), respectively.

Treatment in Adults - Acute Graft-Versus-Host Disease

Systematic Reviews

Zhang et al. (2015) in China reported on a systematic review of prospective studies of ECP for acute GVHD. (45) Literature was searched through September 2014, and 7 cohort studies were included (total N=121). In meta-analyses, pooled overall and CR rates were both 71%. Statistical heterogeneity was considered not high for both results (I^2<50%). The response rate was highest for cutaneous disease (86%), although a funnel plot indicated the presence of publication bias.

Randomized Study

Mehta et al. (2020) reported findings of a single-center, open-label, randomized phase 2 trial with an adaptively randomized Bayesian design that compared prednisone with versus without ECP in patients with acute GVHD. (46) In total, 81 patients were randomized to steroids with ECP (n=51) or steroids alone (n=30). The primary endpoint was treatment success, defined as survival and in remission without need for further therapy and on <1 mg/kg at day 28 and <0.5 mg/kg on day 56 of steroids. Most patients had grade II disease (86% and 97% treated with ECP and steroids alone, respectively). At the end of the trial, the ECP arm met the predefined criteria for the Bayesian predictive probability that ECP had a higher success than steroid monotherapy (>0.80). After 81 patients were enrolled, the statistical threshold was met in favor of ECP for the primary endpoint with a probability of 81.5%. Treatment success occurred in 65% and 53% of patients treated with ECP and steroids only, respectively.

Nonrandomized Studies

Solh et al. (2023) retrospectively assessed the effect of ECP on overall survival among 79 patients with steroid-refractory acute GVHD. (47) Compared to a control group (n=24) that did not receive ECP, OS (p=.011) and disease-free survival (p=.008) were higher in patients who received ECP. Hospital length of stay was significantly shorter in the ECP group (20 vs. 38 days; p=.02). In a multivariable analysis, receipt of ECP was associated with OS (HR, 0.39; 95% CI, 0.20 to 0.75; p=.005) and disease-free survival (HR, 0.32; 95% CI, 0.17 to 0.61; p<.001). Among the patients who received ECP, half achieved CR, 15% improved, and 35% either died or failed to respond. Among the patients who did not receive ECP, only 29% achieved CR.

Greinix et al. (2006) reported on findings from a phase 2 (nonrandomized) study of intensified ECP as second-line therapy in 59 patients with post stem cell transplant, steroid-refractory, acute GVHD (grade 2-4). (48) Extracorporeal photopheresis 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 patients with cutaneous manifestations, 61% with hepatic involvement, and 61% with gut involvement. Further, CR occurred in 87% and 62% of patients with exclusively skin or skin and liver involvement, respectively; only 25% with GVHD of skin, liver, and gut involvement and 40% with skin and gut involvement obtained a CR of GVHD with

ECP therapy. The probability of survival was 59% among patients with CR to ECP, compared with 11% of those who did not achieve CR. Although these results would suggest ECP may be beneficial in the treatment of acute GVHD, the small sample size, few study details in the report, and lack of a standard treatment comparator group limit inferences about the clinical efficacy of ECP for acute GVHD.

Retrospective Studies

Batgi et al. (2021) reported results from a retrospective observational series of 75 patients with steroid-refractory, acute GVHD from 4 transplant centers in Turkey who were treated with ECP. (49) Patients received ECP on 2 consecutive days every 2 weeks until resolution of signs and symptoms, and ECP was reduced to 1 treatment every 2 weeks with complete response. Most patients had grade 3 (28.0%) or grade 4 (46.7%) disease. After a median follow-up of 6 months (range, 1 to 68 months), the overall response rate was 42.7%. Median OS was 5 months for non-responders and 68 months for responders.

Jagasia et al. (2013) reported on an international, retrospective comparative analysis of non-concurrent cohorts who received ECP (n=57) or anticytokine therapy (inolimomab or etanercept; n=41) for steroid-refractory acute GVHD (grade 2 or higher). (50) Extracorporeal photopheresis 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). The 2-year overall survival rate was 59% in the ECP group and 12% in the anticytokine group (p not reported).

