Stem Cell Transplantation in Primary Systemic Amyloidosis: Recommendations

C.T. Kouroukis, R.B. Rumble

Report Date: March 29, 2012

CLINICAL QUESTION
What is the role of stem cell transplantation (SCT) in the treatment of primary systemic (AL, amyloid light-chain) amyloidosis?

TARGET POPULATION
All adult patients with primary (AL) amyloidosis who are being considered for treatment that includes either bone marrow or SCT.

RECOMMENDATIONS AND KEY EVIDENCE

<table>
<thead>
<tr>
<th>High-dose chemotherapy (CT) and autologous SCT is an option for selected patients with primary systemic amyloidosis, preferably within an investigative setting.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence</td>
</tr>
<tr>
<td>Allogeneic SCT is not recommended for patients with primary systemic amyloidosis.</td>
</tr>
<tr>
<td>Evidence</td>
</tr>
</tbody>
</table>
QUALIFYING STATEMENT

The patient selection process and the ultimate decision to perform an SCT should take into account not only disease-related characteristics, but also comorbidities and patient preferences.

FUTURE RESEARCH

Newer agents are being investigated in the treatment of AL amyloidosis. At this time it is not known how they may impact the need for SCT.

IMPLICATIONS FOR POLICY

The number of transplants provincially for systemic AL amyloidosis remains very low, and is unlikely to change in the foreseeable future.

RELATED PROGRAM IN EVIDENCE-BASED CARE REPORTS


Funding

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Phone: 905-527-4322 ext. 42822  Fax: 905 526-6775  E-mail: ccopgi@mcmaster.ca
REFERENCES


Stem Cell Transplantation in Primary Systemic Amyloidosis:  
Summary of Methods and Evidence  
C.T. Kouroukis, R.B. Rumble  
Report Date: March 29, 2012

QUESTION  
What is the role of stem cell transplantation (SCT) in the treatment of primary systemic (AL) amyloidosis?

INTRODUCTION  
Systemic amyloidosis is a protein-misfolding disease caused by deposits of amyloid fibrils within various tissues (1-4). These amyloid fibrils are monoclonal light chains produced by plasma cell clones within bone marrow that enter circulation as free light chains and are ultimately deposited within susceptible tissues (1-3). In the West, AL amyloidosis is the most common form of amyloidosis, with an incidence of approximately 10 patients per million persons per year (3,4). Of these patients, between 10% to 15% will develop overt AL amyloidosis (3). The goal of treatment is to suppress the clone with chemotherapy (1,2,4), similar to the approach taken for multiple myeloma patients; however, in amyloidosis, any outcome achieved is dependent upon the amount of organ dysfunction caused by the deposited amyloid fibrils. When treating amyloidosis patients, the treatment approach must consider that although multiorgan damage does make patients more susceptible to adverse effects, reducing the concentration of free light chains results in rapid clinical and survival benefits (2). Typically, the plasma cell clone is treated using two methods, conventional chemotherapy (CT) or high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) (1-4). While both CT and ASCT have shown clinical and survival benefits, ASCT is associated with both higher complete response and treatment related mortality (TRM) (1,2). This higher TRM is associated with the extent of prior organ damage caused by the disease; therefore, patients considered for ASCT treatment should be assessed for suitability by measuring the concentration of free light chains and the cardiac biomarkers N-terminal pro-natriuretic peptide type-B (NT-proBNP) and troponin (cTn). By carefully considering the patient selection criteria for ASCT, TRM rates have dropped from the 1998 rate of 12% to the current 7% (2).

The goal of this recommendation report is to review the most current evidence comparing these two treatment modalities, and to make a series of clinical
recommendations to inform clinicians, patients, and other stakeholders of the treatment options available.

METHODS

This advice report, produced by the PEBC, CCO, is a convenient and up-to-date source of the best available evidence on SCT in multiple myeloma, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

Literature Search Strategy

The MEDLINE (OVID) database (2006 through October (week two) 2010) was systematically searched for evidence on October 21, 2010 using the strategy that appears in Appendix A. A total of 23 hits were obtained, and after excluding irrelevant papers according to a title and abstract review, three were ordered for full-text review. Of these three, only one met the inclusion criteria and was retained.

