Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can

be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Evidence Table for the Refractory Acute Cardiac Allograft Rejection Indication

<table>
<tr><th rowspan="2">Author/ Year</th><th rowspan="2">Study Design</th><th rowspan="2">Demographics</th><th rowspan="2">Outcome measures</th><th colspan="2">Results</th><th rowspan="2">Methodological Comments</th></tr>
<tr><th>Intervention group</th><th>Control group</th></tr>
<tr><td>Costanzo-Nordin MR, 1992</td><td>Prospective, uncontrolled clinical trial

Inclusion: histological evidence of moderate cardiac Tx rejection despite routine immunosuppressive regimen

Exclusions: leukopenia, hemodynamic compromise

UVAR system; Oral 8-MOP

Up to 2 rounds of photopheresis administered</td><td>N= 7

3 men; 4 women

Age range: 19-64 years</td><td>Change in EMB histology

Efficacy based on EMB results classified as:

Ongoing rejection
Resolving rejection
Absent rejection</td><td>Average 5 months of post-photopheresis follow-up

9 episodes of rejection—5 required 1 photopheresis procedure and 4 required 2 procedures

No adverse events occurred during photopheresis

8/9 rejection episodes successfully treated with photopheresis

Resolution of histological evidence of rejection seen average 33 days after photopheresis

No deaths and 2 infections occurred post-photopheresis (details not provided)</td><td>Not Applicable</td><td>Very small sample size and uncontrolled nature of trial severely limit the usefulness of the results.</td></tr>
<tr><td>Dall'Amico R, 1995</td><td>Prospective, uncontrolled clinical trial

Inclusion: multiple acute rejection episodes (details not provided)

UVAR system; 200 ug 8-MOP administered ex vivo

Photopheresis performed over 2 days interval every 4 weeks for 6 months

Routine immunosuppression regimen: ATG, cyclosporine, azathioprine

Rejection therapy: steroids; OKT3 or methotrexate as needed</td><td>N= 8

6 men; 2 women

Age range: 36-58 years</td><td>Change in EMB histology

Comparison of dose of each immunosuppressive drug before and after photopheresis</td><td>Fraction EMB negative for rejection increased from 13% to 41% after photopheresis

Dose reduction of:

- steroid: 44% (in 7 patients)
- cyclosporine: 21% (in 5 patients)
- azathioprine: 29% (in 3 patients)</td><td>Not Applicable</td><td>Very small sample size and uncontrolled nature of trial severely limit the usefulness of the results.</td></tr>
<tr><td>Dall'Amico R, 1997</td><td>Prospective, uncontrolled clinical trial

Inclusion: history of ≥2 acute rejection episodes during prior 3 months refractory to standard rejection therapy (steroids, OKT3, ATG, or methotrexate)

UVAR system; 100 ug 8-MOP administered ex vivo

2 photopheresis groups:

Group 1—photopheresis performed over 2 days interval every 4 weeks for 6 months
Group 2—photopheresis performed weekly x 1 month then every 2 weeks for 2 months, then monthly for 3 months</td><td>N= 22 (12 in Group 1; 10 in Group 2)

15 men; 7 women

Mean age: 49.8 years in Group 1 and 50.4 years in Group 2</td><td>Change in EMB histology

Grade 0 or 1A considered to represent complete resolution of rejection</td><td><table><tr><th></th><th>Group 1</th><th>Group 2</th></tr><tr><td># drop outs</td><td>1 (lack of vascular access)</td><td>1 (death due to Hep C infection)</td></tr><tr><td># with resolution of rejection (mean time to resolution)</td><td>9/11 (29.5 days)</td><td>9/9 (13.8 days)</td></tr><tr><td># photopheresis treatments/patient</td><td>12</td><td>22</td></tr><tr><td>Mean # rejection relapses per patient during 6 months of photopheresis</td><td>1.36</td><td>0.8</td></tr><tr><td># courses of steroid-based rejection therapy during 6 months of photopheresis</td><td>7</td><td>1</td></tr><tr><td># courses of methotrexate-based rejection therapy during 6 months of photopheresis</td><td>1</td><td>1</td></tr></table>1 patient in Group 1 had herpes zoster infection</td><td>Not Applicable</td><td>Small sample size.

