AETNA BETTER HEALTH®

Clinical Policy Bulletin:
Extracorporeal Photochemotherapy (Photopheresis)

Number: 0241

Policy

I. Aetna considers extracorporeal photochemotherapy (ECP, photopheresis) medically necessary for erythrodermic variants of cutaneous T cell lymphoma (e.g., mycosis fungoides, Sezary syndrome).

II. Aetna considers ECP medically necessary in the treatment of acute cardiac allograft rejection that is refractory to standard immunosuppressive drug treatment (resistant or dependent to high-dose steroids plus refractory to 2 or more of the following, unless contraindicated: azathioprine, cyclosporine, methotrexate, and/or polyclonal and monoclonal antilymphocyte agents (e.g., anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG)).

III. Aetna considers ECP medically necessary in the treatment of rejection (bronchiolitis obliterans) of lung transplants that are refractory to immunosuppressive drug treatment (resistant or dependent to high-dose steroids plus resistant to 2 or more of the following, unless contraindicated: azathioprine, cyclosporine, tacrolimus, and/or polyclonal and monoclonal anti-lymphocyte agents (e.g., ALG and ATG) or where there is a rapid decline in lung function.

IV. Aetna considers ECP medically necessary for the treatment of graft-versus-host disease (GVHD) of an allogeneic bone marrow or stem cell transplant when the disease is refractory to standard immunosuppressive drug treatment.

V. Aetna considers the use of ECP experimental and investigational as a treatment for the following conditions because the effectiveness of this treatment for these diagnoses has not been established:

- Atopic dermatitis
- Allograft rejection of solid organs other than the heart and lung
- Bullous pemphigoid
- Crohn's disease
- Epidermolysis bullosa acquisita
- Morphea
- Multiple sclerosis
Nephrogenic systemic fibrosis (previously known as nephrogenic fibrosing dermopathy)
Pemphigus vulgaris
Pityriasis rubra pilaris
Stage 0-p bronchiolitis obliterans syndrome
Systemic sclerosis (scleroderma)
Type 1 diabetes
Xanthogranulomas

**Background**

Photopheresis, also known as extracorporeal photochemotherapy (ECP), is an immunomodulatory technique based on pheresis of light-sensitive cells. Whole blood is removed from patients who have previously ingested the photosensitizing agent 8-methoxypsoralen (8-MOP) followed by leukapheresis and exposure of the 8-MOP containing leukocytes extracorporeally to ultraviolet-A light before their return to the patient. Two hours after an oral dose of photo-activatable drug, the patient undergoes leukopheresis. The lymphocytes are then exposed to UVA light within the photopheresis device and the photo-irradiated cells are re-infused into the patient.

Photopheresis was approved by the Food and Drug Administration (FDA) in 1988 for treatment of cutaneous T-cell lymphoma, and is considered standard therapy for the early to moderately advanced (stage III) erythrodermic variants of cutaneous T-cell lymphoma (e.g., mycosis fungoides, Sézary's syndrome). However, in a recent randomized controlled study, Child et al (2004) concluded that ECP is not effective in the treatment of plaque stage (1B/T2) mycosis fungoides even in patients with molecular evidence of a peripheral blood T-cell clone. This is in agreement with the findings of Zackheim (2003) who stated the results of ECP for early to moderately advanced erythrodermic mycosis fungoides are favorable. However, results in plaque and tumor stage disease are not impressive.


Photopheresis is usually performed on 2 consecutive days at 4-week intervals with clinical evaluation at 6 months to determine response. Those who show clinical improvement are maintained on this treatment schedule until maximum clearing. An additional 6 months of treatment is typically given after which the patient is gradually weaned off therapy.

Photopheresis for the treatment of scleroderma and other autoimmune diseases is under investigation. The safety and efficacy of this treatment for scleroderma has not been established. Photopheresis, alone or in combination with immunosuppressive therapy, has also been used in the treatment of solid organ (e.g., heart, lung, and kidney) transplant rejection, graft-versus-host disease (GVHD), scleroderma, and other autoimmune diseases. This form of photochemotherapy induces a selective inhibition of the host response to foreign histocompatibility antigens and reverses allograft rejection after organ transplantation.

