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[Intervention Review]

Extracorporeal photopheresis versus standard treatment for acute graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients

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ABSTRACT

Background

Acute graft-versus-host disease (aGvHD) is a major cause of morbidity and mortality after haematopoietic stem cell transplantation (HSCT) occurring in 8% to 59% of the recipients. Currently, the therapeutic mainstay for aGvHD is corticosteroids. However, there is no established standard treatment for steroid-refractory aGvHD. Extracorporeal photopheresis (ECP) is a type of immunomodulatory method amongst different therapeutic options that involves ex vivo collection of peripheral mononuclear cells, exposure to the photoactive agent 8-methoxypsoralen and ultraviolet-A radiation, and re-infusion of these treated blood cells to the patient. The mechanisms of action of ECP are not completely understood. This is an updated version of a Cochrane review first published in 2014.

Objectives

To evaluate the effectiveness and safety of ECP for the management of aGvHD in children and adolescents after HSCT.

Search methods

We searched the Cochrane Register of Controlled Trials (CENTRAL) (Issue 9, 2015), MEDLINE (PubMed) and EMBASE (Ovid) databases from their inception to 23 September 2015. We searched the reference lists of potentially relevant studies without any language restrictions. We searched eight trial registers and four conference proceedings on 29 September 2015.

Selection criteria

Randomised controlled trials (RCTs) comparing ECP with or without standard treatment versus standard treatment alone in paediatric patients with aGvHD after HSCT.

Data collection and analysis

Two review authors independently performed the study selection. We resolved disagreement in the selection of trials by consultation with a third review author.

Main results

We identified no additional studies in the 2015 review update, in total leading to no studies meeting the criteria for inclusion in this review.

Authors' conclusions

The efficacy of ECP in the treatment of aGvHD in paediatric patients after HSCT is unknown and its use should be restricted within the context of RCTs. Such studies should address a comparison of ECP alone or in combination with standard treatment versus standard treatment alone. The 2015 review update brought about no additions to these conclusions.

PLAIN LANGUAGE SUMMARY

Extracorporeal photopheresis for acute graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients

Background

Acute graft-versus-host disease is a common complication after haematopoietic stem cell transplantation (HSCT; transplant of blood-forming stem cells). Immune cells (white blood cells) from the donor recognise the patient's cells as foreign ('non-self'). Therefore, the transplanted immune cells attack the cells of the patient. The main affected organs are skin, liver and gut among other organ tissues. These immune reactions may cause acute inflammation (sudden swelling) followed by chronic (long-term) changes of the organs (e.g. fibrosis; scarring of the lungs). First-line therapy usually consists of immunosuppressive drugs (which reduce the strength of the body's immune system) such as corticosteroids in combination with other immunosuppressive agents in refractory cases (where the disease is resistant to treatment). The use of these immunosuppressive drugs is designed to suppress the immune-mediated attack of the patient's cells. Limited effectiveness and severe side effects of these immunosuppressive drugs have led to the application of several alternative approaches.

Extracorporeal photopheresis (ECP) is an immunomodulatory therapy that involves collection of immune cells from peripheral blood outside the person's body. These immune cells are then exposed to a photoactive agent (a chemical that responds to exposure to light; e.g. 8-methoxypsoralen) with subsequent ultraviolet-A radiation and then re-infused. The immunomodulatory effects of this procedure have not been completely elucidated.

Several current clinical practice recommendations suggest consideration of ECP in paediatric patients with acute graft-versus-host disease after HSCT.

Study characteristics

We searched scientific databases for randomised controlled trials (RCTs; clinical studies where people are randomly put into one of two or more treatment groups) that were designed to evaluate the effectiveness and safety of ECP for the management of acute graft-versus-host disease in children and adolescents (under 18 years of age) after HSCT.

Results

The original version of this review and the first review update found no RCTs that analysed the efficacy of ECP for paediatric patients with acute graft-versus-host disease after HSCT. Current recommendations are based on retrospective (a study in which the outcomes have occurred to the participants before the study began) or observational (a study in which the investigators do not seek to intervene, and simply observed the course of events) studies only. We recommend the use of ECP in paediatric patients after HSCT only in the context of RCTs.

BACKGROUND

Description of the condition

Haematopoietic stem cell transplantation (HSCT) is a curative treatment for children with haematological malignancies, haemoglobinopathies, immune deficiencies and inborn errors of metabolism (Diaconescu 2005; Gaziev 2011; Kennedy-Nasser 2006; Locatelli 2000; Peters 2003; Rapoport 2011; Sullivan 2004; Walters 2000; Walters 2005).

Acute graft-versus-host disease (aGvHD) is considered one of the major potentially life-threatening complications following HSCT, limiting its wider application (Billingham 1966; Sullivan 2004). Its occurrence is based on the reactivity of immune-competent donor cells against host antigens (Ferrara 2004). Depending on risk factors such as type of donor, human leukocyte antigen (HLA) matching, stem cell source and age, aGvHD occurs in 8% to 59% of paediatric HSCT recipients (Ball 2008; Eapen 2004; Flomenberg 2004; Rocha 2000; Woolfrey 2002).

According to a widely accepted pathophysiological model, aGvHD develops in three steps (Fowler 2004; Hill 1997):

- tissue damage and inflammation caused by the preparative regimen;
- donor T-cell activation induced by antigen-presenting cells (APC) of donor as well as host origin, recognition of HLAs in host tissues, in particular minor histocompatibility antigens, donor-derived T-cell activation and differentiation by inflammatory cytokines; and
- T-cell mediated cytotoxic destruction of host tissue in a complex setting of cytokine dysregulation.

Clinically, aGvHD typically affects three major target organs: skin, gastrointestinal tract and liver (Ferrara 2004; Goldberg 2003), resulting in varying symptoms such as rash, erythema, nausea, diarrhoea with abdominal pain, ileus and hyperbilirubinaemia (Ferrara 2004). According to the most commonly used modified Glucksberg criteria, aGvHD is staged by the number of organs affected and the extent of organ involvement (affected proportion of the body surface area or stool volume or serum bilirubin level, or a combination of these), followed by an overall grading (Grade I to IV) (Glucksberg 1974; Przepiorka 1995). The less commonly used International Bone Marrow Transplant Registry (IBMTR) Index defines an overall grade of aGvHD (Grade A to D) (Rowlings 1997).