Uncontrolled nature of trial severely limits the usefulness of the results.</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>1 patient in Group 2 had interstitial pneumonia

1 patient in Group 2 had symptomatic hypotension during a photopheresis procedure (pre-existing anemia and low body weight)</td><td></td><td></td></tr>
<tr><td>Giunti G, 1999</td><td>Prospective, uncontrolled clinical trial

Inclusion: history of recurrent acute rejection despite daily triple immunosuppressive therapy

UVAR system; 200 ug 8-MOP administered ex vivo

Photopheresis performed over 2 consecutive days per week x 1 month, then weekly x 1 month, then biweekly x 2 months, then monthly x 2 months

All episodes of acute rejection treated with methylprednisolone and/or ALG</td><td>N= 6

All men

Age range: 50-66 years</td><td>Change in EMB histology</td><td>Moderate acute rejection episodes decreased from 0.4 to 0.07 rejections per month per patient (p<0.02)</td><td>Not Applicable</td><td>Very small sample size.

Uncontrolled

Limited reporting of results.</td></tr>
<tr><td>Dall'Amico R, 2000</td><td>Prospective, uncontrolled clinical trial

Inclusion: history of acute rejection (grade 3A-3B); ≥2 rejection episodes in 3 months prior to photopheresis despite standard immunosuppression therapy (oral methylprednisolone, cyclosporine, azathioprine)

UVAR system; 200 ug 8-MOP administered ex vivo

Photopheresis performed over 2 consecutive days per week x 1 month, then 2 treatments biweekly x 2 months, then monthly x 3 months

Acute rejection treated with hi dose methylprednisolone and/or OKT3</td><td>N= 11

5 men; 6 women

Age range: 35-65 years</td><td>Change in EMB histology

Grade 0 or 1A considered to represent complete resolution of rejection</td><td>2 drop-outs: 1 death due to hepatitis C infection; 1 patient had rejection relapse unresponsive to photopheresis and hi dose steroids

Results of EMB
<table><tr><th>Histological Grade</th><th>Pre-photopheresis (% of biopsies)</th><th>During Photopheresis (% of biopsies)</th></tr><tr><td>Negative (Grade 0)</td><td>25</td><td>27</td></tr><tr><td>1A</td><td>21</td><td>45</td></tr><tr><td>1B</td><td>6</td><td>2</td></tr><tr><td>2</td><td>6</td><td>8</td></tr><tr><td>3A</td><td>29</td><td>17</td></tr><tr><td>3B</td><td>13</td><td>1</td></tr></table>
6 rejections occurred during 60 month post-photopheresis follow-up:

4 reversed with photopheresis
1 reversed with hi dose steroids
1 reversed with methotrexate after failure of steroids and photopheresis

All rejections reversed after mean time of 14.2 days (range 7-32 days)

During photopheresis there was 1 case of interstitial pneumonia and 1 case of symptomatic hypotension in a patient with anemia and low body weight</td><td>Not Applicable</td><td>Small sample size.

Uncontrolled</td></tr>
<tr><td>Lehrer MS, 2001

(submitted by requestor)</td><td>Case study

Each patient had acute heart transplant rejection (Grade III or IV) refractory to standard immunosuppression therapy (cyclosporine, azathioprine, and prednisone) and anti-rejection therapy

3/4 patients began to experience rejection within weeks of transplantation

Details of photopheresis administration were not provided</td><td>N= 4

3 men; 1 woman

Age range: 20-54 years</td><td>Change in EMB histology</td><td>All patients tolerated the photopheresis well

Photopheresis resulted in a change of the rejection status to Grade 0 or I for all 4 patients

2/4 patients experienced a sustained response to photopheresis (4 months and 6 years after completion of photopheresis). The remaining 2 patients had rejection-related complications within 1 year of completing photopheresis that resulted in death</td><td>Not Applicable</td><td>Small sample size.

