Extracorporeal Photopheresis

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Overview

This Coverage Policy addresses the use of extracorporeal photopheresis (CPT® 36522).

Coverage Policy

Extracorporeal photopheresis is considered medically necessary for ANY of the following indications:

- erythrodermic cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides and Sézary syndrome)
- acute or chronic graft-versus-host disease (GVHD)
- cardiac transplantation (rejection prophylaxis or cellular/recurrent rejection)
- lung transplantation (bronchiolitis obliterans syndrome)

Extracorporeal photopheresis is considered experimental, investigational or unproven for ANY other indication, including ANY of the following:

- solid organ graft rejection, not listed above as covered
- autoimmune diseases (e.g., multiple sclerosis, scleroderma, diabetes mellitus [DM] type 1, rheumatoid arthritis, systemic lupus erythematosus [SLE], psoriasis, and pemphigus)
- atopic dermatitis
- Crohn’s disease
- chronic B cell leukemia
- chronic obstructive bronchitis
- eosinophillic fasciitis
- hepatitis C
- human immunodeficiency virus (HIV)
- myasthenia gravis
- nephrogenic fibrosing sclerosis/dermopathy
- nephrogenic peritonitis
- prevention of re-stenosis after percutaneous transluminal coronary angioplasty (PTCA)
- composite tissue allotransplantation

General Background

Extracorporeal photopheresis, also referred to as ECP, is a type of apheresis. It is a cell-based immunomodulatory therapy that removes blood via a machine and isolates white blood cells. Then, these white blood cells are exposed to a photoactive compound called 8-methoxypsoralen followed by exposure to ultraviolet A light before returning the blood to the patient. The mechanism of action of ECP remains elusive. ECP produces a number of immunological changes and in some patients produces immune homeostasis with clinical improvement. The use of ECP, either alone or in combination with other modalities has been proposed for the treatment of a number of disorders including cutaneous T-cell lymphoma (CTCL), primarily mycosis fungoides and Sézary syndrome, graft-versus-host disease, solid organ graft rejection, and several autoimmune disorders and dermatologic conditions.

U.S. Food and Drug Administration (FDA)

ECP was first approved by the FDA for the treatment of advanced cutaneous T-cell lymphoma (CTCL) in 1988. A number of open and closed systems exist. In the United States, only closed systems have been FDA approved. Therakos (Exton, PA) has developed several generations of closed systems. The closed system CELLEX has recently replaced the UVAR XTS®.

Literature Review

ECP has been used for over 35 years in the treatment of erythrodermic CTCL and over 20 years for chronic and acute GvHD and solid organ transplant rejection. Other proposed indications (organized by American Society for Apheresis Category and Grade) are addressed below.

Systemic sclerosis (SSc) is a systemic connective tissue disorder of unknown etiology characterized by the accumulation of collagen and other extracellular matrix proteins, in skin and other organs. Antinuclear antibodies are present in more than 95% of patients with SSc. Identifying disease subtype, stage, and involved organs is very important in determining the best course of action for treatment. Current therapies use medications that focus on the four main features of the disease: inflammation, autoimmunity, vascular disease, and tissue fibrosis.

Psoriasis is a chronic skin disorder with high genetic predisposition. Plaques and papules are result of hyperproliferation and abnormal differentiation of epidermis which leads to its thickening (acanthosis). There are topical and systemic therapies. Systemic therapies include methotrexate, retinoids, systemic immunosuppression (cyclosporine). Recently, biologic agents are used more frequently.

Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10–30% of children worldwide and frequently occurs in families with other atopic diseases. The treatment of AD requires a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy (including tacrolimus), identification, and elimination of flare factors (especially foods), and, if necessary, systemic therapy. In refractory disease phototherapy (UVA-1, UVB, or PUVA) are used.

Ulcerative colitis (UC) and Crohn’s disease (CD) are chronic inflammatory diseases of the gastrointestinal tract and are collectively known as inflammatory bowel disease (IBD). First-line therapies for IBD include anti-
Inflammatories, steroid, and immunosuppressive medications. Both corticosteroids and 5-aminosalicylic acids (5-ASAs) are effective in achieving remission. In addition, 5-ASAs and immunosuppressant drugs reduce the risk of subsequent relapse of activity in quiescent disease. Unfortunately, complications from chronic steroid administration include steroid resistance, dependency, and the sequelae of long-term steroid use. For those with refractory disease thiopurines, such as azathioprine and 6-mercaptopurine are used. In CD specifically, infliximab, monoclonal antibody to anti-tumor necrosis factor, may induce remission and has been FDA cleared for this purpose.

