8.01.36	Extracorporeal Photopheresis		
Original Policy Date:	February 13, 2002	**Effective Date:**	January 1, 2024
Section:	8.0 Therapy	**Page:**	Page 1 of 36

Policy Statement

Organ Rejection After Solid Organ Transplant

I. Extracorporeal photopheresis may be considered **medically necessary** to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.

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

Graft-Versus-Host Disease Acute

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

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

Chronic

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

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

Autoimmune Diseases

VII. Extracorporeal photopheresis is considered **investigational** 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, autoimmune bullous disorders, severe atopic dermatitis, or Crohn's disease.

Cutaneous T-Cell Lymphoma

VIII. Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat late-stage (III or IV) cutaneous T-cell lymphoma.

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

X. Extracorporeal photopheresis is considered **investigational** as a technique to treat early-stage (I or II) cutaneous T-cell lymphoma that is either previously untreated or responsive to established nonsystemic therapies.

Other

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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 (ie, ECP on 2 consecutive days) weekly for acute GVHD and every 2 weeks for chronic GVHD. Treatment duration is based on clinical response (see 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 PG1).

Table PG1. 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.

Coding

There is a specific code that describes extracorporeal photopheresis:

- **36522**: Photopheresis, extracorporeal

Description

Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory procedure that involves the following 3 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 is added to the lymphocyte fraction, which is then exposed to ultraviolet-A (320-400 nm wavelength) light at a dose of 1 to 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.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 ultraviolet-A 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

Background

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 infections also are affected. This can, in turn, lead to serious infections, including opportunistic infections.

Although first approved for the treatment of cutaneous T-cell lymphoma (CTCL), extracorporeal photopheresis (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[2,3,] and use in other transplant patients followed. Although the specific mechanism of action of ECP is unknown, the reinfusion of treated leukocytes seems specifically to suppress the patient's immune response to the donor organ, although maintaining the body's ability to respond to other antigens.[4,] The specificity of ECP to target the immune response to the transplanted organ allows ECP to decrease organ rejection without an increased risk of infection, common with immunosuppressive drugs.[5,]

Graft-Versus-Host Disease

Given that graft-versus-host disease (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 the 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 (ie, 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 evidence review, photopheresis is not associated with consistent changes in autoantibody levels.

T-Cell Lymphoma

Cutaneous T-Cell Lymphoma

According to the National Cancer Institute, CTCL is a neoplasia of malignant T lymphocytes that initially presents as skin involvement. CTCL is extremely rare, with an estimated incidence of approximately 0.4 per 100,000 annually, but because most are low-grade malignancies with long

survival, the overall prevalence is much higher. Two CTCL variants, mycosis fungoides, and the Sézary syndrome account for approximately 60% and 5% of new cases of CTCL, respectively.

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 to 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 by 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 or 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.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Graft Rejection After Solid Organ Transplant

Clinical Context and Therapy Purpose

The purpose of administering extracorporeal photopheresis (ECP) in patients 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 review.

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.

Review of Evidence
Heart Transplant

Acute Graft Rejection
An RCT has compared the efficacy of ECP with corticosteroids for the treatment of heart transplant rejection.[2,] Costanzo-Nordin et al (1992) enrolled 16 heart transplant patients and randomized them to ECP (n=9) or corticosteroids (n=7). Recipients of orthotopically transplanted hearts who 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 oral prednisone 100 mg/d for 3 days or intravenous methylprednisolone 1 g/d 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, 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 to 20 days) after ECP and 8 days (range, 6 to 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.[6,] Patients who had transplants at a median age of 12.7 years (range, 0.3 to 18.5 years) and received their first ECP treatment at a median age of 15.3 years (range, 7.3 to 31 years) were included. Indications for ECP included rejection with hemodynamic compromise (ie, 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 than compliant patients.

Kirklin et al (2006) conducted a comparative study of 343 heart transplant recipients.[7,] Thirty-six patients were treated with ECP for rejection and formed the treatment group. Patients were 18 years of age or older, treated from 1990 to 1993, and followed to May 2004. Indications for ECP were episodes of rejection with HC rejection (n=12); recurrent (n=9), or persistent (n=11) rejection; or prophylaxis in the presence of antidonor antibodies (n=4). Extracorporeal photopheresis 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 who received 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 the 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.[8,] 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. Extracorporeal photopheresis was performed as 2 treatments weekly for one month, once weekly for 2 months, and then once monthly for 2 months. The 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.[9,] Participants were eligible if they had acute rejection and at least 2 rejection episodes after standard immunosuppressive therapies in the 3 months before ECP. Extracorporeal photopheresis 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 an intravenous pulse of corticosteroids during the first ECP cycle. Patients were followed for 60 months. During follow-up, 1 patient died from the hepatitis C virus and another 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 to 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 of which occurred during the tapering of oral corticosteroids. Four were reversed by ECP, 1 by intravenous corticosteroids, and 1 by methotrexate after the failure of both ECP and intravenous 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 another had interstitial pneumonia. The authors concluded that ECP was a well-tolerated treatment, which permitted 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 Gokler et al (2022) investigated ECP for the prevention of rejection after cardiac transplant in high-risk patients.[10,] 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.[11,] Sixty consecutive adult cardiac transplant recipients at 12 clinical sites (9 in U.S., 3 in Europe) were randomized 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 endpoint 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 1, 9 had 2, and 4 had 3 or more. In the ECP group, 13 patients had none, 14 had 1, 3 had 2, and 3 had 3 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 nonstandardized 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 has 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 lung, 1 heart-lung) who received ECP for BOS.[12,] 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).[13,] 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 to 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.[14,]