An assessment conducted by the BlueCross BlueShield Association Technology Evaluation Center (2001) concluded that ECP does not meet TEC criteria for autoimmune diseases, including: progressive systemic sclerosis (scleroderma);
pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, or other autoimmune bullous (blistering) diseases; systemic lupus erythematosus; multiple sclerosis; psoriatic arthritis or psoriasis vulgaris; rheumatoid arthritis; type I diabetes; and other autoimmune diseases such as atopic dermatitis, juvenile dermatomyositis, or scleromyxedema.

Extracorporeal photopheresis is also being evaluated as a treatment for Crohn’s disease. Available evidence is limited to case reports and small uncontrolled case series (Reinisch et al, 2001; Guariso et al, 2003). An assessment by the National Institute for Health and Clinical Excellence (2009) concluded: “[c]urrent evidence on extracorporeal photopheresis (ECP) for Crohn’s disease is based on reports that include a very small number of patients. These reports describe no major safety issues but they provide little evidence of efficacy. Therefore, this procedure should not be used outside the context of research.”

Based upon an evidence review, the Centers for Medicare and Medicaid Services (CMS, 2006) concluded that ECP is reasonable and necessary for persons with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment. Centers for Medicare and Medicaid Services also concluded that ECP is reasonable and necessary for persons with chronic GVHD whose disease is refractory to standard immunosuppressive drug treatment. There is evidence that photopheresis is effective in the treatment of heart, bone marrow and stem cell transplant rejection. Photopheresis has been reported to be as effective as conventional immunosuppressive agents in reducing rejection episodes in heart transplant recipients. It has also been demonstrated to be effective in treating steroid-resistant chronic GVHD following bone marrow or stem cell transplantation (Foss et al, 2005; Couriel et al, 2006; Bisaccia et al, 2006). By contrast, there is limited scientific evidence to determine the effectiveness of photopheresis in treating rejection of lung or kidney transplants.

Morrell et al (2010) reported that ECP is associated with a reduction in the rate of decline in lung function associated with progressive bronchiolitis obliterans syndrome (BOS). The authors retrospectively analyzed the efficacy and safety of ECP in 60 lung transplant recipients treated for progressive BOS at a single institution between 2000 and 2007. They reported that during the 6-month period before the initiation of ECP, the average rate of decline in forced expiratory volume in 1 second (FEV(1)) was -116.0 ml/month, but the slope decreased to -28.9 ml/month during the 6-month period after the initiation of ECP, and the mean difference in the rate of decline was 87.1 ml/month (95% confidence interval [CI]: 57.3 to 116.9; p < 0.0001). The authors noted that FEV(1) improved in 25.0% of patients after the initiation of ECP with a mean increase of 20.1 ml/month.

Haenssle and colleagues (2004) noted that pityriasis rubra pilaris (PRP) is a rare papulosquamous skin disease of unknown etiology that has been categorized into 5 clinical types based on age at onset, cutaneous features and prognosis. These investigators presented a patient with chronic exanthematic type II atypical adult PRP, whose skin status was significantly improved with monthly ECP. Various therapeutic regimens including narrow-band UV-B, bath PUVA therapy, systemic fumaric acid esters and systemic cyclosporin had failed. Oral retinoids could not be administered due to a type IIa hyper-lipoproteinemia with profound hepatic steatosis and elevated liver transaminases. The observed clinical benefit may encourage future clinical studies analyzing the clinical value of ECP in otherwise unresponsive cases of type II PRP.