Study Selection Criteria

Inclusion Criteria

1. Systematic reviews with or without meta-analysis or clinical practice guidelines (CPGs) if the evidence was obtained with a systematic review (SR).
2. Fully published randomized controlled trials (RCTs) on patients with amyloidosis who received SCT that reported on survival and/or quality of life (QoL).
3. Fully published non-randomized studies on patients with amyloidosis who received SCT and had an appropriate contemporaneous control group that reported on survival or QoL.
4. Reports published in English only.

Synthesizing the Evidence

While no pooling was planned, it would be considered if data allow.

Assessment of Study Quality

The quality of the included evidence was assessed as follows. For systematic reviews that would be used as the sole evidence base for our recommendations, the Assessment of Multiple Systematic Reviews (AMSTAR) tool would be used to assess quality. For CPGs, the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument would be used but only if adaptation of the recommendations was being considered. Any meta-analysis would be assessed for quality using criteria similar to that used for RCTs, where appropriate. RCTs would be assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, but non-randomized, evidence would be assessed according to a full reporting of the patient selection criteria, the interventions each patient received, and of all relevant outcomes.
Figure 1. Selection of studies investigating stem cell transplantation in amyloidosis from the MEDLINE search results.

23 citations retrieved from the MEDLINE database

22 excluded: reasons: e.g., not randomized.

Title and abstract review by single author (BR).

One citation retrieved for full publication review.

None excluded: reasons: e.g., not randomized.

Full publication review by one author (BR).

One full publication identified and included.

RESULTS: Literature Search and Quality of the Included Evidence

Only one report, a systematic review with meta-analysis, was obtained (5). This systematic review with meta-analysis only covered AL amyloidosis.

Quality of the Included Study
A formal assessment of quality was performed on the SR reported by Mhaskar et al (5) using the AMSTAR instrument. Details of the assessment can be found in Appendix B. As the SR was of high quality overall, it was deemed appropriate to use it as the body of evidence in this review.

RESULTS: Clinical evidence
Methods Used by Mhaskar et al, 2009
Evidence was systematically searched for using the PubMed database (dB). The search was performed in two stages: the first gathered RCT evidence, searching from 1966 through March 2008, and the second gathered single-arm prospective studies searching from January 2001 through March 2008. Meeting abstracts from the American Society of Hematology (ASH), the European Society of Hematology, and the American Society of Clinical Oncology (ASCO) were also searched from 2001 through 2008.

Inclusion Criteria Used by Mhaskar et al, 2009
- RCTs comparing ASCT with CT with at least 10 patients in each arm.
• Prospective nonrandomized single-arm studies, with or without historical controls, regardless of the number of patients.
• Each study had to report on at least one of the outcomes of interest: overall survival (OS), event-free survival (EFS), hematological response (complete (CHR) or partial (PHR)), renal response, treatment-related morbidity, or treatment-related mortality (TRM).

Exclusion Criteria Used by Mhaskar et al, 2009
• Retrospective study designs

Study Selection and Quality of Evidence Assessment
The studies to be included were determined by four reviewers, with disagreements resolved by consensus. All studies included were critically appraised on their methods, using the GRADE instrument. Three reviewers independently extracted the data.

Details of the Analysis used by Mhaskar et al, 2009
Comparative Studies (Including RCTS)
Time-to-event data and dichotomous data were pooled and reported using a random-effects model. If these data were not available, the hazard ratio (HR) was assessed using the Parmar method.

Non-Comparative Studies Used by Mhaskar et al, 2009
Proportions were converted into quantities according to the Freeman-Tukey variant of the arcsine square root-transformed proportion. The pooled proportion was calculated from the weighted mean of the transformed proportions, also using the random-effects model.

Heterogeneity was tested for using the I² test, and was explored through sensitivity tests, where warranted. Publication bias was assessed using the funnel plot methods of Begg and Mazumdar and also Egger et al, and none was detected.