Bronchiolitis Obliterans Syndrome 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.[15,] 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.[16,17,] 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 study of 194 patients who developed BOS and received standard treatment (n=143) or standard treatment plus ECP (n=51).[17,] Patients who did not respond to standard immunosuppressive therapy and showed a 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 endpoint 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 the 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 nonresponders in survival and the need for a transplant.

Compared with patients who had BOS and did not receive ECP but were similar in demographics and treatment history, the ECP group had longer survival (p=.046) and underwent fewer transplantations (18 vs. 21; p=.04). Mean time to transplant also was twice as long in the ECP group (1839 days vs. 947 days; p=.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.[18,] 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.[16,] 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.[19,] Fifty-one (78%) patients had undergone double lung transplant, 9 (14%) patients had undergone a single-lung transplant, and 5 (8%) patients had undergone a heart-lung transplant. The median time to chronic lung allograft dysfunction diagnosis was 3 years (interquartile range, 2 to 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 (32%) patients were BOS stage 2; and 9 (14%) patients 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 time was 17 months; 44 patients who continued treatment beyond 3 months received a median of 15 ECP treatments. Eight (12%) patients achieved a 10% or greater improvement in FEV_1, considered a treatment response; 27 (42%) patients experienced no change in FEV_1; and 30 (46%) patients experienced a 10% or greater decline in FEV_1, considered a progressive disease. Median progression-free survival was 13 months (interquartile range, 10 to 19 months) among responders and 4 months (interquartile range, 3 to 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 2008 and 2009.[20,] Median follow-up was 23 months post-transplant (range, 9 to 93 months), and the median age was 38 years (range, 21 to 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 (67%) of 9 patients 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.[21,] Ninety-five percent of patients had received a bilateral lung transplant, and 58% had grade 3 BOS. The indication for ECP was a progressive decline in lung function that was refractory to standard immunosuppressive therapy. The primary endpoint 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 to 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 1 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/month; after ECP, the mean rate of decline was -28.9 mL/month (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 (79%) patients, and lung function improved (increase in FEV_1 above pretreatment values) in 14 (25%) patients. Through 12 months of follow-up, the 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 study limitations 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).[13,] 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; 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 to 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 to 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 ECP for BOS.[12,] All patients were refractory to standard immunosuppressive therapy. ECP was administered every 2 weeks for 2 months and then once monthly for 2 months (for a total of 6 treatments). In 4 of 8 patients with grade 0 or 1 BOS, BOS improved or stabilized after treatment. Mean 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 of lung cancer. The remaining patient survived to retransplantation. Two of the 14 patients developed line-related sepsis, which cleared with antibiotic therapy and catheter removal.

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 derives from a group in Italy. Urbani et al (2004 to 2008) published a series of articles on various potential applications of ECP for liver transplant recipients.[22,23,24,] 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.[22,] 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 treatment 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.[23,] 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 1 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 the need for biopsy. Extracorporeal photopheresis was initiated during the first-week posttransplant; 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) reported on 3 fields of interest for ECP as prophylaxis of allograft rejection in liver transplant patients[24,]:

- 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 evidence review).

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 who experience graft rejection.

Kidney Transplant

The largest reported group of renal patients to receive ECP was at a hospital in 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.[25,] 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. The indication for ECP was acute resistance 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 might have a role as an adjunct to current therapies in patients with refractory rejection. Although this is the largest series of renal patients, it was 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,[26,] 1 was stable at 25 months,[27,] 5 were stable at 1 year,[26,28,] 7 were rejection-free at 2 to 5 years,[27,] and 1 graft was lost.[28,] Long-term outcomes were not reported for 3 patients.[29,30,]

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 patients who have acute or chronic graft-versus-host disease (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 review.

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 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. 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.

Review of Evidence
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.[31,] Relevant literature was searched through February 2013, and the following items were identified: 1 RCT in patients with chronic GVHD,[32,] 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%).

Extracorporeal photopheresis for the treatment of acute and chronic GVHD was addressed in a TEC Assessment (2001) that offered the following observations and conclusions[33,]: For acute GVHD or chronic GVHD in previously untreated patients or in those responding to conventional therapy, no studies met selection criteria and reported results of ECP, alone or in combination with other therapies. Therefore, ECP failed to meet TEC criteria for these indications. Studies focusing on patients with chronic GVHD unresponsive to other therapies reported resolution or marked improvement of lesions in approximately 50% of patients. Finally, studies of patients with acute

GVHD also reported successful outcomes in 67% to 84% of patients with grade 3 disease, but patients with grade 4 disease rarely responded.

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 the clinical response was noted in 3 (37.5%) patients, there were no long-term (>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 4-year OS rate was 67.7%.