Dall’Amico and Messina (2002) stated that ECP is a new type of photochemotherapy used for the treatment of oncological and autoimmune diseases. Additionally, recent reports indicated that this therapy is promising in both pediatric and adult patients who
Extracorporeal Photochemotherapy (Photopheresis)

Develop GVHD resistant to conventional protocols after bone marrow transplantation. These researchers reviewed 31 studies where ECP was used in the treatment of acute and chronic GVHD. A total of 76 (32% female) acute GVHD patients have been considered in 11 series; 59 patients presented with skin involvement; 47 had liver involvement, and 28 had gastro-intestinal manifestations. Treatment duration ranged from 1 to 24 months. A regression of skin manifestations was observed in 83% of the patients with a complete response in 67%. A complete regression of liver and gut manifestations was reported in 38% and 54% of the patients, respectively. The overall patient survival was 53%. Of the 43 patients alive, 8 developed chronic GVHD manifestations. The immunosuppressive therapy was discontinued in 28% of cases and reduced in 46%. A total of 204 (45% female) chronic GVHD patients treated with ECP 1 to 110 months from transplantation have been considered in 20 series. A total of 128 patients presented with skin involvement; 84 with liver, 31 with lung, and 59 with oral manifestations. Treatment duration ranged from 3 to 40 months. A regression of skin manifestations was observed in 76% of patients with a complete response in 38%. An improvement of liver and lung involvement was reported in 48% and 39% of the patients, respectively. Of the 59 patients with oral manifestations, an improvement was obtained in 63% of cases. The overall patient survival was 79%. Extracorporeal photopheresis is a non-aggressive treatment that may benefit patients with both acute and chronic GVHD who do not respond to standard immunosuppressive therapy.

Perfetti and associates (2008) examined the effects of ECP for the treatment of steroid refractory acute GVHD. Extracorporeal photopheresis was given to 23 patients with steroid-refractory acute GVHD (aGVHD, grade II (n = 10), III (n = 7) or IV (n = 6)). The median duration of ECP was 7 months (1 to 33) and the median number of ECP cycles in each patient was 10. Twelve patients (52%) had complete responses. Eleven patients (48%) survived and 12 died, 10 of GVHD with or without infections and 2 of leukemia relapse. The average grade of GVHD was reduced from 2.8 (on the first day of ECP) to 1.4 (on day +90 from ECP) (p = 0.08), and the average dose of intravenous methylprednisolone from 2.17 to 0.2 mg/kg/day (p = 0.004). Complete responses were obtained in 70, 42 and 0% of patients, respectively, with grades II, III and IV aGVHD; complete responses in the skin, liver and gut were 66, 27 and 40%. Patients treated within 35 days from onset of aGVHD had higher responses (83 versus 47%; p = 0.1). A trend for improved survival was seen in grade III-IV aGVHD treated with ECP as compared to matched controls (38 versus 16%; p = 0.08). The authors concluded that ECP is a treatment option for patients with steroid refractory aGVHD and should be considered early in the course of the disease. Moreover, the authors stated that "[t]he good results in patients receiving ECP, within 1 month from the onset of GVHD and when the severity does not exceed grade II-III may warrant a prospective trial to explore the role of photochemotherapy as upfront treatment of aGVHD".

A decision memorandum from the CMS concluded that there is insufficient evidence to support the use of ECP in pemphigus vulgaris and bullous pemphigoid (CMS, 2006).

Richmond and colleagues (2007) stated that nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy, is an idiopathic condition observed in patients with renal disease that is characterized by cutaneous sclerosis that can often result in contractures, pain, functional disability, and systemic complications. Recent reports have suggested a possible link with exposure to gadolinium. No current therapy has clearly demonstrated effectiveness for NSF, although case reports suggested that ECP may be of benefit. These researchers explored the plausibility of a gadolinium linkage with NSF and evaluated the effectiveness of ECP in the treatment of a cohort of patients with NSF (n = 8). Of the 8 patients, 6 had a history of arterial or venous thrombotic disease, and 7 had a documented exposure to gadolinium within 1
week to several months before onset of NSF. Specifically, all patients were exposed to gadodiamide. These investigators treated 5 of the patients with ECP. After a mean number of 34 treatment sessions over a mean of 8.5 months, 3 patients experienced a mild improvement in skin tightening, range of motion, and/or functional capacity. The authors concluded that their findings support the hypothesis that exposure to gadolinium, perhaps specifically gadodiamide, plays a role in the pathogenesis of NSF. They noted that larger epidemiologic studies will be needed to confirm this association. Furthermore, their experience suggest that, if used for extended periods, ECP might have some mild benefit for patients with NSF. They stated that larger, randomized, placebo-controlled trials of ECP should be performed to more specifically assess the benefit of ECP in the treatment of NSF.