A single-center cohort of 9 patients with grade 2 or 3 steroid-refractory acute GVHD was reported by Rubegni et al. (2013). (51) Extracorporeal photopheresis was administered on 2 consecutive days weekly until improvement and then every 2 weeks; treatment was then tapered as tolerated. At 3 months, the 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 (67%) patients showed a complete skin response. Five (83%) of 6 patients with liver and gastrointestinal tract involvement had CRs. All patients developed chronic GVHD, 7 (78%) while still receiving ECP.

Shaughnessy et al. (2010) studied ECP to prevent acute GVHD in 62 patients undergoing standard myeloablative conditioning and allogeneic transplant. (52) Extracorporeal photopheresis 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, 3 or 4 acute GVHD among patients who received ECP. Adjusted OS at 1 year was 83% in the ECP group and 67% among historical controls (relative risk=0.44; 95% CI, 0.24 to 0.80).

Perfetti et al. (2008) reported on a retrospective review of 23 patients with corticosteroid-refractory acute GVHD (n=10 grade 2; n=7 grade 3; and n=6 grade 4). (53) The median duration of ECP was 7 months (range, 1-33 months) and the median number of cycles per patient was

10. Complete responses were seen in 70%, 42%, and 0% of patients with GVHD grades 2, 3, and 4, respectively. Eleven (48%) patients survived, and 12 (52%) died (10 of GVHD and 2 of relapse of leukemia); 83% 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 would suggest that ECP may provide benefit for patients with refractory acute GVHD, there is a lack of certainty in the findings due to the small sample size and the non-comparative study design.

Chronic Graft-Versus-Host Disease

Systematic Reviews

Malik et al. (2014) published a systematic review evaluating ECP for steroid-refractory chronic GVHD. (54) Literature was searched through July 2012 and 18 studies were selected (4 prospective, including 1 RCT [2008] (33) and 14 retrospective; total n=595 patients). In meta-analyses, overall responses and CR rates were 64% and 29%, respectively. The pooled response rate was highest for cutaneous disease (74%) and lowest for lung disease (48%). Statistical heterogeneity was high for all of these results (I^2>60%).

The Ontario Health Technology Advisory Committee (OHTAC; 2006) published the results of a systematic review of ECP for the treatment of refractory chronic GVHD. (55) The OHTAC reported that there was low-quality evidence that ECP improves response rates and survival in patients with chronic GVHD unresponsive to other forms of therapy. Limitations in the literature on ECP for treating refractory GVHD mostly pertained to study quality and size and heterogeneity in both treatment regimens and diagnostic criteria. The OHTAC did, however, recommend a 2-year 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. There is no current evidence on the OHTAC website of an update.

Prospective Studies

Foss et al. (2005) reported results of a prospective (nonrandomized) study of ECP in 25 patients who had extensive corticosteroid-refractory or corticosteroid-resistant chronic GVHD after allogeneic stem-cell transplantation. (56) Extracorporeal photopheresis 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 to 24 months), 20 patients had improvement in cutaneous GVHD, 6 had oral ulcer healing, and 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 cases deemed to be high-risk patients.

Dignan et al. (2014) reported on a series of 38 consecutive adults who received ECP for chronic GVHD. (57) Median patient age was 47 years (range, 18-73 years). Patients had steroid-refractory or steroid-dependent disease or were intolerant of corticosteroids. Thirty-six (95%) patients were receiving immunosuppressive therapy. Extracorporeal photopheresis was administered on 2 consecutive days every 2 weeks until PR was achieved and was then reduced to monthly treatments. Of note, PR was defined as a minimum 50% improvement from baseline in 1 organ and no evidence of GVHD progression in other organs. Median time from transplant

to first ECP was 1.7 years (range, 0.25-7.25 years). Response was assessed after 6 months. Nineteen (50%) patients 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 Graft-Versus-Host-Disease Symptom Scale and Dermatology Life Quality 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 another had an increase in red cell transfusion requirements which was attributed to ECP treatments.