Treatment in Pediatrics

Acute and Chronic Graft-Versus-Host Disease

Systematic Reviews

Three Cochrane reviews, 2 by Weiss et al (2014) and 1 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) evaluate 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 US 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%) patients with skin involvement improved, and 7 (87.5%) of 8 patients with mucosal involvement improved. Among patients with chronic GVHD, all 4 (100%) patients with liver involvement improved, and 22 (95.6%) of 23 patients with skin involvement improved.

The literature also includes small studies that have focused on ECP for the 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 to 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 the 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, 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%) 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 events of ECP were generally mild in all cases. These results are similar to those summarized in the TEC Assessment (2001), previously discussed.

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 to 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 (N=121). In meta-analyses, pooled overall and CR rates were both 71%. Statistical heterogeneity was considered not high for either result (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 nonconcurrent 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=.001) and CR (54% vs. 20% ; p=.001). The 2-year OS 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 the 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 to 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, 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 ($p=.1$). 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 noncomparative 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],[32,] and 14 retrospective; total n=595 patients). In meta-analyses, overall response 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 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 on results of a prospective (nonrandomized) study of ECP in 25 patients who had extensive corticosteroid-refractory or -resistant chronic GVHD after allogeneic cell transplantation.[56,] Extracorporeal photopheresis was administered for 2 consecutive days every 2 weeks in 17 patients and once weekly in 8 patients until the best response or stable disease was achieved. With a 9-month median ECP duration (range, 3 to 24 months), 20 patients had an 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 to 73 years). Patients had a 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 to 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 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 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 US.[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 to 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 to 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 and are consistent with conclusions from a 2001 TEC Assessment. 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.[27,60,61,]

Autoimmune Diseases

Clinical Context and Therapy Purpose

The purpose of administering ECP in patients 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 review.

Populations

The relevant populations of interest are 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 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.

Review of Evidence
Systematic Reviews
The use of ECP for the treatment of autoimmune diseases was addressed by a TEC Assessment (2001) that considered a variety of autoimmune diseases: systemic sclerosis, multiple sclerosis, type 1 diabetes, pemphigoid, severe atopic dermatitis, and Crohn's disease.[62,] The Assessment concluded that, for all indications, the available evidence was insufficient to permit conclusions on outcomes. At the time, photopheresis had been most thoroughly studied as a treatment for scleroderma, in a single-blind RCT by Rook et al (1992)[63,] and 3 small, uncontrolled series. Although the RCT reported positive outcomes in terms of skin manifestations, a number of methodological flaws have been discussed in the literature,[64,65,66,] 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,[63,] a cohort study by Papp et al (2012) enrolled 16 patients from a single institution in Hungary who had diffuse cutaneous systemic sclerosis.[67,] 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.[68,] 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).[69,] This double-blind RCT assessed 49 children with newly diagnosed type 1 diabetes. Forty children (age, 10 to 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-methoxypsoralen, 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.[70,] 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 the 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.[71,] 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.[72,] Extracorporeal photopheresis was administered for 2 consecutive days biweekly for 12 weeks and then monthly for 2 months. Only concomitant topical treatments and antihistamines 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=.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).[73,] Other immunosuppressive treatments were tapered and discontinued before ECP initiation and steroid tapering. ECP was administered on 2 consecutive days every 2 weeks for 24 weeks. Steroids were tapered as tolerated during this 24-week period. Nineteen (61%) patients completed 24 weeks of treatment; 7 (23%) patients achieved steroid-free remission at week 24 (the primary endpoint), 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. Methodological flaws in the scleroderma trial limit the 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 patients who have cutaneous or noncutaneous 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 review.

Populations

The relevant population of interest are individuals with cutaneous or noncutaneous 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 noncutaneous T-cell lymphomas: medical management and immunosuppression.

Outcomes

The general outcomes of interest are OS, 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.

Cutaneous T-Cell Lymphoma

Advanced-Stage (III or IV) Cutaneous T-Cell Lymphoma

Review of Evidence

Systematic Reviews

The 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 (1987).[74,] 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.[75,] 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, the response was defined as 25% or greater improvement for 4 weeks. With 7 years of follow-up, median OS was 9 years from diagnosis and 7 years from the start of ECP (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.[76,77,78,79,80,81,] These data have informed several evidence-based guidelines and consensus statements on the use of ECP in CTCL.[82,83,84,] The National Cancer Institute has consistently recommended ECP as first-line treatment for patients with stage III or IV CTCL.[85,]

Early-Stage (I or II) Cutaneous T-Cell Lymphoma

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-a [n=45]).[86,] Many of these patients were refractory to numerous other therapies, including topical corticosteroids, interferon-a, 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.[87,] Thus, the actual disease spectrum and burden represented in the available database likely vary between studies, and this complicates conclusions about the efficacy of ECP in this setting. Nonetheless, given the unfavorable prognosis for patients with early-stage CTCL that progresses on nonsystemic therapies, the relative lack of adverse events with ECP compared with

other systemic treatments, and the good response rates often observed with ECP, ECP may provide 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) Cutaneous T-Cell Lymphoma

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) Cutaneous T-Cell Lymphoma

Given the unfavorable prognosis for patients with early-stage CTCL that progresses on nonsystemic therapies, the relative lack of adverse events with ECP compared with other systemic treatments, and the good response rates often observed with ECP, ECP may be considered as a treatment for patients with refractory or progressive early-stage CTCL.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2014 Input

In response to requests, input was received through 2 academic medical centers and 5 Blue Distinction Centers for Transplant when this policy was under review in 2014. Respondents agreed unanimously that extracorporeal photopheresis (ECP) should not be medically necessary for previously untreated acute graft-versus-host disease (GVHD) but should be medically necessary for acute GVHD that is refractory to medical therapy.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Transplant

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.[88], 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. Patients with rapidly declining FEV_1, lack of significant neutrophilia, or restrictive allograft syndrome.