Traditionally, aGvHD was defined by its occurrence before day 100 after HSCT (Shulman 1988). However, advances in the practice of HSCT (including different stem cell sources, intensity of conditioning regimens, immunosuppression, donor lymphocyte infusions) have resulted in a more time-variable presentation of aGvHD and, therefore, the Consensus Conference of the National Institutes of Health developed a new classification (Ferrara 2006; Filipovich 2005). Here, the diagnosis of aGvHD is based on the typical clinical symptoms and not on the time point of manifestation, defining classic aGvHD (onset before 100 days), recurrent aGvHD, delayed aGvHD (onset after 100 days) and persistent aGvHD.

Description of the intervention

As aGvHD has a significant impact on morbidity and mortality, prophylaxis plays a major role (Ram 2009). Prevention is based on T-cell modulation, including the following strategies: inhibition of T-cell activation and function (calcineurin inhibitor), inhibition of T-cell proliferation (methotrexate, mycophenolate mofetil) and elimination of T cells (alemtuzumab, anti-thymoglobulin) (Shah 2007; Storb 1986).

While there is a widely accepted consensus on standard first-line therapy for aGvHD (systemic steroids), second-line therapy includes a large variety of drugs and methods (Jacobsohn 2008). Clinical trials comparing outcomes with different approaches are scarce (Bacigalupo 2006).

Whereas people with Grade I aGvHD usually do not need any additional treatment, people with Grade II to IV aGvHD will be treated with continuous prophylactic immunosuppression and the addition of systemic steroids in the majority of cases (Salmasian 2010; Van Lint 1998). The overall response to this treatment is about 60%; however, people not responding to first-line therapy have a worse outcome with a decreased probability of overall survival (Weisdorf 1990).

There is no established standard treatment for steroid-refractory aGvHD (Ho 2008). Depending on the agents used for prophylaxis, people not responding to systemic corticosteroids after five to seven days are treated with a variety of second-line agents including general immunosuppressants, monoclonal as well as polyclonal antibodies, biological toxin conjugate, tumour necrosis factor (TNF)- α blockade, mesenchymal stem cells and phototherapy (Auletta 2009). With the exception of phototherapy, all these interventions are associated with a high risk of infections and, in malignant disease, with a possibly increased risk of relapse (Baker 2010).

Extracorporeal photopheresis (ECP) has been successfully applied in the treatment of cutaneous T-cell lymphoma (CTCL) since the 1980s (Edelson 1987). Following this observation, the method has been implemented for a wider spectrum of immunologically mediated diseases, such as systemic scleroderma, autoimmune disorders, solid organ rejection, and aGvHD and chronic graft-versus-host disease (cGvHD) (Szodoray 2010).

In the setting of aGvHD in children, ECP has primarily been used in steroid-refractory disease. Response rates ranging from 50% to 100% have been reported, depending on the organ involved (Foss 2005; Greinix 2006; Messina 2003; Smith 1998; Sniecinski 1994). Adverse reactions are uncommon (less than 0.003%), transient and mild (nausea, hypotension, dizziness, cytopenia, skin infection at site of venous access, abnormal clotting to heparin) (Kanold 2003). Moreover, ECP does not seem to be associated with an increased risk of systemic infection and relapse of malignant disease (Dall'Amico 2002; Hackstein 2009; Scarisbrick 2008).

During ECP, peripheral mononuclear cells (PMNC) are collected by leukapheresis, incubated with the photoactive and photosensitising drug 8-methoxypsoralen (8-MOP), exposed to ultraviolet-A (UV-A) light and then re-infused into the patient (Betha 1999; Girardi 2002; Heald 1989). Psoralen occurs naturally in the seeds of the furocoumarin family of plants and its exposure to UV-A light (wavelength 200 to 350 nm) facilitates the intercalation

of psoralen with deoxyribonucleic acid (DNA), leading to the formation of both monofunctional and bifunctional adducts, which results in programmed cell death (apoptosis) of the majority of cells (Yoo 1996). Initially, people received psoralen orally prior to leukapheresis (Bethua 1999). However, oral application resulted in an inconstant absorption of the drug and considerable gastrointestinal adverse effects (Brickl 1984). The now generally used ex vivo method, with the incubation of the collected cells in a bag, significantly reduces the exposure of the patient to 8-MOP (Schooneman 2003).

How the intervention might work

The mechanisms of action of ECP are not completely understood. It has been shown that the procedure induces apoptosis in mononuclear white blood cells (Voss 2010). However, only a small percentage of the PMNC are treated and, therefore, an immunomodulatory effect of the apoptotic cells is hypothesised (Heshmati 2003). One suspected mechanism is that apoptotic T-cell fragments presented by dendritic cells induce an anti-idiotypic T-suppressor activity, or downregulate a pre-existing T-cell response modulating immune tolerance and cytokine production (Bladon 2006; Legitimo 2007; Xia 2009). In summary, the postulated mechanisms involved include: reduced stimulation of effector, deletion of effector T cells, induction of regulatory T cells, increase of anti-inflammatory cytokines (i.e. TNF- β , interleukin (IL)-10) and reduction of proinflammatory cytokines (IL-1 β , IL-6, TNF- α) (Fimiani 2004). On the basis of this hypothesis, photopheresis seems to downregulate the T-cell alloreactivity that plays a central role in the pathogenesis of graft-versus-host disease (GvHD) after HSCT (Lamioni 2005; Maeda 2005).

Why it is important to do this review

aGvHD remains one of the major challenges in terms of transplant-related morbidity and mortality after stem cell transplantation in children. All conventional therapies including the well-established first-line therapy (systemic steroids) have considerable adverse effects and probably increase the risk of infections and relapse of malignant disease. Therefore, it is essential to develop new therapeutic approaches for the selective immune control of aGvHD without generalised immunosuppression-related complications (infections and pharmacological toxicity issues) (Wolff 2011).

ECP seems to be an effective immunomodulatory therapy with very mild, if any, adverse effects and it may, therefore, be a promising alternative option for improving morbidity and mortality in children with aGvHD.

The current review is the first update of the initial review and its protocol (Weitz 2012; Weitz 2014).

OBJECTIVES

To evaluate the effectiveness and safety of ECP for the management of aGvHD in children and adolescents after HSCT.