Retrospective Studies

Kansu et al. (2022) reported results of a retrospective observational study that included 53 patients with steroid-refractory chronic GVHD who were treated with ECP at a single-center in the U.S. (58) Extracorporeal photopheresis was performed using the Therakos UVAR XTS and CELLEX closed-circuit systems. All patients initiated ECP therapy with 2 treatments weekly for 4 weeks followed by 2 consecutive days every 2 weeks as a maintenance therapy; tapering and discontinuation of ECP therapy was done at the discretion of the treating physician. Results demonstrated that after a median duration of ECP of 14 months (range, 3.0-56 months), CR was seen in 9 (17%) patients and PR was seen in 34 (64.2%) patients; the overall response rate was 81.2%. The OS at 1 and 3 years was 84.9% and 36.7%, respectively.

Dal et al. (2021) reported results from a retrospective observational series of 100 patients with steroid-refractory chronic GVHD who were treated with ECP at 4 transplant centers in Turkey. (59) Patients received ECP on 2 consecutive days every 2 weeks until resolution of signs and symptoms, and ECP was reduced to 1 treatment every 2 weeks with CR. Most patients had severe (grade ≥3) disease (77%), and 50% had involvement of more than 1 organ. Overall and CR rates were 58% and 35%, respectively. After a median follow-up of 13 months (range, 1-261 months), OS was 41%. Median OS was 2 months for non-responders and 91 months for responders (p<.001).

Section Summary: Graft-Versus-Host Disease

Evidence for the use of ECP for the treatment of GVHD assesses acute GVHD and chronic GVHD in pediatric and adult populations. The published literature includes systematic reviews, a randomized study, prospective and retrospective studies, and case series. These data have consistently shown improvements in GVHD unresponsive to standard therapy. Additionally, there is a lack of other treatment options for these patients; adverse events of ECP are minimal; and, if there is a response to ECP, some patients are able to reduce or discontinue treatment with corticosteroids and other immunosuppressive agents. (28, 60, 61)

AUTOIMMUNE DISEASES

Clinical Context and Therapy Purpose

The purpose of administering ECP in individuals who have autoimmune diseases is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations
The relevant populations of interest are individuals with autoimmune diseases (e.g., 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's disease).

Interventions
The therapy being considered is ECP.

The number of treatments varies by medical condition and treatment response. Each procedure can take between 2 and 4 hours.

Comparators
The following practices are currently being used to treat autoimmune diseases: medical management and immunosuppression.

Outcomes
The general outcomes of interest are overall survival, recurrence of graft failure, reduction in immunosuppressive agents, and treatment-related adverse events (e.g., infections).

Follow-up varies by treatment response and medical condition. The clinical follow-up to assess treatment response may take up to 6 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Photopheresis has been most thoroughly studied as a treatment for scleroderma, in a single-blind RCT by Rook et al. (1992) (62) 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, (63-65) 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 on other small case series regarding systemic sclerosis conflict with each other and do not resolve the difficulties in interpreting the randomized trial.

Scleroderma (Systemic Sclerosis)
In addition to the RCT by Rook et al. (1992) previously discussed, (62) a cohort study by Papp et al. (2012) enrolled 16 patients from a single institution in Hungary who had diffuse cutaneous systemic sclerosis. (66) Extracorporeal photopheresis 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.

Multiple Sclerosis
Cavaletti et al. (2006) published a small case series of 5 patients with immunorefractory relapsing-remitting multiple sclerosis who received ECP. (67) Extracorporeal photopheresis appeared safe and tolerable in these patients, with some evidence for a reduction in the relapse rate and symptom stabilization. However, this case series is insufficient to support conclusions on the use of ECP for multiple sclerosis.