Not a true clinical trial.

Uncontrolled</td></tr>
</table>

Legend: Tx—transplantation EMB—endomyocardial biopsy 8-MOP—8-methoxypsoralen

Evidence Table for Refractory Chronic Graft versus Host Disease

Author/ Year	Study Design	Demographics	Outcome measures	Results		Methodological Comments
				Intervention group	Control group	
Foss, 2005	Prospective, uncontrolled, single center clinical trial Inclusion: steroid-resistant or refractory cGvHD while on a standard immunosuppressive regimen UVAR system; 8-MOP administered ex vivo 2 ECP groups: Group 1 (n= 16)—ECP performed over 2 day interval every 2 weeks Group 2 (n= 7)—ECP performed over 2 day interval weekly ECP performed til response plateau of ≥ 2 months or progression (details not provided) All episodes of acute rejection treated with methylprednisolone and/or ALG Response assessed monthly while ECP performed and defined as: Skin-- ≥50% improvement in rash; improvement in joint mobility or ability to pinch skin over involved areas Liver-- ≥50% decrease in serum bilirubin GI—decrease frequency of stools	N= 25 (23 adults) 16 men; 7 women Age range: 18 - 59 years	Overall response rate (response in ≥ 1 area of disease) overall survival correlation between clinical parameters and response to ECP was determined Change in dose of immunosuppression drugs	ECP performed for a median of 9 months (range 3-24 months) Overall response rate= 64% 20/ 25 patients: improvement of cutaneous manifestations of cGvHD 6/13 patients: healing of oral mucosal ulcerations 3/6 patients: increased flexibility of joints 1/25 patient: 50% improvement of DLCO 1/25 patient: resolution of diarrhea Median survival= 51 months (measured from day 0 of transplantation) Median survival for responders v. non-responders not significantly different 15 patients had serious adverse events (not ECP related) 1 patient discontinued ECP due to primary disease recurrence 10 deaths reported but details not provided Dose reduction/discontinuation of: - steroid: 11 patients - MMF: 12 patients - tacrolimus: 5 patients No significant correlation found between various clinical parameters and response	Not applicable	Small sample size Lack of control group No patients ≥65 years of age studied
Garban, 2005	Prospective, uncontrolled, single center clinical trial Inclusion: steroid-resistant acute or cGvHD Cobe system used to separate cells; 8-MOP added ex vivo 6 courses of ECP given during the first 3 weeks (induction regimen); if complete response or no response seen, no more courses given; if partial response, 1 course/week given til complete response seen (consolidation regimen) Complete response= total resolution of all	N= 15 chronic Age range: 14-62 years	Complete clinical response Partial clinical response Change in hemoglobin and platelet counts	12 patients with cutaneous involvement had complete response; most responses occurred in the first weeks of treatment Cutaneous and GI involvement resolved in parallel fashion; hepatic improvement was only transient; stabilization of bronchiolitis obliterans occurred without need for steroids 4 patients became totally free of immunosuppression for more than 1 year 6 patients died from relapse of malignant disease 4/15 patients developed thrombocytopenia; most patients did not receive RBC transfusions Duration of response (range): none to 72 months	Not applicable	Small sample size Lack of control group No patients ≥65 years of age studied Only general statements provided regarding the response to treatment; lacking detailed listing of data/results.