Graft-Versus-Host Disease

Acute Graft-Versus-Host Disease

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 the treatment of acute GVHD.[89,] This conclusion was based on older studies.[53,90,]

Acute and Chronic Graft-Versus-Host Disease

National Cancer Institute

In its guidelines on childhood hematopoietic cell transplantation, the National Cancer Institute listed ECP as a second-line treatment for patients with acute GVHD resistant to first-line methylprednisolone.[91,] For chronic GVHD therapy, the guidelines recommended that steroids are first-line therapy, but steroid-sparing approaches, including ECP, are being developed. In this setting, ECP has shown "some efficacy in some patients."

Cutaneous T-Cell Lymphoma

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on primary cutaneous lymphomas (v. 1.2023) list 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 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 Sezary syndrome or erythrodermic mycosis fungoides.[85,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

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 review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Solid organ transplants			
NCT04792294	Multicenter Analysis of Efficacy and Outcomes of Extracorporeal Photopheresis as Treatment of Chronic Lung Allograft Dysfunction	800	Dec 2021 (status unknown, last update March 2021)
NCT02181257	Extracorporeal Photopheresis for the Management of Progressive Bronchiolitis Obliterans Syndrome in Medicare-Eligible Recipients of Lung Allografts	690	Dec 2028 (ongoing)
GVHD			
NCT00637689	Improving Outcomes Assessment in Chronic GVHD	601	Feb 2025 (ongoing)
NCT01460914	Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis	100	Oct 2050 (ongoing)
CTCL			
NCT01460914	Outcomes of Cutaneous T-Cell Lymphoma and Chronic Graft-Versus-Host Disease in Patients Treated with Extracorporeal Photopheresis	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	Jan 2024 (ongoing)
Multiple Sclerosis			
NCT05168384	Safety and Efficacy of Extracorporeal Photopheresis (ECP) in the Treatment of Multiple Sclerosis (PHOMS)	45	Apr 2024 (ongoing)
Systemic Sclerosis			
NCT04986605	The Effectiveness of ECP in Diffuse Cutaneous Systemic Sclerosis	15	June 2026 (ongoing)
Unpublished			
Solid organ transplants			
NCT0572107	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 Photophoresis	158	Apr 2021

CTCL: cutaneous T-cell lymphoma; GVHD: graft-versus-host disease; NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. Marques MB, Tuncer HH. Photopheresis in solid organ transplant rejection. J Clin Apher. Apr 2006; 21(1): 72-7. PMID 16619230