Type 1 Diabetes
An RCT on the use of ECP to treat diabetes was published by Ludvigsson et al. (2001). (68) This double-blind RCT assessed 49 children with newly diagnosed type 1 diabetes. Forty children (age, 10-18 years) completed the trial and were followed for 3 years. All received standard treatment with insulin therapy and diet, exercise, and self-management education. Of these patients, 19 received active ECP treatment with oral 8-methoxypsorslen, and 21 received placebo tablets and sham pheresis. Hemoglobin A_{1c} level did not differ statistically between groups.

Bullous Disorders
Sanli et al. (2010) retrospectively assessed 11 patients with drug-resistant autoimmune bullous diseases. (69) Extracorporeal photopheresis was performed between 2005 and 2010. Patients were treated on 2 consecutive days at 4-week intervals. Of 8 patients with pemphigus vulgaris, 7 (87.5%) experienced CR after 2 to 6 cycles. Of 3 patients with epidermolysis bullosa acquisita, 2 (67%) had CR and 1 (33%) had PR. All patients with pemphigus vulgaris reduced corticosteroid dose. Decrease in the frequency of ECP resulted in progression of lesions for 3 patients with pemphigus vulgaris and 2 patients with epidermolysis bullosa acquisita. No adverse events were observed. Prospective RCTs are necessary to adequately assess the efficacy of ECP for patients with drug-resistant autoimmune bullous diseases.

Severe Atopic Dermatitis
Some patients with atopic dermatitis do not respond to standard treatments and require immunosuppression with traditional (e.g., systemic corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate) or biologic (e.g., alefacept, rituximab, intravenous immunoglobulin, infliximab, omalizumab) agents for chronic disease. Rubegni et al. (2013)

reported on 7 patients and summarized previous case series and case reports of patients with varying disease severity who were treated with ECP. (70) Of 81 total patients, 69 (85%) were considered responders to ECP. Wolf et al. (2013) subsequently published a case series of 10 adults with severe, refractory atopic dermatitis of at least 1-year duration. (71) Extracorporeal photopheresis 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 standard deviation baseline 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 standard deviation Scoring of Atopic Dermatitis was 54.5 (22.8), a statistically significant improvement (p=0.015) of uncertain clinical significance. Improvements in quality-of-life measures were not statistically significant.

Crohn's Disease

Patients with steroid-dependent Crohn's 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's disease in clinical remission (Crohn's Disease Activity Index, <150). (72) Other immunosuppressive treatments were tapered and discontinued before ECP initiation and steroid tapering. Extracorporeal photopheresis was administered on 2 consecutive days every 2 weeks for 24 weeks. Steroids were tapered as tolerated during this 24-week period. Nineteen (61%) patients completed 24 weeks of treatment; 7 (23%) patients achieved steroid-free remission at week 24 (the primary end point), and 20 (65%) patients, maintained remission with a 50% or greater reduction in steroid dose from baseline. Three (10%) patients maintained steroid-free remission after 48 weeks of ECP (frequency decreased to monthly after week 24), and 3 others who discontinued steroids experienced mild disease (Crohn's Disease Activity Index, <220) at 48 weeks of ECP. One catheter-related complication was reported.

Section Summary: Autoimmune Disorders

Evidence for the use of ECP for the treatment of autoimmune diseases, including scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, multiple sclerosis, diabetes, autoimmune bullous disorders, severe atopic dermatitis, and Crohn's 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 limits applicability of the data. In the type 1 diabetes trial, no difference in hemoglobin A_{1c} levels were observed between those treated with and without ECP.

CUTANEOUS T-CELL LYMPHOMA

Clinical Context and Therapy Purpose

The purpose of administering ECP in individuals who have cutaneous or non-cutaneous T-cell lymphomas is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with cutaneous or non-cutaneous T-cell lymphomas.

Interventions
The therapy being considered is ECP.

The number of treatments varies by medical condition and treatment response. Each procedure can take between 2 and 4 hours.