Regarding the appropriate duration of ECP, an article from eMedicine recommends ECP weekly for 2 consecutive days each week, tapering to every other week until rejection resolves (Introcaso et al, 2007). A systematic review (Dall’Amico and Messina, 2002) assessed 31 studies of ECP for GVHD, and noted that treatment duration ranged from 3 to 40 months.

Shaughnessy et al (2010) stated that GVHD is partly mediated by host antigen-presenting cells (APCs) that activate donor T cells. Extracorporeal photopheresis can modulate APC function and benefit some patients with GVHD. These investigators reported the results of a study using ECP administered before a standard myeloablative preparative regimen intended to prevent GVHD. Grades II to IV acute GVHD developed in 9 (30 %) of 30 recipients of HLA-matched related transplants and 13 (41 %) of 32 recipients of HLA-matched unrelated or HLA-mismatched related donor transplants. Actuarial estimates of overall survival (OS) at day 100 and 1-year post transplant were 89 % (95 % CI: 78 to 94 %) and 77 % (95 % CI: 64 to 86 %), respectively. There were no unexpected adverse effects of ECP. Historical controls receiving similar conditioning and GVHD prophylaxis regimens but no ECP were identified from the database of the Center for International Blood and Marrow Transplant Research and multi-variate analysis indicated a lower risk of grades II to IV acute GVHD in patients receiving ECP (p = 0.04). Adjusted OS at 1 year was 83 % in the ECP study group and 67 % in the historical control group (relative risk 0.44; 95 % CI: 0.24 to 0.80) (p = 0.007). The authors concluded that these preliminary findings may indicate a potential survival advantage with ECP for transplant recipients undergoing standard myeloablative hematopoietic cell transplantation. Moreover, they stated that longer follow-up, larger sample sizes, and randomized comparisons to standard approaches are needed.

Kusztal et al (2011) stated that ECP is considered a promising immunomodulatory therapy of acute allograft rejection in organ transplantation and GVHD. These researchers investigated the biological responses of 10 patients who underwent kidney transplantation with ECP as prophylactic treatment. They received conventional immunosuppressive therapy plus ECP immediately after transplantation: 12 to 16 applications over the course of 2.5 months. ECP procedures were performed using an automated system for leukocyte separation and photo-activation with methoxsalen. All recipients were followed by estimated glomerular filtration rate (eGFR) and peripheral T, B, natural killer, T-regulatory (Treg) and dendritic cells (DC) counts and phenotypes. An acute rejection episode appeared in one control group recipient. The ECP group showed a positive trend to an higher GFR at months 3 (53 ± 11 versus 47.1 ± 9; p = 0.17) and 6 (57.5 ± 10 versus 53.6 ± 3; p = 0.03, Wilcoxon test). An increased percentage of Treg (CD3+ CD4+ CD25+) among the total CD3 cell count (4.9 % ± 1 % to 9.4 % ± 15 %) as well as inducible Treg (CD3+ CD8+ CD28-) was observed among CD3 cells (3.3 % ± 3 % to 11.8 % ± 8 %, p = 0.025) within 3 months of ECP treatment. A significant difference in the percentage of Treg was noted at month 3 (completed ECP)
between the ECP and the control groups (9.4 % ± 15 % versus 3 % ± 1 %; p = 0.01). Addition of ECP to standard immunosuppression was associated with a significantly higher GFR at 6 months and with a significant increase in natural Treg among CD3 cells. The authors stated that these preliminary results are promising.

Gurcan and Ahmed (2011) noted that long-term remission in epidermolysis bullosa acquisita (EBA) patients is difficult to achieve. Patients who are resistant or develop side effects to conventional immunosuppressive therapy (CIST) have been treated with several other agents. These researchers reviewed the clinical outcome in patients treated with a single drug or combination, and determined if long-term remission can be induced. Data on 71 patients were analyzed. There are no controlled trials. The regimens used included dapsone, colchicine, mesalazine, cyclosporine, mycophenolic acid, intravenous immunoglobulin, rituximab, daclizumab, extracorporeal photochemotherapy, and plasmapheresis. The use of CIST, especially in wide spread and recalcitrant patients, usually does not produce a prolonged clinical remission and can have hazardous side effects. Intravenous immunoglobulin, rituximab and immunoadsorption have been successfully used in some, but the benefits from their use may require additional studies.