METHODS

Criteria for considering studies for this review

Types of studies

We intended to consider randomised controlled trials (RCTs) for this review if they had assessed any clinical outcome as described in

the [Types of outcome measures](#) section. For medical reasons (e.g. we did not consider aGvHD as a stable condition), we intended to include only trials with a parallel group design. We excluded studies restricted to adults (18 years of age or older). For studies including both children and adults, we arbitrarily set a limit of more than 50% of children participating in the study for it to be included in this review.

Types of participants

We planned to include children and adolescents under 18 years of age who had undergone HSCT therapy with presence of aGvHD independent of the underlying disease and donor source. We considered all stages and grades of aGvHD, independent of the type of organ involvement.

Types of interventions

For the purpose of this review, we considered systemic steroids as standard treatment for first-line therapy and general immunosuppressants (e.g. mycophenolate mofetil), monoclonal antibodies (e.g. daclizumab and infliximab) and polyclonal antibodies (e.g. anti-thymoglobulin) as standard treatment for second-line therapy of aGvHD.

The following comparisons of ECP for aGvHD after HSCT were conceivable:

- ECP versus standard treatment in paediatric patients with aGvHD as first-line treatment;
- ECP plus standard treatment versus standard treatment alone in paediatric patients with aGvHD as first-line treatment;
- ECP versus standard treatment in paediatric patients with steroid-refractory aGvHD (second-line treatment);
- ECP plus standard treatment versus standard treatment alone in paediatric patients with steroid-refractory aGvHD (second-line treatment).

These comparisons constitute four separate groups and we anticipated analysing them separately.

Types of outcome measures

Primary outcomes

- Response to ECP treatment, defined as either classical response rates (i.e. number of children in complete or partial remission) or percentage achieving reduction in either Glucksberg or IBMTR score, or steroid-tapering under therapy with ECP (defined as number of children with at least 25% reduction in steroid dose).

Secondary outcomes

- Overall survival (defined as the time to death from any cause starting at the day of HSCT).
- Relapse-free survival (defined as the time of recurrence of aGvHD after complete response).
- Adverse events.
- Quality of life.
- Cost of intervention per month.

Search methods for identification of studies

For the initial review, we searched the following electronic databases: the Cochrane Central Register of Controlled Trials

(CENTRAL) (Issue 9, 2012), MEDLINE/PubMed (from 1945 to 12 September 2012) and EMBASE (Ovid) (from 1980 to 12 September 2012). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are shown in the appendices ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#)). For the 2015 search update, we used the same strategy without modifications to identify studies from the date of the last search to 23 September 2015.

We carried out an electronic search of the following conference proceedings using the regular search with keyword terms ("extracorporeal"; "photopheresis"; "photochemotherapy"; "psoralen"; "graft-versus-host") on 12 September 2012. The search for conference proceedings was repeated on 29 September 2015 without modifications.

- International Society for Paediatric Oncology (SIOP) (from 2007 to 2015);
- American Society of Clinical Oncology (ASCO): *Journal of Clinical Oncology* (1995 to 2015);
- American Society of Hematology (ASH): *Blood* (2001 to 2015);
- European Group for Blood and Marrow Transplantation (EBMT): *Bone Marrow Transplantation* (2000 to 2015).

We additionally searched the following clinical trials registries for ongoing or recently completed trials, and for locating potential links to other related databases and resources on 12 September 2012. Regular search with keywords ("extracorporeal"; "photopheresis"; "photochemotherapy"; "psoralen"; "graft-versus-host") was used where applicable, no time restrictions applied and the search not limited to trials involving children. For the 2015 update of this review, we reran the search for clinical trials on 29 September 2015.

- ISRCTN registry (controlled-trials.com/);
- ClinicalTrials.gov (clinicaltrials.gov/);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/);
- Trials Central (www.trialscentral.org/) (search via "condition": "graft vs host disease");
- Internet Portal of the German Clinical Trials Register (DRKS) (www.drks.de/);
- NCIC Clinical Trials Group (www.ctg.queensu.ca/);
- National Cancer Institute (www.cancer.gov/) (under heading "childhood cancers" and "cancers in childhood and adolescents" using "research" button);
- Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au/trialSearch.aspx).

We applied no language restrictions. We also searched the reference lists of relevant articles and review articles.

Data collection and analysis

Selection of studies

The original 2014 review was undertaken by four review authors (MW, BS, JM, DB). One review author (MW) screened all titles and abstracts of the references identified by the search strategies for relevance. We only excluded citations that were clearly irrelevant at this stage. We considered citations as irrelevant that included only adults, were animal studies, did not describe aGvHD and

used stem cell sources other than haematopoietic. Two review authors independently screened the remaining titles, excluded all irrelevant publications and recorded details of the studies together with the reasons for exclusion. We resolved any disagreement on the eligibility of studies through discussion and consensus. As a second step, we obtained full-text versions of all potentially relevant papers. Two review authors (MW, DB) independently screened these manuscripts, identified potentially relevant studies and assessed the eligibility of studies for inclusion. We resolved any disagreements on the eligibility of studies through discussion and consensus. For this 2015 update, an additional review author (MS) screened titles, abstracts and potentially relevant studies.

Data extraction and management

We planned that one review author (MW) would extract data using a data extraction form developed by the review authors and would transcribe data into Review Manager 5 ([RevMan 2014](#)). Another review author (JM) was to verify all data entry for discrepancies. In case of any disagreement on data extraction and management issues, we planned to solve these issues through discussion and consensus or, if necessary, through a third review author. We intended to request missing data from the original investigators.

We planned to extract the following information:

- 'Characteristics of included studies' table: study characteristics would have included place of publication, date of publication, population characteristics, setting, detailed nature of intervention, detailed nature of comparator and detailed nature of outcomes. A key purpose of this information is to define unexpected clinical heterogeneity in the included studies independently from the analysis of results.
- Results of included studies with respect to each of the main outcomes described above. We intended to record reasons why an included study did not contribute data on a particular outcome and to consider the possibility of selective reporting of results on particular outcomes.