2. Costanzo-Nordin MR, Hubbell EA, O'Sullivan EJ, et al. Photopheresis versus corticosteroids in the therapy of heart transplant rejection. Preliminary clinical report. Circulation. Nov 1992; 86(5 Suppl): II242-50. PMID 1424007
3. Rose EA, Barr ML, Xu H, et al. Photochemotherapy in human heart transplant recipients at high risk for fatal rejection. J Heart Lung Transplant. 1992; 11(4 Pt 1): 746-50. PMID 1498142
4. Hivelin M, Siemionow M, Grimbert P, et al. Extracorporeal photopheresis: from solid organs to face transplantation. Transpl Immunol. Jul 2009; 21(3): 117-28. PMID 19409991
5. Szczepiorkowski ZM, Bandarenko N, Kim HC, et al. Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. Jun 2007; 22(3): 106-75. PMID 17394188
6. Carlo WF, Pearce FB, George JF, et al. Single-center experience with extracorporeal photopheresis in pediatric heart transplantation. J Heart Lung Transplant. Jun 2014; 33(6): 624-8. PMID 24661684
7. Kirklin JK, Brown RN, Huang ST, et al. Rejection with hemodynamic compromise: objective evidence for efficacy of photopheresis. J Heart Lung Transplant. Mar 2006; 25(3): 283-8. PMID 16507420
8. Maccherini M, Diciolla F, Laghi Pasini F, et al. Photopheresis immunomodulation after heart transplantation. Transplant Proc. 2001; 33(1-2): 1591-4. PMID 11267432
9. Dall'Amico R, Montini G, Murer L, et al. Extracorporeal photochemotherapy after cardiac transplantation: a new therapeutic approach to allograft rejection. Int J Artif Organs. Jan 2000; 23(1): 49-54. PMID 12118837
10. Gökler J, Aliabadi-Zuckermann A, Zuckermann A, et al. Extracorporeal Photopheresis With Low-Dose Immunosuppression in High-Risk Heart Transplant Patients-A Pilot Study. Transpl Int. 2022; 35: 10320. PMID 35401042
11. Barr ML, Meiser BM, Eisen HJ, et al. Photopheresis for the prevention of rejection in cardiac transplantation. Photopheresis Transplantation Study Group. N Engl J Med. Dec 10 1998; 339(24): 1744-51. PMID 9845709
12. Villanueva J, Bhorade SM, Robinson JA, et al. Extracorporeal photopheresis for the treatment of lung allograft rejection. Ann Transplant. 2000; 5(3): 44-7. PMID 11233043
13. Benden C, Speich R, Hofbauer GF, et al. Extracorporeal photopheresis after lung transplantation: a 10-year single-center experience. Transplantation. Dec 15 2008; 86(11): 1625-7. PMID 19077900
14. Salerno CT, Park SJ, Kreykes NS, et al. Adjuvant treatment of refractory lung transplant rejection with extracorporeal photopheresis. J Thorac Cardiovasc Surg. Jun 1999; 117(6): 1063-9. PMID 10343253
15. Benden C, Haughton M, Leonard S, et al. Therapy options for chronic lung allograft dysfunction-bronchiolitis obliterans syndrome following first-line immunosuppressive strategies: A systematic review. J Heart Lung Transplant. Sep 2017; 36(9): 921-933. PMID 28662986
16. Del Fante C, Scudeller L, Oggionni T, et al. Long-Term Off-Line Extracorporeal Photochemotherapy in Patients with Chronic Lung Allograft Rejection Not Responsive to Conventional Treatment: A 10-Year Single-Centre Analysis. Respiration. 2015; 90(2): 118-28. PMID 26112178
17. Jaksch P, Scheed A, Keplinger M, et al. A prospective interventional study on the use of extracorporeal photopheresis in patients with bronchiolitis obliterans syndrome after lung transplantation. J Heart Lung Transplant. Sep 2012; 31(9): 950-7. PMID 22884382
18. Leroux J, Hirschi S, Essaydi A, et al. Initiation of extracorporeal photopheresis in lung transplant patients with mild to moderate refractory BOS: A single-center real-life experience. Respir Med Res. May 2022; 81: 100913. PMID 35525096
19. Greer M, Dierich M, De Wall C, et al. Phenotyping established chronic lung allograft dysfunction predicts extracorporeal photopheresis response in lung transplant patients. Am J Transplant. Apr 2013; 13(4): 911-918. PMID 23406373

20. Lucid CE, Savani BN, Engelhardt BG, et al. Extracorporeal photopheresis in patients with refractory bronchiolitis obliterans developing after allo-SCT. Bone Marrow Transplant. Mar 2011; 46(3): 426-9. PMID 20581885
21. Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. J Heart Lung Transplant. Apr 2010; 29(4): 424-31. PMID 19853479
22. Urbani L, Mazzoni A, Catalano G, et al. The use of extracorporeal photopheresis for allograft rejection in liver transplant recipients. Transplant Proc. Dec 2004; 36(10): 3068-70. PMID 15686696
23. Urbani L, Mazzoni A, De Simone P, et al. Avoiding calcineurin inhibitors in the early post-operative course in high-risk liver transplant recipients: The role of extracorporeal photopheresis. J Clin Apher. 2007; 22(4): 187-94. PMID 17294458
24. Urbani L, Mazzoni A, Colombatto P, et al. Potential applications of extracorporeal photopheresis in liver transplantation. Transplant Proc. May 2008; 40(4): 1175-8. PMID 18555142
25. Jardine MJ, Bhandari S, Wyburn KR, et al. Photopheresis therapy for problematic renal allograft rejection. J Clin Apher. 2009; 24(4): 161-9. PMID 19536814
26. Kumlien G, Genberg H, Shanwell A, et al. Photopheresis for the treatment of refractory renal graft rejection. Transplantation. Jan 15 2005; 79(1): 123-5. PMID 15714180
27. Dall'Amico R, Murer L. Extracorporeal photochemotherapy: a new therapeutic approach for allograft rejection. Transfus Apher Sci. Jun 2002; 26(3): 197-204. PMID 12126206
28. Dall'Amico R, Murer L, Montini G, et al. Successful treatment of recurrent rejection in renal transplant patients with photopheresis. J Am Soc Nephrol. Jan 1998; 9(1): 121-7. PMID 9440096
29. Baron ED, Heeger PS, Hricik DE, et al. Immunomodulatory effect of extracorporeal photopheresis after successful treatment of resistant renal allograft rejection. Photodermatol Photoimmunol Photomed. Apr 2001; 17(2): 79-82. PMID 11338406
30. Sunder-Plassman G, Druml W, Steininger R, et al. Renal allograft rejection controlled by photopheresis. Lancet. Aug 19 1995; 346(8973): 506. PMID 7637500
31. Abu-Dalle I, Reljic T, Nishihori T, et al. Extracorporeal photopheresis in steroid-refractory acute or chronic graft-versus-host disease: results of a systematic review of prospective studies. Biol Blood Marrow Transplant. Nov 2014; 20(11): 1677-86. PMID 24867779
32. Flowers ME, Apperley JF, van Besien K, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood. Oct 01 2008; 112(7): 2667-74. PMID 18621929
33. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Extracorporeal photopheresis for graft-versus-host disease. TEC Assessments. 2001;Volume 16:Tab 9.
34. Hautmann AH, Wolff D, Hahn J, et al. Extracorporeal photopheresis in 62 patients with acute and chronic GVHD: results of treatment with the COBE Spectra System. Bone Marrow Transplant. Mar 2013; 48(3): 439-45. PMID 22922407
35. Ussowicz M, Musiał J, Mielcarek M, et al. Steroid-sparing effect of extracorporeal photopheresis in the therapy of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Transplant Proc. Nov 2013; 45(9): 3375-80. PMID 24182819
36. Weitz M, Strahm B, Meerpohl JJ, et al. Extracorporeal photopheresis versus standard treatment for acute graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients. Cochrane Database Syst Rev. Feb 25 2014; (2): CD009759. PMID 24569960
37. Weitz M, Strahm B, Meerpohl JJ, et al. Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients. Cochrane Database Syst Rev. Feb 25 2014; (2): CD009898. PMID 24569961
38. Buder K, Zirngibl M, Bapistella S, et al. Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell

transplantation in children and adolescents. Cochrane Database Syst Rev. Jun 09 2022; 6(6): CD009898. PMID 35679154
39. Kitko CL, Abdel-Azim H, Carpenter PA, et al. A Prospective, Multicenter Study of Closed-System Extracorporeal Photopheresis for Children with Steroid-Refractory Acute Graft-versus-Host Disease. Transplant Cell Ther. May 2022; 28(5): 261.e1-261.e7. PMID 35124293
40. Perotti C, Del Fante C, Tinelli C, et al. Extracorporeal photochemotherapy in graft-versus-host disease: a longitudinal study on factors influencing the response and survival in pediatric patients. Transfusion. Jun 2010; 50(6): 1359-69. PMID 20113452
41. Halle P, Paillard C, D'Incan M, et al. Successful extracorporeal photochemotherapy for chronic graft-versus-host disease in pediatric patients. J Hematother Stem Cell Res. Jun 2002; 11(3): 501-12. PMID 12183835
42. Salvaneschi L, Perotti C, Zecca M, et al. Extracorporeal photochemotherapy for treatment of acute and chronic GVHD in childhood. Transfusion. Oct 2001; 41(10): 1299-305. PMID 11606832
43. Berger M, Pessolano R, Albiani R, et al. Extracorporeal photopheresis for steroid resistant graft versus host disease in pediatric patients: a pilot single institution report. J Pediatr Hematol Oncol. Oct 2007; 29(10): 678-87. PMID 17921848
44. Kozlov A, Estrina M, Paina O, et al. Extracorporeal Photopheresis in Children with Chronic Graft-Versus-Host Disease. Pharmaceuticals (Basel). Aug 17 2021; 14(8). PMID 34451905
45. Zhang H, Chen R, Cheng J, et al. Systematic review and meta-analysis of prospective studies for ECP treatment in patients with steroid-refractory acute GVHD. Patient Prefer Adherence. 2015; 9: 105-11. PMID 25653504
46. Mehta RS, Bassett R, Rondon G, et al. Randomized phase II trial of extracorporeal phototherapy and steroids vs. steroids alone for newly diagnosed acute GVHD. Bone Marrow Transplant. Jun 2021; 56(6): 1316-1324. PMID 33398094
47. Solh MM, Farnham C, Solomon SR, et al. Extracorporeal photopheresis (ECP) improves overall survival in the treatment of steroid refractory acute graft-versus-host disease (SR aGvHD). Bone Marrow Transplant. Feb 2023; 58(2): 168-174. PMID 36352015
48. Greinix HT, Knobler RM, Worel N, et al. The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. Haematologica. Mar 2006; 91(3): 405-8. PMID 16531267
49. Batgi H, Dal MS, Erkurt MA, et al. Extracorporeal photopheresis in the treatment of acute graft-versus-host disease: A multicenter experience. Transfus Apher Sci. Oct 2021; 60(5): 103242. PMID 34420882
50. Jagasia M, Greinix H, Robin M, et al. Extracorporeal photopheresis versus anticytokine therapy as a second-line treatment for steroid-refractory acute GVHD: a multicenter comparative analysis. Biol Blood Marrow Transplant. Jul 2013; 19(7): 1129-33. PMID 23623892
51. Rubegni P, Feci L, Poggiali S, et al. Extracorporeal photopheresis: a useful therapy for patients with steroid-refractory acute graft-versus-host disease but not for the prevention of the chronic form. Br J Dermatol. Aug 2013; 169(2): 450-7. PMID 23534380
52. Shaughnessy PJ, Bolwell BJ, van Besien K, et al. Extracorporeal photopheresis for the prevention of acute GVHD in patients undergoing standard myeloablative conditioning and allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. Jun 2010; 45(6): 1068-76. PMID 19915634
53. Perfetti P, Carlier P, Strada P, et al. Extracorporeal photopheresis for the treatment of steroid refractory acute GVHD. Bone Marrow Transplant. Nov 2008; 42(9): 609-17. PMID 18660840
54. Malik MI, Litzow M, Hogan W, et al. Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis. Blood Res. Jun 2014; 49(2): 100-6. PMID 25025011
55. Ontario Health Technology Advisory Committee. OHTAC Recommendation: Extracorporeal Photopheresis. 2006; http://www.hqontario.ca/english/providers/program/ohtac/tech/recommend/rec_ecp_032806.pdf. Accessed September 6, 2023.
56. Foss FM, DiVenuti GM, Chin K, et al. Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of