Lucid et al (2011) stated that ECP has been shown to be a promising treatment for chronic GVHD; however, only a few case reports are available that examine the effectiveness of ECP for bronchiolitis obliterans (BO) after allogeneic stem cell transplantation (allo-SCT). Because of the poor response to traditional therapies, ECP has been explored as a possible therapeutic option for severe BO after allo-SCT. A total of 9 patients received ECP between July 2008 and August 2009 after a median follow-up of 23 months (range of 9 to 93 months) post-transplant. The primary indication for ECP was the development of BO in patients who had failed prior multi-drug regimens. The median number of drugs used for BO management before ECP was 5 (range of 2 to 7); this included immunosuppressive therapy. Six of 9 (67 %) patients responded to ECP after a median of 25 days (range of 20 to 958 days). No ECP-related complications occurred. ECP seemed to stabilize rapidly declining pulmonary function tests in about 2/3 of patients with severe and heavily pre-treated BO that developed after allo-SCT. The authors concluded that these findings support the need for a larger prospective study to confirm the impact of ECP on BO, and to consider earlier intervention with ECP to improve the outcome of BO after allo-SCT. Limitations of this study included its retrospective nature, small sample size, and short follow-up.

In a prospective study, Wolf et al (2012) examined the effect of a defined 20-week ECP protocol in patients with severe, refractory atopic dermatitis. The patient inclusion criteria included (i) disease duration of at least 1 year, (ii) "SCORing Atopic Dermatitis" (SCORAD; an objective clinical tool for assessing the severity (i.e., extent, intensity) of atopic dermatitis) greater than 45, and (iii) resistance to first-line therapy, including topical steroids, topical calcineurin inhibitors, and 1 form of phototherapy (UVA, UVB, or PUVA) or 1 second-line therapy, including systemic steroids or cyclosporine. A total of 10 patients (4 women and 6 men; age range of 29 to 61 years) were enrolled and treated with 2 sessions of standard ECP in 2-week intervals for 12 weeks and 4-week intervals thereafter until week 20. The patients' clinical status and response was determined by SCORAD at baseline and every 2 weeks, and quality of life was assessed every 4 weeks using SKINDEX, SF-36, and FACT scores. There was a statistically significant (p = 0.015) reduction of the mean SCORAD by 10.3 (95 % CI: 2.5 to 18.0) from 64.8 at baseline to 54.5 (i.e., 15.9 % reduction) at week 20. In a subset of patients (all of female sex), the relative reduction in SCORAD after ECP was more than 25 % at week 20. Improvement in quality of life measured by SKINDEX, SF-36, and FACT did not reach statistical significance. The authors concluded that they detected a small but
significant therapeutic effect of ECP in patients with severe, refractory atopic dermatitis. The findings of this small study need to be validated by well-designed studies with larger sample size and longer follow-up.

Stage 0-p BOS (i.e., an average decline in FEV1 of 10 to 19 % of the basal value of 2 measurements at least 3 weeks apart) refers to a decline in lung function that is thought to be predictive of BOS, but does not establish the diagnosis of BOS (Riise et al, 2011).

Russo et al (2012) noted that since 1960, different classes of immunosuppressive drugs have been used in the post-transplant follow-up. Each is assessed for its effectiveness in preventing rejection but also on the basis of the many side effects induced by prolonged treatment. To reduce these side effects, continuous development of knowledge and medical technology to create cutting-edge therapies in the field is necessary. One of these is ECP, which is a useful therapeutic tool for the development of immunomodulation supported by CD8+ clone-specific cytotoxic lymphocytes. The T cells targeted by ECP are modified by photo-activation and seem to develop marked immunogenicity with no suppression of the immune response. Recent studies suggested the possible utility of ECP in the treatment of glomerulonephritis and in countering rejection after transplantation of organs including the kidney.