Assessment of risk of bias in included studies

We planned that two review authors (MW, DB) independently assess each included study for risk of bias using the definitions for the different risk of bias items as stated in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and any other potential threats to validity ([Higgins 2011](#); [Kjaergard 2001](#); [Moher 1998](#); [Schulz 1995](#)). We intended to assess the risk of bias for blinding of outcome assessors and incomplete outcome data separately for each outcome. We would have considered a trial as having a low risk of bias if we assessed all domains as adequate. We would have considered a trial as having a high risk of bias if we assessed one or more domain as inadequate or unclear. We planned to report the 'Risk of bias' table as part of the 'Characteristics of included studies' table and present a 'Risk of bias' summary figure that detailed all of the judgements made for all included studies in the review ([Higgins 2011](#)). For each included study, we wanted to assess selective reporting bias by comparing the methods and results section of the individual studies. We planned to resolve any disagreements on the assessment of risk of bias through discussion and consensus, or, if necessary, through

discussion with a third review author (JM or BS). We intended to explore the impact of the level of bias through undertaking sensitivity analyses (see [Sensitivity analysis](#)).

Measures of treatment effect

We wanted to analyse extracted data using Review Manager 5 ([RevMan 2014](#)).

We planned to extract hazard ratios with their 95% confidence intervals (CI) for time-to-event outcomes such as mortality. If hazard ratios were not provided, we planned to use the indirect estimation methods described by Parmar and Williamson to calculate them ([Parmar 1998](#); [Williamson 2002](#)). As an alternative, we wanted to use the proportions of participants with the respective outcomes measured at certain time points to calculate risk ratios (RR).

We aimed to express results for binary outcomes as RRs with 95% CIs as measures of uncertainty.

For continuous outcomes, we planned to express the results as mean differences (MD), with 95% CIs as measures of uncertainty.

Unit of analysis issues

Since for medical reasons we only wanted to include parallel-group randomised trials, unit of analysis issues related to cross-over and cluster-randomised trials were not relevant for this systematic review. In the context of ECP, 'body part randomisation' and 'body part analyses' do not make sense, so related issues do not need to be discussed here. In case of parallel-group designs with three or more treatment groups, we planned to divide up the control group into several parts, so that the total number added up to the original size of the group.

Dealing with missing data

We intended to ask the original investigators for missing data regarding study selection, data extraction and 'Risk of bias' assessment. To optimise the strategy for dealing with missing data, we wanted to conduct an intention-to-treat analysis, which includes all participants who did not receive the assigned intervention according to the protocol as well as those who were lost to follow-up. If unsuccessful, we aimed to address the potential impact of missing data on the findings of the review in the [Discussion](#) section.

Assessment of heterogeneity

We planned to assess statistical heterogeneity using the I^2 statistic ([Higgins 2002](#); [Higgins 2003](#)). This measure describes the percentage of total variation across studies that is caused by heterogeneity rather than by chance ([Higgins 2003](#)). The values of the I^2 statistic lie between 0% and 100%. We planned to use a simplified categorisation of heterogeneity with the following categories: low (I^2 less than 30%), moderate (I^2 between 30% and 60%) and high (I^2 more than 60%) ([Deeks 2011](#)).

If moderate or high heterogeneity were detected, we planned to explore clinical heterogeneity by examining differences between groups as detailed below ([Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

We minimised the likelihood of publication bias by using a comprehensive search strategy without language restrictions and we searched trial registries. In addition to the evaluation of reporting bias as described in the [Assessment of risk of bias in included studies](#) section, we planned to assess reporting bias by constructing a funnel plot if we identified a sufficient number of studies (i.e. at least 10 studies included in a meta-analysis). When there are fewer studies, the power of the tests is too low to distinguish chance from real asymmetry ([Sterne 2011](#)).

Data synthesis

We plan for future updates to conduct meta-analyses of pooled data from all contributing studies using Review Manager 5 ([RevMan 2014](#)). We intended to use a fixed-effect model for the primary analysis. If we had found high clinical, methodological or statistical heterogeneity (I^2 more than 50%), we planned to use, as a secondary analysis, a random-effects model and to report the results from both models. We planned to summarise studies for which pooling of results was not possible descriptively.

Subgroup analysis and investigation of heterogeneity

We planned to assess clinical heterogeneity by examining differences due to:

- underlying disease demanding HSCT;
- type of stem cell source;
- age of participants;
- age at commencement of ECP;
- type of conditioning regimen;
- type of prophylaxis regimen.

Sensitivity analysis

We planned to investigate the robustness of our results through a sensitivity analysis on the basis of risk of bias in the included studies by defining the following groups:

- low risk of bias (adequate sequence generation and allocation concealment; successful blinding of all participants, care providers and outcome assessors; incomplete outcome data less than 20%; no selective reporting or other sources of bias);
- high risk of bias (no adequate sequence generation and allocation concealment; no adequate blinding of all participants, care providers and outcome assessors; incomplete outcome data more than 20%; selective reporting or other sources of bias);
- unclear risk of bias (rating of unclear risk of bias in at least one of these seven categories).

We aimed to perform sensitivity analyses for each risk of bias item separately.

RESULTS

Description of studies

Results of the search

We found no RCTs meeting the inclusion criteria for the original version of this review and its 2015 update (see: [Characteristics of excluded studies](#) table; [Characteristics of ongoing studies](#) table).

We performed the initial search on 12 September 2012. [Figure 1](#) shows the result of the search strategy. The initial search yielded 60 articles including two duplicates in CENTRAL, MEDLINE (PubMed),

EMBASE (Ovid) and conference proceedings ([Figure 1](#)). After title and abstract screening, we excluded 46 of the unique articles for the following reasons:

Figure 1. Identification of potentially eligible reports.

- 46 were interventions other than ECP.

We screened 12 full texts but we found no RCTs to include in the initial review. We found a further 10 studies from searching the references of the full-text articles. These additional articles were also not RCTs and we excluded them following full-text screening. Reasons for exclusion were as follows:

- 13 were case report/case series;
- four were reviews reporting case reports/case series;
- three were prospective, not randomised, not controlled clinical trials;
- one was a retrospective case series;
- one was an RCT including less than 50% children.

We performed the latest search on 23 September 2015, yielding 20 new articles in CENTRAL, MEDLINE (PubMed), EMBASE (Ovid)

and conference proceedings (Figure 2). After title and abstract screening, we excluded 15 of the articles for the following reasons:

Figure 2. Identification of potentially eligible reports in 2015 update.