Comparators
The following practices are currently being used to treat those with cutaneous or non-cutaneous T-cell lymphomas: medical management and immunosuppression.

Outcomes
The general outcomes of interest are overall survival, reduction in immunosuppressive agents, and treatment-related adverse events (e.g., infections).

Follow-up varies by treatment response and medical condition. The clinical follow-up to assess treatment response may take up to 6 months. For advance-stage disease, long-term follow-up is out to 5 years based on survival rates. For early-stage disease, follow-up extends beyond 20 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Advanced-Stage (III or IV) Cutaneous T-Cell Lymphoma
Systematic Reviews
The Ontario Health Technology Advisory Committee (OHTAC) (2006) published the results of a systematic review of ECP for the treatment of erythrodermic cutaneous T-cell lymphoma (CTCL). (55) The OHTAC reported that there was low-quality evidence that ECP improves response rates and survival in patients with CTCL 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 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. There is no current evidence on the OHTAC website of an update.

Nonrandomized Studies

The initial report on the use of ECP as therapy for CTCL was published by Edelson et al. in 1987. (73) Twenty-seven (73%) of 37 patients with otherwise resistant CTCL responded, with a mean 64% decrease in cutaneous involvement after a mean of 22 weeks. Responders included 8 (80%) of 10 patients with lymph node involvement, 24 (83%) of 29 with exfoliative erythroderma, and 20 (71%) of 28 whose disease was resistant to standard chemotherapy. Adverse events of standard chemotherapy, such as bone marrow suppression, gastrointestinal erosions, and hair loss, did not occur.

Knobler et al. (2012) reanalyzed these data using current response criteria and reported no change in overall response rate. (74) 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 overall survival was 9 years from diagnosis and 7 years from the start of ECP (the mean age at study entry was 57 years [range, 24 to 80 years]). 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. (75-80) These data have informed several evidence-based guidelines and consensus statements on the use of ECP in CTCL. (81-83) The National Cancer institute (NCI) has consistently recommended ECP as first-line treatment for patients with stage III or IV CTCL. (84)

<u>Early Stage (I or II) Cutaneous T-Cell Lymphoma</u>

Between 1987 and 2007, data were reported from at least 16 studies including 124 patients with CTCL in early stages IA, IB, or II who were treated with ECP alone (n=79) or in combination with other agents (e.g., retinoids and interferon-alfa [n=45]). (85) 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 suggested that ECP may provide benefit in early stage CTCL, none of the studies were randomized or comparative. Furthermore, many preceded universal acceptance of standardized elements of classification and diagnosis of CTCL, such as those proposed by the World Health Organization and the World Health Organization-European Organization for Research and Treatment of Cancer. (86) 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 non-systemic 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 benefit as a treatment for patients with refractory or progressive early stage CTCL. In contrast, because early-stage CTCL typically responds to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience near-normal life expectancy.

Section Summary: Cutaneous T-Cell Lymphoma

Advanced-Stage (III or IV) CTCL

A systematic review of small case series has shown that some patients with stages III or IV CTCL who have failed therapy may benefit from ECP and have improved survival rates.

Early-Stage (I or II) CTCL

Given the unfavorable prognosis for patients with early-stage CTCL that progresses on non-systemic 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 as a treatment for patients with refractory or progressive early-stage CTCL.

Summary of Evidence

Graft Rejection after Solid Organ Transplant

Heart Transplant

For individuals who are heart transplant recipients who experience acute graft rejection refractory to immunosuppression who receive extracorporeal photopheresis (ECP), the evidence includes a small randomized controlled trial (RCT). Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The small RCT, while suggesting similar outcomes for ECP and corticosteroids, is insufficient to permit conclusions on the utility of ECP. Studies with more patients and longer follow-up are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are heart transplant recipients who experience recurrent and/or refractory graft rejection who receive ECP, the evidence includes a comparative study and small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence is consistent on the beneficial effect of ECP for cardiac transplant patients with graft rejection refractory to standard therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are heart transplant recipients who require prophylaxis to prevent graft rejection who receive ECP, the evidence includes a small RCT and a prospective pilot study. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The small randomized trial is insufficient to permit conclusions on the utility of ECP. The pilot study was non-comparative and evaluated outcomes in high-risk cardiac transplant patients. Studies with more patients and longer follow-up are needed. The evidence

is insufficient to determine that the technology results in an improvement in the net health outcome.