Nephrogenic systemic fibrosis (NSF), formerly called nephrogenic fibrosing dermopathy, is a rare but severe systemic disorder in patients with acute or chronic kidney disease (CKD), almost exclusively associated with the administration of gadolinium (Gd) containing contrast agents. Avoidance of Gd administration, if possible, has been recommended for patients with GFR <30 mL/min; resulting in decreased reports of new cases. Replacement of renal function through renal transplant has been associated with cessation of progression and reversal in some patients. It should be noted that dialysis has not been associated with improvement once symptoms are established. Initiation of prophylactic hemodialysis shortly after exposure to Gd may decrease the likelihood of the harmful effect.

Pemphigus vulgaris is a rare, potentially fatal, autoimmune mucocutaneous blistering disease. Introduction of corticosteroids reduced the mortality rate from 70 to 100% to 30%. However, long-term administration of high-dose corticosteroids can be associated with severe adverse effects. Other therapeutic options include dapsone, gold, and systemic antibiotics, which are often used in combination with other immunosuppressant agents (azathioprine, methotrexate, cyclophosphamide).

Dermatomyositis (DM)/polymyositis (PM) are forms of idiopathic inflammatory myopathy, with significant morbidity and mortality even with standard treatments. Muscle weakness, usually insidious at onset but worsening over time, is characteristic of both. Severity is variable. Most patients respond to corticosteroid therapy initially. Recurrent or resistant disease may require higher corticosteroid doses, azathioprine, methotrexate, rituximab, or intravenous immune globulin. Remission occurs in most of the patients after months of immunosuppressive and intensive supportive therapy, especially in juvenile DM.

**Professional Societies/Organizations**

The Writing Committee of the American Society for Apheresis (ASA) updated their Guidelines on the Use of Therapeutic Apheresis in Clinical Practice in 2016 (Schwartz, et al., 2016). Using an evidence-based approach, the ASA developed Category Definitions for Therapeutic Apheresis as follows:

- **Category I:** Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
- **Category II:** Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
- **Category III:** Optimum role of apheresis therapy is not established. Decision making should be individualized.
- **Category IV:** Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful.

and evidence grading 'Grade' descriptions as follows:

- Grade 1A: Strong recommendation, high-quality evidence
- Grade 1B: Strong recommendation, moderate-quality evidence
- Grade 1C: Strong recommendation, low-quality or very low-quality evidence
- Grade 2A: Weak recommendation, high-quality evidence
- Grade 2B: Weak recommendation, moderate-quality evidence
- Grade 2C: Weak recommendation, low-quality or very low-quality evidence

The ASA addressed these following indications specific to ECP (organized by Category and Grade):
<table>
<thead>
<tr>
<th>Indication</th>
<th>Category</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous T-cell lymphoma; mycosis fungoides; Sezary syndrome (Erythrodermic)</td>
<td>I</td>
<td>IB</td>
</tr>
<tr>
<td>Cardiac transplantation, Cellular/recurrent rejection</td>
<td>II</td>
<td>IB</td>
</tr>
<tr>
<td>Graft-versus-host disease, (Chronic, skin or non-skin)</td>
<td>II</td>
<td>IB</td>
</tr>
<tr>
<td>Lung transplantation, Bronchiolitis obliterans syndrome</td>
<td>II</td>
<td>IC</td>
</tr>
<tr>
<td>Graft-versus-host disease, (Acute, skin or non-skin)</td>
<td>II</td>
<td>IC</td>
</tr>
<tr>
<td>Cardiac transplantation, Rejection prophylaxis</td>
<td>II</td>
<td>2A</td>
</tr>
<tr>
<td>Scleroderma (systemic sclerosis)</td>
<td>III</td>
<td>2A</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>III</td>
<td>2B</td>
</tr>
<tr>
<td>Atopic (neuro-) dermatitis</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma; mycosis fungoides; Sezary syndrome (Non-erythrodermic)</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Inflammatory bowel disease, Crohn’s Disease</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Nephrogenic systemic fibrosis</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Pemphigus vulgaris, Severe</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Dermatomyositis/polymyositis</td>
<td>IV</td>
<td>2C</td>
</tr>
</tbody>
</table>

**National Comprehensive Cancer Network Guidelines™ ([NCCN Guidelines™](https://www.nccn.org): The Primary Cutaneous Lymphoma guideline (v.2.2019) notes that ECP is one of several suggested treatment regimens for patients with mycosis fungoides/Sezary syndrome.

**American Heart Association:** A scientific statement from the American Heart Association on Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management states that the mechanism by which extracorporeal photopheresis works to prevent or treat transplant rejection has not been well defined, although irradiated T-helper cell-induced immunosuppression is the main theory (Colvin, et al., 2015).