response and survival incorporating prognostic factors. Bone Marrow Transplant. Jun 2005; 35(12): 1187-93. PMID 15852025
57. Dignan FL, Aguilar S, Scarisbrick JJ, et al. Impact of extracorporeal photopheresis on skin scores and quality of life in patients with steroid-refractory chronic GVHD. Bone Marrow Transplant. May 2014; 49(5): 704-8. PMID 24566709
58. Kansu E, Ward D, Sanchez AP, et al. Extracorporeal photopheresis for the treatment of chronic graft versus host disease. Hematology. Dec 2022; 27(1): 785-794. PMID 35802815
59. Dal MS, Batgi H, Erkurt MA, et al. Extracorporeal photopheresis in steroid-refractory chronic graft-versus-host disease: A retrospective multicenter study. Transfus Apher Sci. Oct 2021; 60(5): 103243. PMID 34420879
60. Greinix HT, Volc-Platzer B, Knobler R. Criteria for assessing chronic GVHD. Bone Marrow Transplant. Mar 2000; 25(5): 575. PMID 10713639
61. Rubegni P, Cuccia A, Sbano P, et al. Role of extracorporeal photochemotherapy in patients with refractory chronic graft-versus-host disease. Br J Haematol. Jul 2005; 130(2): 271-5. PMID 16029456
62. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Extracorporeal photopheresis for autoimmune disease. TEC Assessments. 2001;Volume 16:Tab 10.
63. Rook AH, Freundlich B, Jegasothy BV, et al. Treatment of systemic sclerosis with extracorporeal photochemotherapy. Results of a multicenter trial. Arch Dermatol. Mar 1992; 128(3): 337-46. PMID 1550365
64. Fries JF, Seibold JR, Medsger TA. Photopheresis for scleroderma? No!. J Rheumatol. Jul 1992; 19(7): 1011-3. PMID 1512753
65. Melski JW. Price of technology. A blind spot. JAMA. Mar 18 1992; 267(11): 1516-8. PMID 1538542
66. Trentham DE. Photochemotherapy in systemic sclerosis. The stage is set. Arch Dermatol. Mar 1992; 128(3): 389-90. PMID 1550373
67. Papp G, Horvath IF, Barath S, et al. Immunomodulatory effects of extracorporeal photochemotherapy in systemic sclerosis. Clin Immunol. Feb 2012; 142(2): 150-9. PMID 22036269
68. Cavaletti G, Perseghin P, Dassi M, et al. Extracorporeal photochemotherapy: a safety and tolerability pilot study with preliminary efficacy results in refractory relapsing-remitting multiple sclerosis. Neurol Sci. Apr 2006; 27(1): 24-32. PMID 16688596
69. Ludvigsson J, Samuelsson U, Ernerudh J, et al. Photopheresis at onset of type 1 diabetes: a randomised, double blind, placebo controlled trial. Arch Dis Child. Aug 2001; 85(2): 149-54. PMID 11466190
70. Sanli H, Akay BN, Ayyildiz E, et al. Remission of severe autoimmune bullous disorders induced by long-term extracorporeal photochemotherapy. Transfus Apher Sci. Dec 2010; 43(3): 353-359. PMID 21035398
71. Rubegni P, Poggiali S, Cevenini G, et al. Long term follow-up results on severe recalcitrant atopic dermatitis treated with extracorporeal photochemotherapy. J Eur Acad Dermatol Venereol. Apr 2013; 27(4): 523-6. PMID 22540319
72. Wolf P, Georgas D, Tomi NS, et al. Extracorporeal photochemotherapy as systemic monotherapy of severe, refractory atopic dermatitis: results from a prospective trial. Photochem Photobiol Sci. Jan 2013; 12(1): 174-81. PMID 22948099
73. Reinisch W, Knobler R, Rutgeerts PJ, et al. Extracorporeal photopheresis (ECP) in patients with steroid-dependent Crohn's disease: an open-label, multicenter, prospective trial. Inflamm Bowel Dis. Feb 2013; 19(2): 293-300. PMID 22573600
74. Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med. Feb 05 1987; 316(6): 297-303. PMID 3543674
75. Knobler R, Duvic M, Querfeld C, et al. Long-term follow-up and survival of cutaneous T-cell lymphoma patients treated with extracorporeal photopheresis. Photodermatol Photoimmunol Photomed. Oct 2012; 28(5): 250-7. PMID 22971190
76. Freiman A, Sasseville D. Treatment of mycosis fungoides: overview. J Cutan Med Surg. 2006; 10(5): 228-33. PMID 17234106