- two were animal studies (mouse model);
- six were interventions other than ECP;
- one was a survey;
- one did not concern GvHD;
- five were conference abstracts without references to published studies.

We screened five full-text articles but we found no RCTs to include in this review update. We found a further six studies while searching the references of the full-text articles. These additional articles were also not eligible RCTs and we excluded them after abstract screening. Reasons for exclusion were as follows:

- six were case series.

The search of the trial registers (run 29 September 2015) identified no additional eligible studies apart from the one identified in the initial 2014 review (NCT00609609; see [Characteristics of ongoing studies](#) table).

Included studies

We found no RCTs in the 2015 update meeting the inclusion criteria for this review. The one RCT identified in the 2014 review, which potentially includes children is still ongoing (NCT00609609; see [Characteristics of ongoing studies](#) table).

Excluded studies

For this 2015 review update, we excluded data from two case series and three reviews.

See [Characteristics of excluded studies](#) table.

Risk of bias in included studies

We found no studies meeting the inclusion criteria for the original version of this review or its 2015 update. For that reason, the assessment of risk of bias was not applicable.

Effects of interventions

We found no studies meeting the inclusion criteria for this review or its 2015 update. For that reason, the effectiveness and safety of ECP for the management of aGvHD in children and adolescents after HSCT remains unclear.

DISCUSSION

Acute GvHD remains one of the major challenges for transplant-related morbidity and mortality after HSCT in paediatric patients. ECP represents an alternative second-line treatment option in paediatric patients with aGvHD after HSCT. However, neither the original version of the review (Weitz 2014), nor the 2015 update, identified any RCTs. Therefore, there are no data from RCTs available to support or refute treatment with ECP in children and adolescents with aGvHD after HSCT. Therefore, this systematic review cannot establish whether such a treatment is effective in paediatric patients with aGvHD after HSCT.

We limited the search strategy to children and adolescents under 18 years of age. We found 22 studies for the initial 2014 review including several case reports, case series and observational studies with ECP as intervention in paediatric patients with GvHD after HSCT. Only seven out of 22 studies involved children with aGvHD. We identified one non-randomised, non-controlled prospective study including 33 children with aGvHD resistant to conventional immunosuppressive therapy (Messina 2003). Depending on the original disorder and haematopoietic stem cell source, immunosuppressive prophylaxis consisted ciclosporin A alone, short-term methotrexate plus rabbit antithymoglobulin (ATG) ciclosporin A combined with steroids. The clinical stage in

patients with organ involvement was graded for each organ and then combined to an overall grade following published criteria (Ferrara 1991; Przepiorka 1995; Sullivan 1991). Patients with aGvHD had involvement of skin (33 children), liver (15 children) and gastrointestinal tract (20 children). Resistance to conventional immunosuppressive therapy after complete remission was defined as lack of clinical stabilisation or improvement after treatment with prednisolone at a dose of 2.5 mg/kg for at least seven days and no response to at least two lines of alternative immunosuppressive treatment options (such as ciclosporin A, tacrolimus or other). The median Lansky/Karnofsky performance score at the start of the ECP was 60% (range 30% to 90%) in the children with aGvHD. Photopheresis was carried out on two consecutive days at weekly intervals for the first month, every two weeks for the second and third month, followed by monthly intervals for at least three months. Clinical evaluation of the children was done at months one, two, three and six after initiation of ECP. Complete response was defined as clinical stage 0 or I, partial response as improvement greater than 50% and no response as stable or progressive disease or improvement less than 50%. In the children with aGvHD, median Lansky/Karnofsky performance score improved significantly to 100% (range 80% to 100%). The response of children with aGvHD was complete response in 54%, partial response in 21% and no response in 24.3%. The five-year probability of overall survival in children with aGvHD responding to ECP was significantly better compared with non-responders (responders: 69.5%, 95% CI 50.2% to 80.9%; non-responders: 12.5%, 95% CI 0% to 34.5%). Fourteen children died due to complications of aGvHD, infection or relapse of the primary disease. The five studies identified during the 2015 review were non-randomised and retrospective or summarised studies that did not meet the search criteria.

These studies provide only limited evidence for the efficacy of ECP in paediatric patients with aGvHD after HSCT. Therefore, they should not be used to establish recommendations in paediatric patients after HSCT. Further evaluation in controlled trials, preferably in RCTs, is urgently needed. However, performing RCTs in this age group will be challenging due to the limited number of children, the variable disease presentation and the lack of well-defined response criteria. International multicentre trials will be needed to study the efficacy of ECP in aGvHD in children after HSCT. There is one prospective RCT investigating the efficacy of ECP in people with aGvHD that has finished recruiting participants (including children) (NCT00609609; see [Characteristics of ongoing studies](#) table). The preliminary results of the trial are estimated for April 2016 and may help to define the role of ECP

in the treatment of aGvHD in children and may provide a basis for the design of paediatric studies addressing the efficacy in a more detailed way including the comparison of different treatment schedules. Furthermore, the cost-effectiveness of ECP in aGvHD needs to be analysed before detailed recommendations regarding the use of this new treatment modality in children with aGvHD can be elaborated.

AUTHORS' CONCLUSIONS

Implications for practice

There is no randomised evidence for the use of extracorporeal photopheresis in paediatric patients with acute graft-versus-host disease (aGvHD) after haematopoietic stem cell transplantation (HSCT). The available evidence is based on case reports, case series and observational studies. Hence, data from one ongoing trial are urgently needed to provide sufficient evidence for the use of extracorporeal photopheresis in paediatric patients with aGvHD after HSCT. Its application should be limited to a controlled setting, such as clinical trials, ideally randomised controlled trials (RCTs).