All meta-analysis was performed using Stata (Release 9) in accordance with the guidelines published in the Quality of Reporting of Meta-Analyses statement.

Funding Sources Reported by Mhaskar et al, 2009
This systematic review with meta-analysis was funded by a grant from Johnson & Johnson Pharmaceutical Research & Development. The details of the studies included in the obtained systematic review appear in Table 1.

Table 1: Details of the individual studies included in the systematic review.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Patient characteristics (median age, performance status, N)</th>
<th>Arm 1 (N)</th>
<th>Arm 2 (N)</th>
<th>Overall survival</th>
<th>Complete hematologic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td></td>
<td>IV HDM+ASCT (50)</td>
<td>Oral Mel+oral Dex (50)</td>
<td>HR: 1.78, p=0.04 (95%CI, 1.03-3.08) in favour of CT</td>
<td>NR</td>
</tr>
<tr>
<td>Jaccard et al, 2007</td>
<td>Age 58 (40-69), ECOG status: 0-2, International multicentre trial, N=100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Non-randomized two-arm trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (range)</th>
<th>SWOG Status</th>
<th>N</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>HR</th>
<th>CI</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gono et al, 2004</td>
<td>59.5 (44-78)</td>
<td>0-2</td>
<td>31</td>
<td>VAD+Mel+ASCT</td>
<td>VAD</td>
<td>0.80</td>
<td>0.14-4.61</td>
<td>NR</td>
</tr>
<tr>
<td>Van Gameren et al, 2002</td>
<td>53 (43-62)</td>
<td>0-2</td>
<td>18</td>
<td>VAD+HDM+ASCT</td>
<td>Mel+prednisone</td>
<td>2.83</td>
<td>0.82-9.77</td>
<td>NR</td>
</tr>
</tbody>
</table>

## Single-arm studies with no controls

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (range)</th>
<th>SWOG Status</th>
<th>N</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>HR</th>
<th>CI</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gertz et al, 2004</td>
<td>54 (42-71)</td>
<td>0-2</td>
<td>30</td>
<td>SCT+IV Mel</td>
<td>NA</td>
<td>39</td>
<td>0.19-0.59</td>
<td>NR</td>
</tr>
<tr>
<td>Gertz et al, 2002</td>
<td>54 (31-70)</td>
<td></td>
<td>66</td>
<td>SCT+IV Mel</td>
<td>NA</td>
<td>21</td>
<td>0.11-0.32</td>
<td>NR</td>
</tr>
<tr>
<td>Blum et al, 2003</td>
<td>56 (35-67)</td>
<td>0-2</td>
<td>13</td>
<td>CTx+PBSCT+total body RT</td>
<td>NA</td>
<td>54</td>
<td>0.23-0.85</td>
<td>NR</td>
</tr>
<tr>
<td>Skinner et al, 2004</td>
<td>56.9 (0-80)</td>
<td>2</td>
<td>394</td>
<td>IV Mel+ASCT</td>
<td>NA</td>
<td>44</td>
<td>0.39-0.50</td>
<td>NR</td>
</tr>
<tr>
<td>Perz et al, 2004</td>
<td>54 (34-65)</td>
<td>0-2</td>
<td>28</td>
<td>2-5 cycles of VAD followed by HDM+ASCT</td>
<td>NA</td>
<td>29</td>
<td>0.10-0.47</td>
<td>NR</td>
</tr>
<tr>
<td>Perfetti et al, 2006</td>
<td>51 (31-65)</td>
<td>2</td>
<td>22</td>
<td>IV HDM+ASCT Mel</td>
<td>NA</td>
<td>50</td>
<td>0.27-0.73</td>
<td>NR</td>
</tr>
<tr>
<td>Sanchorawala et al, 2007</td>
<td>55.5 (32-65)</td>
<td>2</td>
<td>62</td>
<td>HDM+SCT, 2 cycles</td>
<td>NA</td>
<td>NR</td>
<td>56</td>
<td>0.43-0.70</td>
</tr>
<tr>
<td>Cohen et al, 2007</td>
<td>57 (34-73)</td>
<td></td>
<td>45</td>
<td>Mel+SCT (Mel followed with adjuvant Dex+Thal)</td>
<td>NA</td>
<td>24</td>
<td>0.11-0.38</td>
<td>NR</td>
</tr>
<tr>
<td>Gertz et, 2007</td>
<td>55-59</td>
<td></td>
<td></td>
<td>HDM+SCT</td>
<td>NA</td>
<td>33</td>
<td>0.27-0.39</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Note:** N, number; Mel, melphalan; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; HDM, high-dose melphalan; ASCT, autologous stem cell transplantation; HR, hazard ratio; CI confidence interval; CT, chemotherapy; Dex, dexamethasone; NR, not reported; PBSCT, peripheral blood stem cell transplant; SWOG, Southwest Oncology Group; VAD, vincristine+adriamycin + dexamethasone; NA, not applicable; Thal, thalidomide; VMCP, vincristine + melphalan+cyclophosphamide+prednisone.
Meta-analysis results.