Lai et al (2012) stated that the fundamental role of antibodies in the development of acute graft rejection has been established recently. Antibody-mediated acute rejection may develop at any time during the post-renal transplant period. Several therapeutic approaches have been proposed in the last decades. However, there is no standardized therapy. These researchers reported the Sapienza University experience of combined plasma treatment and high-dose intravenous immunoglobulin ± ECP. From January 2006 to September 2009, 6 patients were treated at Sapienza University. In 5 cases (83 %) complete regression of the acute rejection was observed, followed by stable renal function (median creatinine value at 1-year follow-up: 1.5 mg/dL). No adverse events were reported. The authors concluded that this approach seems to give good results in terms of graft survival and procedure safety. Moreover, they stated that further studies on a larger number of patients are needed to confirm the validity of these findings. Furthermore, comparison between the authors’ protocol and other treatments is necessary.

Benden et al (2012) noted that lung transplantation has evolved as an accepted therapy in selected adults and children with end-stage lung diseases. Outcomes following lung transplantation have improved in the recent era with a 5-year survival of greater than 70 % and an overall good functional status of surviving recipients. Many of the advances have been achieved by the use of modern immunosuppressive agents. To date, multiple strategies exist that may be employed when utilizing immunosuppression. These agents can be used in a variety of roles that may include induction, maintenance or rescue therapy, many of which are illustrated in this review including the current evidence to support their use. Infections in lung transplant recipients remain a significant cause of morbidity and mortality. Special considerations are required with the substantial burden of chronic infection in candidates with cystic fibrosis lung disease before transplantation. Furthermore, recent progress and advances in prevention and treatment of post-transplantation infectious complications were detailed. Chronic lung allograft dysfunction remains to be the burden of lung transplantation in the long-term. Unfortunately, there is no well-established therapy to address it. However, therapy attempts include change/augmentation of immunosuppression, use of neomacrolides and ECP, all of which were reviewed in detail.
Kalyanannis and Mallouri (2012) noted that over the last decades significant advances have been made in the field of donor selection, alternative transplant sources, immunosuppressive treatment and supportive care, as well as in the better understanding of the immunobiology of allogeneic hematopoietic stem cell transplantation (alotx). Nevertheless, several factors still affect unfavorably the outcome of the procedure. Graft-versus-host disease remains the leading cause of morbidity, non-relapse mortality and treatment failure post alotx. So far, steroids are the widely used 1st-line treatment for GVHD achieving considerable response rate however, patients who fail to respond to the initial therapy have a dismal prognosis and no standard treatment is well-established for them to date. In recent years, ECP has been proposed as a safe and effective treatment for steroid-refractory GVHD. Overall responses of 75% have been reported in the cutaneous and mucosal involvement and 45 to 65% in other organ manifestations (e.g., lung, liver and intestinal), allowing reduction and even discontinuation of steroids, thus contributing towards a significant reduction of morbidity. Although the mechanism of action of ECP is not fully understood, it seems that it has an immunomodulatory rather than an immunosuppression effect and induces immunotolerance, preserving the beneficial graft-versus-tumor effect. Given these very promising results in steroid-refractory or steroid-dependent GVHD, currently, ECPs being investigated as both first-line and prevention therapy also.

In a review on "Bronchiolitis obliterans after allo-SCT: Clinical criteria and treatment options", Uhling and colleagues (2012) stated that "though several studies have been performed in patients with BO after HSCT and lung transplantation, the studies are difficult to interpret because of the heterogeneity in the treatment schedules, diagnostic criteria and response assessment criteria. A prospective study randomized study of extracorporeal photopheresis treatment performed by Flower et al revealed a significant improvement of cGVHD in the skin, and indicated a steroid sparing effect on cGVHD in general. No effect on lung function parameters was noted .... Solid evidence regarding the efficacy of the various available treatment modalities in BO is still sparse".