Implications for research

Controlled trials, preferably RCTs, are urgently needed to support or refute the use of extracorporeal photopheresis in children with aGvHD after HSCT. Future RCTs will need the incorporation of reliable and validated scoring systems to assess disease manifestations; well-defined response criteria and relevant outcome measures including quality of life and long-term effects. Furthermore, the efficacy of extracorporeal photopheresis may depend on which organ system is affected and a subgroup analysis according to disease manifestation will help to clarify this issue. If the value of extracorporeal photopheresis is unambiguously established, comparative trials defining the advantages and disadvantages of the various extracorporeal photopheresis regimens should follow.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abu-Dalle 2014	Review article reporting on efficacy of ECP for aGvHD and cGvHD treatment
Apisarnthanarax 2003	Retrospective study on 2 paediatric patients and 62 adults with cGvHD
Balda 1996	Case report on 1 child with cGvHD
Besnier 1997	Case series of 3 paediatric patients and 4 adults with aGvHD (2 people) and cGvHD (5 people)
Biagi 2000	Case report of 2 paediatric patients with cGvHD
Bisaccia 2011	Case report of 1 paediatric patient with chronic cutaneous GvHD
Bruserud 2014	Review article reporting on results from clinical studies of ECP treatment in aGvHD and cGvHD
Child 1999	Case series of 11 adults with cGvHD
D'Incan 2000	Case series of 3 paediatric patients with GvHD
Dall'Amico 1997	Case series of 4 paediatric patients with GvHD
Das-Gupta 2014	Retrospective, uncontrolled study on 128 patients (less than 50% paediatric) with aGvHD
Dhir 2014	Review article reporting on pathobiology of cGvHD/aGvHD, biomarker development and treatment strategies
Flowers 2008	Multicentre prospective phase 2 randomised controlled study in people with chronic cutaneous GvHD including less than 50% paediatric patients
Foss 2003	Review article reporting on case series of paediatric patients with aGvHD or cGvHD treated with ECP
Foss 2005	Study not randomised, not controlled. Prospective single-arm study on 23 adults and 2 paediatric patients with chronic cutaneous and visceral GvHD
Halle 2002	Case series of 8 paediatric patients with cGvHD

Study	Reason for exclusion
Jagasia 2013	Retrospective study of 98 patients (less than 50% paediatric) with aGvHD
Kanold 2003	Case series of paediatric patients with cGvHD
Kanold 2005	Review article reporting case series of paediatric patients with aGvHD or cGvHD treated with ECP
Looks 1997	Case report of 1 paediatric patient with aGvHD
Messina 2003	Prospective, not randomised, uncontrolled study of 77 paediatric patients with acute (33 children) or chronic (44 children) immunosuppressive-resistant GvHD
Perotti 1999	Prospective, not randomised, uncontrolled study in 1 child with aGvHD and 6 children with cGvHD
Peters 2000	Review article reporting on different therapeutic options for GvHD
Rossetti 1995	Case report of 1 paediatric patient with cGvHD
Rossetti 1996	Case series of 9 paediatric patients with aGvHD and 8 children with cGvHD
Salvaneschi 2001	Case series of paediatric patients with aGvHD and 13 children with cGvHD
Zecca 2000	Review article reporting on different therapeutic options for GvHD

aGvHD: acute graft-versus-host disease; cGvHD: chronic graft-versus-host disease; ECP: extracorporeal photopheresis; GvHD: graft-versus-host disease.

Characteristics of ongoing studies [ordered by study ID]

NCT00609609

Trial name or title	A Randomized Phase II Study for the Evaluation of Extracorporeal Photopheresis (ECP) in Combination with Corticosteroids for the Initial Treatment of Acute Graft-Versus-Host Disease (GvHD)
Methods	Phase 2, randomised, unblinded, controlled trial with a parallel design, open label
Participants	Participants of both gender, no healthy volunteers accepted Inclusion criteria • Participants must be recipients of allogeneic bone marrow or stem cell grafts • Participant must weigh > 40 kg • Participants must have new-onset, clinical grade II-III acute or late-acute GvHD of the GI tract, liver or skin that developed post transplantation. The diagnosis of GvHD must be pathologically confirmed in at least 1 organ or highly suspected clinically. Pathological confirmation may occur after registration and after the start of therapy. Definition of late acute GvHD vs. acute GvHD: the diagnosis of late acute GvHD includes clinical features that are identical to acute GvHD; however, late acute GvHD is diagnosed on or after day 100 post transplantation • These manifestations include a maculopapular rash, abnormal liver studies (cholestatic jaundice) or nausea/vomiting/diarrhoea or a combination of these. Participants must not have any concurrent classical features of chronic GvHD in addition to the above manifestations. Features of chronic GvHD include dry eyes and mouth; contractures; sclerodermal, lichenoid skin changes; or a combination of these • In the clinical judgement of the principle investigator, participants must be able to sustain a platelet count $\geq 20,000/\text{mL}$ and haematocrit $\geq 27\%$, with or without transfusions • Absolute white blood count > 1500/mL • Participant must be willing to comply with all study procedures

NCT00609609 (Continued)

- All participants with childbearing potential, including males and females, must commit to using adequate contraceptive precautions throughout their participation in the study and for 3 months following the last ECP treatment

Exclusion criteria

- Participants developing chronic GvHD following immunomodulation with immunosuppression withdrawal or donor lymphocyte infusion
- Any clinical manifestation consistent with de novo chronic GvHD or overlapped syndrome of acute and chronic GvHD
- Participants who are unable to tolerate the volume shifts associated with ECP treatment due to the presence of any of the following conditions: uncompensated congestive heart failure, pulmonary oedema, severe asthma or chronic obstructive pulmonary disease, hepatorenal syndrome
- Active bleeding
- International normalised ratio > 2
- Participants cannot have received methylprednisolone > 2 mg/kg/day for more than 72 hours prior to registration
- Participants cannot have received any other immunosuppression for treatment of GvHD other than calcineurin inhibitors and corticosteroids. Participants are allowed to have had any GvHD prophylaxis with the exception of ECP
- Participants with known hypersensitivity or allergy to psoralen
- Participants with known hypersensitivity or allergy to both citrate and heparin
- Participants with co-existing photosensitive disease (e.g. porphyria, systemic lupus erythematosus, albinism) or coagulation disorders
- Uncontrolled, persistent hypertriglyceridaemia (levels > 800 mg/dL)

Interventions	Arm 1: corticosteroids; drug: methylprednisolone 2 mg/kg/day with a taper to no less than 1 mg/kg/day by day 14, followed by a tapering schedule according to the suggested guidelines (trade names: Medrol, Depo-Medrol, Solu-Medrol) Arm 2: ECP plus corticosteroids; procedure: 8-9 photopheresis treatments weekly for days 1-14, 6 treatments weekly for days 15-28 and then 2 treatments weekly until day 60. After day 60, the doctor will decide whether ECP is worth continuing, and the frequency of treatments; drug: methylprednisolone 2 mg/kg/day with a taper to no less than 1 mg/kg/day by day 14, followed by a tapering schedule according to the suggested guidelines (trade names: Medrol, Depo-Medrol, Solu-Medrol)
Outcomes	Treatment failure (time frame: first analysis after first 20 participants; acute GvHD will be scored every week for 8 weeks)
Starting date	January 2008 to January 2015
Contact information	Amin Alousi, MD from M.D. Anderson Cancer Center, Houston, TX, US
Notes	Participants (< 18 years of age) are eligible for this study if their body weight is > 40 kg. It is uncertain how many children will be included in this study. As of the 2015 review update, the study is still ongoing and no results are yet available. Study completion is expected for April 2016

ECP: extracorporeal photopheresis; GI: gastrointestinal; GvHD: graft-versus-host disease.