**Centers for Medicare & Medicaid Services (CMS):**

- **National Coverage Determinations (NCDs):** Extracorporeal Photopheresis (110.4) is a longstanding NCD that covers:
  - Palliative treatment of skin manifestations of cutaneous T-cell lymphoma that has not responded to other therapy (1988)
  - Acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment (2006)
  - Chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment (2006)
  - Treatment of bronchiolitis obliterans syndrome (BOS) following lung allograft transplantation only when extracorporeal photopheresis is provided under a clinical research study that meets certain criteria (2012).
- **Local Coverage Determinations (LCDs):** None.

**Use Outside of the US**

The UK Photopheresis Society updated their consensus statement on the role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection (Alfred, et al., 2017). Using an evidence-based approach, they have the following recommendations:

**Strength of recommendation**

- **A:** There is good evidence to support the use of the procedure.
- **B:** There is fair evidence to support the use of the procedure.
- C: There is poor evidence to support the use of the procedure.
- D: There is fair evidence to support the rejection of the use of the procedure.
- E: There is good evidence to support the rejection of the use of the procedure.

Quality of evidence
- I: Evidence obtained from at least one properly designed, randomized controlled trial.
- II-i: Evidence obtained from well-designed controlled trials without randomization.
- II-ii: Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group.
- II-iii: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III: Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
- IV: Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts of evidence).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
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<tbody>
<tr>
<td>CTCL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonerythrodermic (stage IA-IIB)</td>
<td>E</td>
<td>I</td>
</tr>
<tr>
<td>Erythrodermic (stage III/IVA/B1/0)</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>CTCL (ECP and combination therapy)</td>
<td></td>
<td></td>
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<tr>
<td>ECP + interferon-alpha</td>
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<td></td>
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<tr>
<td>Nonerythrodermic (stage IA-IIB)</td>
<td>C/B</td>
<td>II-ii</td>
</tr>
<tr>
<td>Erythrodermic (stage III/IVA/B1/0)</td>
<td>C</td>
<td>II-ii</td>
</tr>
<tr>
<td>ECP + total skin electron beam therapy</td>
<td>B</td>
<td>II-ii</td>
</tr>
<tr>
<td>ECP + PUVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrodermic</td>
<td>C</td>
<td>II-i</td>
</tr>
<tr>
<td>ECP + FAMP</td>
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<td></td>
</tr>
<tr>
<td>Erythrodermic</td>
<td>C</td>
<td>II-i</td>
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<tr>
<td>GvHD</td>
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<tr>
<td>Chronic GvHD</td>
<td></td>
<td></td>
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<tr>
<td>Cutaneous/mucous membrane</td>
<td>A</td>
<td>II-ii</td>
</tr>
<tr>
<td>Hepatic</td>
<td>B</td>
<td>II-iii</td>
</tr>
<tr>
<td>Gastro-intestinal/pulmonary</td>
<td>D</td>
<td>II-ii</td>
</tr>
<tr>
<td>Acute GvHD</td>
<td>B</td>
<td>II-ii</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>B</td>
<td>II-ii</td>
</tr>
<tr>
<td>Hepatic</td>
<td>B</td>
<td>II-ii</td>
</tr>
<tr>
<td>Gastrointestinal/pulmonary</td>
<td>C</td>
<td>II-iii</td>
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<td>Transplantation rejection</td>
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<tr>
<td>Cardiac</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Renal</td>
<td>C</td>
<td>II-iii</td>
</tr>
<tr>
<td>Lung</td>
<td>C</td>
<td>II-iii</td>
</tr>
<tr>
<td>Liver</td>
<td>C</td>
<td>II-iii</td>
</tr>
</tbody>
</table>

**Coding/Billing Information**

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:
### CPT® Codes | Description
---|---
36522 | Photopheresis, extracorporeal


#### References


11. Centers for Medicare and Medicaid Services (CMS). National Coverage Determination (NCD) for Extracorporeal Photopheresis (110.4). 2012. Accessed March 2019. Available at URL address: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=113&ncdver=3&SearchType=Advanced&CoverageSelection=Both&NCSelection=NC%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=SAD%7cEd&PolicyType=Both&s=All&KeyWord=Extracorporeal+Photopheresis&KeyWordLookUp=Title&KeyWordSearchType=Exact&q=true&bc=IAAAACAAAAAAA%3d%3d

12. Colvin MM, American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; American Heart Association Heart Failure and Transplantation Committee of the Council on Cardiopulmonary Critical Care, Perioperative and Resuscitation; American Heart Association