77. Keehn CA, Belongie IP, Shistik G, et al. The diagnosis, staging, and treatment options for mycosis fungoides. Cancer Control. Apr 2007; 14(2): 102-11. PMID 17387295
78. Knobler E. Current management strategies for cutaneous T-cell lymphoma. Clin Dermatol. 2004; 22(3): 197-208. PMID 15262305
79. Scarisbrick JJ. Staging and management of cutaneous T-cell lymphoma. Clin Exp Dermatol. Mar 2006; 31(2): 181-6. PMID 16487086
80. Whittaker SJ, Foss FM. Efficacy and tolerability of currently available therapies for the mycosis fungoides and Sezary syndrome variants of cutaneous T-cell lymphoma. Cancer Treat Rev. Apr 2007; 33(2): 146-60. PMID 17275192
81. Gao C, McCormack C, van der Weyden C, et al. Prolonged survival with the early use of a novel extracorporeal photopheresis regimen in patients with Sézary syndrome. Blood. Oct 17 2019; 134(16): 1346-1350. PMID 31467061
82. Scarisbrick JJ, Taylor P, Holtick U, et al. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. Br J Dermatol. Apr 2008; 158(4): 659-78. PMID 18241274
83. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome. Eur J Cancer. May 2006; 42(8): 1014-30. PMID 16574401
84. Whittaker SJ, Marsden JR, Spittle M, et al. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. Br J Dermatol. Dec 2003; 149(6): 1095-1107. PMID 14696593
85. National Cancer Institute. Mycosis Fungoides (Including Sezary Syndrome) Treatment (PDQ) Health Professional Version. June 27, 2023; https://www.cancer.gov/types/lymphoma/hp/mycosis-fungoides-treatment-pdq Accessed September 6, 2023.
86. Miller JD, Kirkland EB, Domingo DS, et al. Review of extracorporeal photopheresis in early-stage (IA, IB, and IIA) cutaneous T-cell lymphoma. Photodermatol Photoimmunol Photomed. Oct 2007; 23(5): 163-71. PMID 17803594
87. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. May 15 2005; 105(10): 3768-85. PMID 15692063
88. Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant. May 2019; 38(5): 493-503. PMID 30962148
89. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. Aug 2012; 18(8): 1150-63. PMID 22510384
90. Messina C, Locatelli F, Lanino E, et al. Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation. Br J Haematol. Jul 2003; 122(1): 118-27. PMID 12823353
91. National Cancer Institute. Childhood Hematopoietic Cell Transplantation (PDQ) Health Professional Version. February 4, 2022; https://www.cancer.gov/types/childhood-cancers/hp-stem-cell-transplant#_5 Accessed September 6, 2023.
92. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice Guidelines in Oncology: Primary Cutaneous Lymphomas. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf. Accessed September 6, 2023.
93. Center for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Extracorporeal Photopheresis (110.4). 2012; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=113. Accessed September 6, 2023.

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or specialty consultation report(s)
- Progress notes pertaining to request including:
- Current disease status (For GVHD also identify acute versus chronic)
- Previous treatment (systemic and non-systemic) and responses
- Reason for ECP treatment
- Treatment plan
- ECP treatment notes (if applicable)

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	36522	Photopheresis, extracorporeal
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/13/2012	BCBSA Medical Policy adoption
06/26/2009	Policy Title Revision, Medically Necessary criteria added Title changed from Photopheresis as a Treatment of Autoimmune Disease and Graft-versus- Host Disease to Extracorporeal Photochemotherapy.
10/05/2012	Policy title change from Extracorporeal Photochemotherapy with position change
07/31/2015	Coding update
09/30/2015	Policy revision without position change
04/01/2017	Policy revision without position change
12/01/2017	Policy revision without position change
12/01/2018	Policy revision without position change
12/16/2019	Policy revision without position change
01/01/2024	Policy reactivated. Previously archived from 08/01/2020 to 12/31/2023

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Extracorporeal Photopheresis 8.01.36** **Policy Statement:** **Organ Rejection After Solid Organ Transplant** I. Extracorporeal photopheresis may be considered **medically necessary** to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment. II. Extracorporeal photopheresis is considered **investigational** in all other situations related to treatment or prevention of rejection in solid organ transplantation. **Graft-Versus-Host Disease Acute** III. Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat acute graft-versus-host disease (GVHD) that is refractory to medical therapy. IV. Extracorporeal photopheresis is considered **investigational** as a technique to treat acute GVHD that is either previously untreated or is responding to established therapies. **Chronic** V. Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat chronic GVHD that is refractory to medical therapy. VI. Extracorporeal photopheresis is considered **investigational** as a technique to treat chronic GVHD that is either previously untreated or is responding to established therapies.

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
	Autoimmune Diseases VII. Extracorporeal photopheresis is considered **investigational** 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, autoimmune bullous disorders, severe atopic dermatitis, or Crohn's disease. **Cutaneous T-Cell Lymphoma** VIII. Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat late-stage (III or IV) cutaneous T-cell lymphoma. IX. Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat early-stage (I or II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies. X. Extracorporeal photopheresis is considered **investigational** as a technique to treat early-stage (I or II) cutaneous T-cell lymphoma that is either previously untreated or responsive to established nonsystemic therapies. **Other** XI. Extracorporeal photopheresis is considered **investigational** for all other indications.