Lung Transplant
For individuals who are lung transplant recipients who experience acute graft rejection who receive ECP, the evidence includes a small retrospective study and small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence is very limited and any conclusions drawn lack certainty. A prospective, randomized trial is needed specifically evaluating the treatment of patients with acute graft rejection. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are lung transplant recipients with bronchiolitis obliterans syndrome (BOS) refractory to corticosteroids who receive ECP, the evidence includes a prospective study and numerous retrospective analyses. Relevant outcomes are OS, change in disease status, and treatment-related mortality and morbidity. Studies have shown inconsistent results across BOS grades. Prospective, RCTs are necessary with analyses stratified by syndrome grade. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Liver Transplant
For individuals who are liver transplant recipients who experience graft rejection and receive ECP, the evidence includes a small nonrandomized study, a retrospective study, and a case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence does not permit conclusions on the utility of ECP in this population. There is a need for RCTs comparing immunosuppressive therapy alone with immunosuppressive therapy with ECP. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Kidney Transplant
For individuals who are kidney transplant recipients who experience recurrent graft rejection who receive ECP, the evidence includes a small prospective study and numerous case reports. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence does not permit conclusions on the effect of ECP on net health outcome. Prospective RCTs, comparing immunosuppressive therapy with immunosuppressive therapy using ECP and examining histologic confirmation of treatment response, are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

<u>Graft-Versus-Host Disease (GVHD)</u>
For individuals who have acute or chronic GVHD refractory to medical treatment who receive ECP, the evidence includes systematic reviews, a randomized study, retrospective studies, and case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence has consistently shown that ECP reduces the

incidence of GVHD that is unresponsive to standard therapy. Additionally, there is a lack of other treatment options for these patients; adverse events related to ECP are minimal; and, if there is a response to ECP, patients may be able to reduce or discontinue treatment with corticosteroids and other immunosuppressive agents. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Other Indications, Not Related to Solid Organ Transplant

Autoimmune Disease

For individuals who have autoimmune diseases (e.g., 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's disease) who receive ECP, the evidence includes isolated RCTs, small prospective and retrospective studies, and case reports. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The current literature assessing the various autoimmune diseases is not sufficiently robust to support conclusions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Cutaneous T-Cell Lymphoma

For individuals who have advanced-stage (stage III or IV) cutaneous T-cell lymphoma (CTCL) who receive ECP, the evidence includes a systematic review and numerous small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Evidence from these small case series has shown a favorable response to ECP treatment and an increase in survival in a proportion of these patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have refractory or progressive early-stage (stage I or II) CTCL who receive ECP, the evidence includes a systematic review. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Given the unfavorable prognosis for patients with early-stage CTCL that progresses on non-systemic therapies, the relative lack of adverse events with ECP compared with other systemic treatments, and the good response rates often observed with ECP, this therapy is an option for those with refractory or progressive early-stage CTCL. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

Lung Transplant

International Society for Heart and Lung Transplantation

A 2019 document from the International Society for Heart and Lung Transplantation addressed the use of ECP in patients with chronic lung allograft dysfunction/bronchiolitis obliterans syndrome. (87) The guideline listed ECP as a therapeutic option and stated that ECP may be most beneficial in patients with a slow decline in forced expiratory volume in 1 second (FEV_1) and increased neutrophilia on bronchoalveolar lavage. ECP is less likely to reduce disease

progression in patients with rapidly declining FEV_1, lack of significant neutrophilia, or restrictive allograft syndrome.