	manifestations of cGvHD and discontinuation of all immunosuppression drugs Partial response= ≥ 50% resolution of skin manifestations or 100% resolution but continuation of immunosuppression; ≥50% improvement in one involved organ (details not provided)					
Couriel, 2005	Retrospective chart review, single center Inclusion: all patients regardless of age with steroid-refractory cGvHD who were treated with ECP between 01/98 and 10/02 cGvHD diagnosis based on clinical manifestations, not the date of onset UVAR system; 8-MOP administered ex vivo ECP performed 2-4x/week til partial response observed, then # of treatments was decreased by 1/week; maintenance consisted of 2 treatments every 2 weeks; treatment discontinuation, amount of titration, and duration was determined by treating physician	N= 71 33 men; 38 women Age range: 5-70 years (median= 39 years)	Response to therapy (complete, partial, mixed or no response) Non-relapse mortality Overall survival Predictors of non-relapse mortality, and timing of the response were also analyzed	Overall response rate: 61% (n= 43; 14 complete response, 29 partial response) Median time from onset of ECP to complete response: 27 days (13-238) 30/43 patients maintained the initial response for a median duration of 18 months (0.4-65 months); the remaining 13 of 43 initial responders progressed after a median of 23 days (16-188) Overall survival at 5 years: 19% Cumulative incidence of non-relapse mortality: 46% Causes of death: GvHD plus infection- 67%, relapse- 29%, infection outside setting of GvHD or its treatment- 2%, hemorrhage- 2% 4 patients with mild, reversible toxicity that did not require discontinuing ECP- abdominal pain (n=1), hypertension (n=1), hypotension (n=1), fever (n=1) thrombocytopenia at onset of ECP was associated with a lower response response to ECP and platelet count at initiation of ECP were the strongest predictors of non-relapse mortality	Not applicable	Retrospective design lack of control group Unsure of number of pediatric patients and how pediatric results impacted the overall results Used the new definition of chronic GvHD to categorize patients
Rubegni, 2005	Prospective, uncontrolled, single center clinical trial Inclusion: patients with steroid-refractory cGvHD UVAR system; 8-MOP administered ex vivo Frequency of ECP was not stated	N= 32 20 men; 12 women Age range: 18-60 years	Response to therapy (per organ of involvement) Overall outcome calculated using the following categories: Determinant= complete response in all involved organs + ≥50% reduction in immunosuppression Good= status assigned if outcome is between determinant and ineffective Ineffective= disease progression in an organ, or need to increase immunosuppression, or complete response	Overall outcome: 78% responders (22% Determinant, 56% Good) ; 22% non-responders Minor side effects noted (slight hypotension, venipuncture site hematomas)	Not applicaable	Small sample size Lack of control group Lack of information regarding ECP regimen

			not seen in any organ + immunosuppression not reduced by ≥50% Score of Determinant or Good= responder; Ineffective= non-responder			
Ilhan, 2004	Case study, uncontrolled Inclusion: patients with steroid-refractory Cutaneous and/or visceral cGvHD UVAR system; 8-MOP administered ex vivo ECP performed over 2 consecutive days every 4 weeks til GvHD signs/symptoms resolved (8 months maximum)	N= 8 2 men; 6 women Age range: 17-45 years	Response to therapy (per organ of involvement) Change in dose of immunosuppression drugs	6/8 patients had a favorable response (e.g., improvement in respiratory function, complete resolution of cutaneous and oral mucosal lesions, regression of cholestatic parameters) 1 patient experienced Grade 4 thrombocytopenia	Not applicable	Observational study design Small sample size Lack of control group No patients ≥65 years of age studied Only general statements provided regarding the response to treatment; lacking detailed listing of data/results. For example, according to the authors there was a reduced need for hospitalization but no data were provided to support this statement.
Apisarnthanarax, 2003	Retrospective chart review, single center Inclusion: steroid-refractory or dependent cutaneous cGvHD who were treated with at least 4 weeks of ECP between 09/98 and 08/01 cGvHD diagnosis based on date of onset after transplantation (>100 days) UVAR or UVAR XTS system; 8-MOP administered ex vivo ECP performed using varying schedules and intensity depending on disease severity over the 36 month study period	N= 32 Men: women ratio= 1:1.3 Age range: 5-70 years (30 adults)	Response to therapy (complete, partial, steroid-sparing) Overall and cGvHD-related mortality	34% of patients had steroid-refractory disease 66% had steroid-dependent disease Median number of ECP sessions= 6/month Median number of total sessions= 34 ECP sessions discontinued due to: - lack of response or response plateau in 10 patients - resolution of disease in 5 patients - death due to visceral GvHD progression or infection in 5 patients - access difficulty in 1 patient - central line infection in 1 patient - fluid overload in 1 patient - deep vein thrombosis in 1 patient Overall response rate= 56% Complete response rate= 22% Responders received median of 6 sessions and nonresponders received a median of 7 sessions/month	Not applicable	Retrospective design lack of control group Used the old definition of chronic GvHD to categorize and select patients for inclusion High variability regarding ECP regimen used for each patient