APPENDICES

Appendix 1. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

- For **Stem cell transplantation**, we used the following text words:

stem cell transplantation OR stem cell transplantations OR SCT OR hematopoietic stem cell transplantation OR HSCT OR peripheral blood stem cell transplantation OR peripheral stem cell transplantation OR PBSCT OR stem cell OR stem cells OR stem cell* OR bone marrow transplantation OR BMT OR hematopoietic stem cell mobilization OR hematopoietic stem cell mobilisation OR allograft OR allografts OR allograft* OR allogeneic transplantation OR allogeneic marrow transplantation OR allogeneic OR homologous transplantation OR myeloablative therapy OR myeloablative agonist OR myeloablative agonists OR myeloablative* OR mega therapy OR high-dose therapy OR high dose therapy OR stem cell rescue OR bone marrow rescue OR bone marrow grafting OR bone marrow cell transplantation OR cord blood stem cell transplantation OR placental blood stem cell transplantation OR umbilical cord stem cell transplantation

- For **Graft versus host disease**, we used the following text words:

graft versus host disease OR graft vs host disease OR chronic graft versus host disease OR chronic graft vs host disease OR acute graft versus host disease OR acute graft vs host disease OR GVHD OR cGVHD OR aGVHD OR graft versus leukemia OR graft vs leukemia OR homologous wasting disease OR graft versus host reaction OR graft vs host reaction

- For **Photopheresis**, we used the following text words:

photopheresis OR extracorporeal photopheresis OR Photopheresis, Extracorporeal OR Photochemotherapy, Extracorporeal OR ECP OR Extracorporeal Photochemotherapy OR Extracorporeal Photochemotherapies OR Photochemotherapies, Extracorporeal OR photochemotherapy OR photodynamic therapy OR photodynamic therapies OR phototherapy OR PDT OR phototherapies OR ultraviolet therapy OR ultraviolet therapies OR UVA-irradiation OR photoradiation OR ficusin OR psoralene OR psoralen OR psoralens OR 66-97-7 OR 8-methoxypsoralen OR 8-MOP OR 8MOP OR 8 MOP OR Methoxsalen OR 298-81-7 OR photochemical OR photochemicals OR photosensitizer* OR photosensitiser*

- For **Children**, we used the following text words:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy

Final search 1 AND 2 AND 3 AND 4

The search was performed in title, abstract or keywords

[* = zero or more characters]

Appendix 2. Search strategy for MEDLINE/PubMed

- For **Stem cell transplantation**, we used the following MeSH headings and text words:

stem cell transplantation OR stem cell transplantations OR SCT OR hematopoietic stem cell transplantation OR HSCT OR peripheral blood stem cell transplantation OR peripheral stem cell transplantation OR PBSCT OR stem cell OR stem cells OR stem cell* OR bone marrow transplantation OR BMT OR hematopoietic stem cell mobilization OR hematopoietic stem cell mobilisation OR allograft OR allografts OR allograft* OR allogeneic transplantation OR allogeneic marrow transplantation OR allogeneic OR homologous transplantation OR myeloablative therapy OR myeloablative agonist OR myeloablative agonists OR myeloablative* OR mega therapy OR high-dose therapy OR high dose therapy OR stem cell rescue OR bone marrow rescue OR bone marrow grafting OR bone marrow cell transplantation OR cord blood stem cell transplantation OR placental blood stem cell transplantation OR umbilical cord stem cell transplantation

- For **Graft versus host disease**, we used the following MeSH headings and text words:

graft versus host disease OR graft vs host disease OR chronic graft versus host disease OR chronic graft vs host disease OR acute graft versus host disease OR acute graft vs host disease OR GvHD OR cGVHD OR aGVHD OR graft versus leukemia OR graft vs leukemia OR homologous wasting disease OR graft versus host reaction OR graft vs host reaction

- For **Photopheresis**, we used the following MeSH headings and text words:

photopheresis OR extracorporeal photopheresis OR Photopheresis, Extracorporeal OR Photochemotherapy, Extracorporeal OR ECP[tiab] OR Extracorporeal Photochemotherapy OR Extracorporeal Photochemotherapies OR Photochemotherapies, Extracorporeal

OR photochemotherapy OR photodynamic therapy OR photodynamic therapies OR phototherapy OR PDT[tiab] OR phototherapies OR ultraviolet therapy OR ultraviolet therapies OR UVA-irradiation OR photoradiation OR ficusin OR psoralene OR psoralen OR psoralens OR 66-97-7 OR 8-methoxypsoralen OR 8-MOP OR 8MOP OR 8 MOP OR Methoxsalen OR 298-81-7 OR photochemical OR photochemicals OR photosensitizer* OR photosensitiser*

- For **Children**, we used the following MeSH headings and text words:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn

- For **Randomised controlled trials (RCTs)/clinical controlled trials (CCTs)**, we used the following MeSH headings and text words:

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND humans[mh]

Final search: 1 AND 2 AND 3 AND 4 AND 5

[pt = publication type; tiab = title, abstract; sh = subheading; mh = MeSH term; * = zero or more characters; RCT = randomised controlled trial; CCT = controlled clinical trial]

Appendix 3. Search strategy for EMBASE (Ovid)

- For **Stem cell transplantation**, we used the following Emtree terms and text words:

- exp stem cell transplantation/
- (stem cell transplantation or stem cell transplantations or SCT).mp.
- exp hematopoietic stem cell transplantation/
- (hematopoietic stem cell transplantation or HSCT).mp.
- exp peripheral blood stem cell transplantation/
- (peripheral blood stem cell transplantation or PBSCT).mp.
- exp stem cell/
- (stem cell or stem cells or stem cell\$).mp.
- exp bone marrow transplantation/
- (bone marrow transplantation or BMT).mp.
- exp stem cell mobilization/
- (hematopoietic stem cell mobilization or hematopoietic stem cell mobilisation).mp.
- exp allograft/
- (allograft or allografts or allograft\$).mp.
- exp allotransplantation/
- (allogeneic transplantation or allogeneic marrow transplantation).mp.
- allogen\$.mp.
- homologous transplantation.mp.
- myeloablative therapy.mp.
- exp myeloablative agent/
- (myeloablative agonist or myeloablative agonists).mp.
- myeloablative\$.mp.
- (mega therapy or high-dose therapy or high dose therapy).mp.
- exp bone marrow rescue/
- (stem cell rescue or bone marrow rescue).mp.
- bone marrow grafting.mp.
- bone marrow cell transplantation.mp.
- exp cord blood stem cell transplantation/
- (cord blood stem cell transplantation or placental blood stem cell transplantation or umbilical cord stem cell transplantation).mp.
- or/1-29

- For **Graft versus host disease**, we used the following Emtree terms and text words:

- exp graft versus host reaction/
- (graft versus host disease or graft vs host disease).mp.
- exp chronic graft versus host disease/

4. (chronic graft versus host disease or chronic graft vs host disease).mp.
5. exp acute graft versus host disease/
6. (acute graft versus host disease or acute graft vs host disease).mp.
7. (GVHD or cGVHD or aGVHD).mp.
8. exp graft versus leukemia effect/
9. (graft versus leukemia or graft vs leukemia).mp.
10. homologous wasting disease.mp.
11. (graft versus host reaction or graft vs host reaction).mp.
12. or/1-11

- For **Photopheresis**, we used the following Emtree terms and text words:

1. PUVA/
2. (photopheresis or extracorporeal photopheresis).mp.
3. (Extracorporeal Photochemotherapy or Extracorporeal Photochemotherapies or ECP).mp.
4. photochemotherapy.mp. or exp photochemotherapy/
5. exp photodynamic therapy/
6. (photodynamic therapy or photodynamic therapies).mp.
7. exp phototherapy/
8. (phototherapy or phototherapies or PDT).mp.
9. (ultraviolet therapy or ultraviolet therapies).mp.
10. exp ultraviolet radiation/ or exp ultraviolet A radiation/
11. UVA-irradiation.mp.
12. photoradiation.mp.
13. exp psoralen/
14. (ficusin or psoralene or psoralen or psoralens).mp.
15. 66-97-7.rn.
16. exp methoxsalen/
17. (8-methoxypsoralen or 8-MOP or 8MOP or 8 MOP or Methoxsalen).mp.
18. 298-81-7.rn.
19. (photochemical or photochemicals).mp.
20. exp photosensitizing agent/
21. (photosensitizer\$ or photosensitiser\$).mp.
22. or/1-21

- For **Children**, we used the following Emtree terms and text words:

1. infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
2. adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
3. primary school/ or high school/ or kindergarten/ or nursery school/ or school/
4. or/1-3
5. (infant\$ or newborn\$ or (new adj born\$) or baby or baby\$ or babies or neonate\$ or perinat\$ or postnat\$).mp.
6. (child\$ or (school adj child\$) or schoolchild\$ or (school adj age\$) or schoolage\$ or (pre adj school\$) or preschool\$).mp.
7. (kid or kids or toddler\$ or adoles\$ or teen\$ or boy\$ or girl\$).mp.
8. (minors or minors\$ or (under adj ag\$) or underage\$ or juvenil\$ or youth\$).mp.
9. (puber\$ or pubescen\$ or prepubescen\$ or prepubert\$).mp.
10. (pediatric\$ or paediatric\$ or peditric\$).mp.
11. (school or schools or (high adj school\$) or highschool\$ or (primary adj school\$) or (nursery adj school\$) or (elementary adj school) or (secondary adj school\$) or kindergar\$).mp.
12. or/5-11
13. 4 or 12

- For **Randomised controlled trials (RCTs)/clinical controlled trials (CCTs)**, we used the following Emtree terms and text words:

1. Randomized Controlled Trial/
2. Controlled Clinical Trial/
3. randomized.ti,ab.
4. placebo.ti,ab.
5. randomly.ti,ab.
6. trial.ti,ab.
7. groups.ti,ab.
8. drug therapy.sh.
9. or/1-8

10. Human/
11. 9 and 10

Final search 1 and 2 and 3 and 4 and 5

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title, abstract; / = Emtree term; \$ = zero or more characters ; RCT = randomised controlled trial; CCT = controlled clinical trial]

WHAT'S NEW

Date	Event	Description
7 October 2015	New search has been performed	The search for eligible studies was updated to September 2015.
7 October 2015	New citation required but conclusions have not changed	No new studies could be included in the review. As a result the conclusions have not changed.

CONTRIBUTIONS OF AUTHORS

Marcus Weitz: conception, design and co-ordination of the review. Identifying studies meeting the inclusion criteria (both by initial screening of the titles and abstracts and by screening of the full-text articles). Data extraction, data management and interpretation of the data. Writing of the review and approval of the final version.

Brigitte Strahm: interpretation of the data, clinical expertise, providing general advice on the review and approval of the final version.

Joerg Meerpohl: data extraction and data management. Methodological support, data extraction, data management and interpretation as well as general advice on the review. Approval of final version.

Maria Schmidt: new review author for the 2015 update. Identifying studies meeting the inclusion criteria (both by initial screening of the titles and abstracts and by screening of the full-text articles). Data extraction, data management and interpretation of the data. Writing of the review and approval of the final version.

Dirk Bassler: identifying studies meeting the inclusion criteria (both by initial screening of the abstracts and the full-text articles). Data management and interpretation of data. Involvement in writing the review and approval of the final version.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No source of support, Other.

External sources

- No source of support, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Graft vs Host Disease [*therapy]; Hematopoietic Stem Cell Transplantation [*adverse effects]; Photopheresis [*methods]

MeSH check words

Adolescent; Child; Humans