On April 30, 2012, a National Coverage Determination (NCD) by the Centers for Medicare & Medicaid Services stated that ECP for the treatment of bronchiolitis obliterans syndrome (BOS) following lung allograft transplantation will be covered only when ECP is provided under a clinical research study that meets criteria. An accompanying decision memorandum (CMS, 2012) stated that the evidence is insufficient to conclude that, in Medicare beneficiaries with BOS developing after lung allograft transplantation refractory to standard immunosuppressive therapy, ECP will improve patient centered health outcomes. However, based on its previously published criteria for considering CED, CMS concluded that evidence of basic safety, potential for patient-centered health outcome improvement, and demonstrated difficulty of conducting appropriate clinical trials are sufficient in combination to persuade CMS to propose coverage for ECP therapy for BOS after lung allograft transplantation within approved clinical research studies.

Epler (2010) stated that constrictive bronchiolitis is a bronchiolar airway disease that surrounds the lumen with fibrotic concentric narrowing and obliteration. The mosaic pattern seen on the expiratory high-resolution chest CT scan is diagnostic in an individual with shortness of breath, early inspiratory crackles, and irreversible airflow obstruction. Swyer-James-MacLeod syndrome is no longer considered a congenital disorder but as constrictive bronchiolitis detected in young adults who had infectious pneumonia during infancy. For lung transplant recipients, tacrolimus continues to be an important immune suppression medication, extracorporeal photopheresis may improve the decline of pulmonary function, and azithromycin may be effective in some lung
transplant recipients for treatment of bronchiolitis obliterans syndrome for prevention of constrictive bronchiolitis.

Also, an UpToDate review on “Bronchiolitis in adults” (King, 2014) does not mention the use of extracorporeal photochemotherapy/photopheresis as a therapeutic option of constrictive bronchiolitis.

Plieri et al (2014) presented the case of a patient with generalized morphea whose disease completely resolved after combination therapy with ECP and broad-band UVA treatments. This was single case study that used combinational treatments. Furthermore, an UpToDate review on “Treatment of morphea (localized scleroderma) in adults” (Jacob, 2014) states that “Treatments of morphea with penicillin, penicillamine, colchicine, hydroxychloroquine, mycophenolate mofetil, cyclosporine, bosentan, infliximab, and extracorporeal phototherapy have been reported. There is little evidence to support the efficacies of these treatments”.

Liszewski et al (2014) stated that necrobiotic xanthogranuloma (NXG) is a disease of fibrotic or telangiectatic granulomatous papules and nodules that can ultimately progress into ulcerated plaques. Although the exact cause of NXG is unknown, it most often occurs in patients with paraproteinemia secondary to a hematologic disease. Consequently, therapy for NXG is targeted at treating the underlying hematologic disease, and subsequent paraproteinemia, with alkylating agents, antimetabolites, radiation, and/or immunosuppressive agents. Cases refractory to these therapies often have poor outcomes. These investigators reported the successful treatment of 2 patients with refractory NXG with 2 different modalities: (i) ECP and (ii) intravenous immunoglobulin (IVIG). The first case showed a patient without paraproteinemia who had success with ECP and IVIG, and the second is a patient with paraproteinemia treated effectively with IVIG. The authors concluded that the beneficial response of these patients to IVIG, as well as ECP, showed that they may be an effective treatment option for refractory NXG. These preliminary findings need to be validated in well-designed studies.

Furthermore, an UpToDate review on “Juvenile xanthogranuloma (JXG)” (Puttgen, 2014) does not mention extracorporeal photopheresis as a therapeutic option.

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**CPT codes covered if selection criteria are met:**

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**ICD-9 codes covered if selection criteria are met:**

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http://qawww.aetna.com/cpb/medical/data/200_299/0241_draft.html 04/22/2015
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**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

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<td>Pityriasis rubra pilaris</td>
</tr>
<tr>
<td>710.0</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>710.1</td>
<td>Systemic sclerosis [scleroderma]</td>
</tr>
<tr>
<td>710.2</td>
<td>Sicca syndrome</td>
</tr>
<tr>
<td>710.4</td>
<td>Polymyositis</td>
</tr>
<tr>
<td>714.0 - 714.9</td>
<td>Rheumatoid arthritis and other inflammatory polyarthropathies</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