				18/28 (64%) initially on steroids had a 50% reduction in dose (6/18 eventually discontinued all steroid use) 3 patients had complications related to the indwelling catheter Minor treatment-related side effects such as transient hypotension noted but not quantified		
Seaton, 2003	Prospective, uncontrolled, single center clinical trial Inclusion: patients with steroid-refractory cGvHD UVAR or UVAR XTS system; 8-MOP administered either IV or ex vivo ECP performed over 2 consecutive days every 2 weeks for 4 months then monthly; at 6 months a decision was made to halt or continue treatment depending on clinical response and patient preference	N= 28 20 men; 8 women Age range: 18-51 years	Response to therapy (per organ of involvement) Clinical response= >25% change in score + stable or reduced immunosuppression doses	Median duration of treatment: 6 months (range, 1-58) Cutaneous outcome: 8/21 responders at 3 months; 10/21 at 6 months; complete remission in 1/21 Hepatic outcome: 7/25 responders at 3 months Pulmonary outcome: median vital capacity in 8 patients reduced by 2% 5 patients had severe complications: 4 deaths due to advanced cGvHD, 1 case of ARDS that fully resolved Pre-treatment immunosuppression doses remained stable in 15/28, were reduced in 9/28, and were increased in 4/28	Not applicable	Small sample size Lack of control group No patients ≥65 years of age studied
French, 2002	Retrospective, uncontrolled, single center clinical study Inclusion: patients with cGvHD that developed >100 days after transplantation UVAR system; 8-MOP administered orally ECP performed over 2 consecutive days once a month (total duration of treatment not stated)	N= 12 7 men; 5 women Age range: 25-59 years	Response to therapy (per organ of involvement): complete response, partial response, no change	Response rate: Cutaneous- 8/12 (2 complete responses) Musculoskeletal- 5/6 (1 complete response) Oral/mucosal- 5/5 (0 complete response) Hepatic- 2/2 (1 complete response) 9/12 patients had a decrease in the dose of at least 1 immunosuppressive drug	Not applicable	Retrospective study design Small sample size Lack of control group No patients ≥65 years of age studied Used the old definition of chronic GvHD to categorize and select patients for inclusion Focus of study was on assessing the correlation of ECP response with degree of T cell clonality, and not on health outcomes. Safety/toxicity not addressed.
Child, 1999	Case study, uncontrolled Inclusion: refractory cGvHD UVAR system; 8-MOP administered ex vivo ECP performed 2x a month for 4 months, then 1x a month for 3 months	N= 11 9 men; 2 women Age range: 18-47 years	Response to therapy (per organ of involvement)	3 drop-outs: 1 death from cyclosporine-induced renal failure; 1 pneumonia that was successfully treated and patient restarted on ECP; 1 withdrawal after 4 months by patient request Overall improvement rate= 48% In majority of patients the improvement in skin disease was greater during the first 4 months of treatment than during the next 3 months	Not applicable	Observational study design Small sample size Lack of control group