American Society for Apheresis
In 2023 the American Society for Apheresis published evidence-based guidelines for the use of ECP in the treatment of BOS and CLAD. These guidelines indicate that ECP has been used in the context of severe, refractory BOS, with efficacy demonstrated by FEV1 stabilization or improvement. The optimal duration of ECP for treatment of BOS is unknown. In published studies, the number of treatment cycles for ECP ranged between 6 and 24. If clinical stabilization occurs with ECP, long-term continuation may be warranted to maintain clinical response. (Category II, Grade 1C Recommendation) (88)

Graft-Versus-Host Disease (GVHD) (Acute)
American Society of Blood and Marrow Transplantation
In 2012, evidence-based recommendations from the American Society of Blood and Marrow Transplantation (now the American Society for Transplantation and Cellular Therapy) advised that ECP cannot be considered superior to horse antithymocyte globulin for treatment of acute GVHD. (89) This conclusion was based on older studies. (53, 90)

Acute and Chronic GVHD
European Society for Blood and Marrow Transplantation
In 2024, the European Society for Blood and Marrow Transplantation published updated prophylaxis and management guidelines for acute and chronic GVHD. (91) The guidelines state that while there is no standard second-line treatment for both acute and chronic GVHD, ECP is listed as therapy for use for second-line treatment. The guideline does comment that not enough data exists to compare the efficacy of different second-line treatments.

Cutaneous T-Cell Lymphoma
National Comprehensive Cancer Network
National Comprehensive Cancer Network guidelines on primary cutaneous lymphomas (v.1.2025) lists the use of ECP as a category 2A treatment alone or in combination with other agents 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. The guidelines add that ECP may be more appropriate as systemic therapy in patients with or at risk of blood involvement (B1 or B2). (92)

National Cancer Institute
The National Cancer Institute lists ECP (alone or in combination with total-skin electron-beam radiation) as a phototherapeutic option for patients with stage III or IV Sézary syndrome or erythrodermic mycosis fungoides. (84)

Medicare National Coverage
Solid Organ Transplants

Effective 2006, the Centers for Medicare & Medicaid Services (CMS) concluded that ECP is reasonable and necessary for persons with "acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment." (93)

Effective 2012, CMS also provided coverage for ECP 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 certain conditions. (93)

Graft-Versus-Host Disease
Effective 2006, CMS provided coverage of ECP for patients with chronic GVHD "whose disease is refractory to standard immunosuppressive drug treatment." (93)

Autoimmune Disorders
There are no national coverage decisions on the use of ECP for the treatment of autoimmune disease.

Cutaneous T-Cell Lymphoma
Effective 1988, CMS provided coverage for ECP as "palliative treatment of skin manifestations of cutaneous T-cell lymphoma that has not responded to other therapy." (93)

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Solid organ transplants			
NCT02181257	Extracorporeal Photopheresis for the Management of Progressive Bronchiolitis Obliterans Syndrome in Medicare-Eligible Recipients of Lung Allografts	280	Dec 2028 (ongoing)
Graft-versus-host-disease (GVHD)			
NCT00637689	Improving Outcomes Assessment in Chronic GVHD	601	Feb 2026 (ongoing)
NCT01460914	Outcomes of Cutaneous T-Cell Lymphoma and Chronic GVHD in Patients Treated with Extracorporeal Photopheresis (ECP)	100	Oct 2050 (ongoing)
CTCL			
NCT01460914	Outcomes of Cutaneous T-Cell Lymphoma and Chronic GVHD in Patients Treated with Extracorporeal Photopheresis (ECP)	100	Oct 2050 (ongoing)

NCT05680558	THERAKOS® CELLEX Photopheresis System as an Interventional Therapy for the Treatment of Early Stage CTCL (Mycosis Fungoides), an Open-label, Single-arm, Multi-center, Phase II Study	74	Jul 2026 (recruiting)
NCT05157581	Open Label, Single-cohort, and Single-center Phase II Study Evaluating Tumor-specific Immunity After Extracorporeal Photopheresis in Patients With Sézary Syndrome at Single-cell Resolution	15	Dec 2026 (recruiting)
Diabetes			
NCT05413005	Efficacy of Extracorporeal Photopheresis (ECP) in the Treatment of Type 1 Diabetes Mellitus (OPERA)	10	Jun 2025 (ongoing)
Multiple Sclerosis			
NCT05168384	Safety and Efficacy of Extracorporeal Photopheresis (ECP) in the Treatment of Multiple Sclerosis (PHOMS)	45	Jun 2025 (ongoing)
Systemic Sclerosis			
NCT04986605	The Effectiveness of ECP in Diffuse Cutaneous Systemic Sclerosis	15	Jun 2027 (ongoing)
Unpublished			
Solid organ transplants			
NCT05721079	Prophylactic Use of Extracorporeal Photopheresis (ECP) After Lung Transplantation	62	Dec 2022
GVHD			
NCT03204721	Prevention of Graft-versus-host Disease in Patients Treated With Allogeneic Stem Cell Transplantation: Possible Role of Extracorporeal Photopheresis	158	Apr 2021

NCT: national clinical trial; No: number; CTCL: cutaneous T-cell lymphoma; GVHD: graft-versus-host disease.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36522
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
10/15/2025	Document updated with literature review. Coverage unchanged. Reference 88 and 91 added; others removed/revised.
03/15/2024	Document updated with literature review. The following changes were made to Coverage: Added: Lung Transplant Rejection: Extracorporeal photopheresis (ECP) may be considered medically necessary for treatment of bronchiolitis obliterans syndrome (BOS) or chronic lung allograft dysfunction (CLAD) when refractory to standard treatment. References 2 and 3 added.
02/01/2024	Document updated with literature review. Coverage unchanged. References 10, 15, 16, 18, 37, 38, 46, 57, 86 added; some removed; others revised.
07/15/2022	Reviewed. No changes.
01/01/2022	Document updated with literature review. Coverage unchanged. Reference 38, 40, 42 and 51 added, others updated.
01/01/2021	Document updated with literature review. Coverage unchanged. Reference 69 added; some removed; others revised.
09/01/2020	Reviewed. No changes.

05/01/2019	Document updated with literature review. Coverage unchanged. No new references added.
04/15/2018	Reviewed. No changes.
04/01/2017	Document updated with literature review. Coverage unchanged.
02/15/2016	Reviewed. No changes.
03/15/2015	Document updated with literature review. The following changes have been made to the coverage section: Graft-Versus-Host Disease (GVHD) has been divided into Acute and Chronic statements. Acute GVHD has changed to be considered medically necessary when listed criteria are met. The following two additional examples of Autoimmune Diseases have been added to the experimental, investigational and/or unproven statement: severe atopic dermatitis and Crohn's disease. The following statement has been added: Extracorporeal photopheresis is considered experimental, investigational and /or unproven for all other indications.
03/15/2012	Document updated with literature review, and completely revised. Title was changed from Extracorporeal Photophoresis, and subject matter was expanded, with the following statements added to Coverage: Extracorporeal photopheresis (ECP) may be considered medically necessary: 1. To treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment; 2. Treatment of late-stage (III/IV) cutaneous T-cell lymphoma; or 3. Treatment of early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies. Extracorporeal photopheresis (ECP) is considered experimental, investigational and unproven for all other indications including, but not limited to: 1. Treatment or prevention of rejection in solid-organ transplantation (other than specified above); 2. Treatment of acute graft-versus-host disease or chronic graft-versus-host disease that is either previously untreated or is responding to established therapies; 3. Treatment of early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or is responding to established nonsystemic therapies; Treatment of 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.
03/01/2009	Revised/updated entire document
01/01/2007	Revised/updated entire document
12/01/2006	Revised/updated entire document
10/01/2004	New medical document