				All patients able to reduce dose of immunosuppressive drugs Response rate: Cutaneous- 10/10 (0 complete response) Oral/mucosal- 2/4 (0 complete response) Hepatic- 1/6 (0 complete response) Pulmonary- 2/5 (0 complete response) No significant side effects		
Smith, 1998	Prospective, uncontrolled, single center, pilot clinical study Inclusion: refractory cGvHD UVAR system; 8-MOP administered orally—dose of 8-MOP adjusted based on serum levels ECP performed over 2 consecutive days every 3 weeks then 2-3x per week; frequency of treatment then modified on an individual basis	N= 18	Response to therapy (per organ of involvement) : complete response, partial response, no response	3 complete responses 3 partial responses 2 responses with progression of disease 10 no response 11/18 deaths related to GvHD progression, primary disease relapse, and/or infection Toxicities included: GI upset, catheter-related complications (n= 5) including sepsis (n= 4) , increased need for red blood cell and platelet transfusions (n= 1)	Not applicable	Small sample size Lack of control group Variable administration of ECP Used the old definition of chronic GvHD to categorize and select patients for inclusion
Greinix, 1998	Case study, uncontrolled Inclusion: all consecutive patients with refractory cGvHD that were treated with ECP since 1993 UVAR system; 8-MOP administered ex vivo ECP performed over 2 consecutive days every 2 weeks for 3 months and then every 4 weeks until resolution of sign/symptoms of cGvHD	N= 15	Response to therapy (per organ of involvement): complete response, partial response, no change, no response Survival	Response rate: Cutaneous- 15/15 (12 complete responses) Musculoskeletal- 4/4 (0 complete response) Oral/mucosal- 11/11 (11 complete response) Hepatic- 9/10 (7 complete response) Ocular- 5/6 (1 complete response) Thrombocytopenia- 2/3 (2 complete responses) Survival: 14/15 after median follow-up of 15 months; the 1 death was due to relapse of non-Hodgkin's lymphoma	Not applicable	Observational study design Small sample size Lack of control group
Besnier, 1997	Case study, uncontrolled Inclusion: steroid-refractory or intolerant cGvHD Cobe system used to separate cells; 8-MOP added ex vivo ECP performed over 3x per week for 3 weeks and then frequency tapered per sign/symptoms of cGvHD	N= 5 (only 3 were adults) Age range: 26-42 years	Response to therapy (per organ of involvement) Need for immunosuppression	42 year old patient had initial improvement without immunosuppressive drugs then relapse of cutaneous signs/symptoms 7 months after discontinuing cGvHD 39 year old patient had significant improvement of muscular cGvHD after 3 weeks of ECP along with decrease in immunosuppressive drug regimen; by 3 months patient had regained normal strength and all immunosuppression drugs stopped; clinically stable at 1 year 26 year old patient with severe bronchiolitis obliterans necessitating placement on wait list for lung had slight decrease in steroid dose after ECP treatments; clinically stable at 6 months but still awaiting transplantation	Not applicable	Observational study design Small sample size Lack of control group

Legend: cGvHD—chronic graft versus host disease; 8-MOP—8 methoxypsoralen

Evidence Table for the Pemphigus/Pemphigoid Indication

Author/ Year	Study Design	Demographics	Outcome measures	Results		Methodological Comments
				Intervention group	Control group	
Shih et al. 2005	Review: Treatment of PV : current and Emerging.	Re: ECP-N=13 patients in 6 studies (3 by Rook) – Age 31-78 yrs. Mean 46.5	Stop progression: All progressed.	NA. All 13 patients in 6 studies were treated with ECP	None	Underpowered, too small sample sizes
Wollina 1999	Retrospective cohort - Short-Time ECP in the treatment of drug-resistant autoimmune Bullous diseases	N=7 31-85 yrs	Complete remission	6 of 7 patients experienced complete remission on 8-methyoxy-psoralen with ECP	None	N=7 Some PV some PB
Liang 1992	Case Report: PV treated with photophoresis	N=1 31 yrs old	Near complete remission	Success	NA	N=1
Rook 1990	Case Reports	N=4	Near complete remission	Partial success for 4 patients	NA	N=4
Gollnick 1993	Case Report	N=1	Near complete remission	Partial success	NA	N=1