<table>
<thead>
<tr>
<th>Comparative studies</th>
<th>OS</th>
<th>CHR</th>
<th>PHR</th>
<th>Renal response</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR=1.79</td>
<td>OR=0.64</td>
<td>OR=0.35</td>
<td>OR=0.88</td>
<td>RR=22.0</td>
</tr>
<tr>
<td></td>
<td>(95%CI, 1.11-2.91)</td>
<td>(95%CI, 0.25-1.64)</td>
<td>(95%CI, 0.06-2.10)</td>
<td>(95%CI, 0.30-2.53)</td>
<td>(95%CI, 1.32-365.5)</td>
</tr>
<tr>
<td></td>
<td>p=0.18</td>
<td>p=ns</td>
<td>p=ns</td>
<td>p=ns</td>
<td>p=0.03</td>
</tr>
<tr>
<td></td>
<td>in favour of CC;</td>
<td>I²=0 (p=ns)</td>
<td>I²=10 (p=ns)</td>
<td>I²=7.8% (p&lt;0.05)</td>
<td>I²=12 (95%CI, 0.09-0.14)</td>
</tr>
<tr>
<td></td>
<td>I²=71.5% (p=0.002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-comparative</td>
<td>OS=0.35</td>
<td>OR=0.34</td>
<td>OR=0.34</td>
<td>OR=0.34</td>
<td>RR=22.0</td>
</tr>
<tr>
<td>studies</td>
<td>(95%CI, 0.26-0.44)</td>
<td>(95%CI, 0.17-0.50)</td>
<td>(95%CI, 0.95-1.58)</td>
<td>(95%CI, 0.95-1.58)</td>
<td>(95%CI, 1.32-365.5)</td>
</tr>
<tr>
<td></td>
<td>I²=73.3% (p=0.05)</td>
<td>I²=85.7% (p&lt;0.05)</td>
<td>I²=70.8% (p&lt;0.05)</td>
<td></td>
<td>p=0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Notes: OS, overall survival; CHR, complete hematological response; PHR, partial hematological response; TRM, treatment-related mortality; HR, hazard ratio; CI, confidence interval; CC, conventional chemotherapy; ns, nonsignificant; OR, odds ratio; RR, risk ratio; ASCT, autologous stem cell transplantation.

**Treatment-Related Morbidity:**

**Comparative Studies**

The RCT by Jaccard et al (2007) reported a TRM of 24% in the SCT arm and none in the CT arm, indicating a significant risk associated with the use of SCT compared with CT alone (RR, 22.0 95% CI, 1.324 to 365.5; p=0.03). One of the non-RCTs reported 21% (3/14) cytomegalovirus or Pneumocystis carinii infections on the ASCT arm compared with none on the CT arm. Another reported 100% ASCT patients experiencing neutropenia and mucositis compared with none in the CT arm.

**Non-Comparative Studies**

Infection was the most common treatment-related morbidity observed (14% to 63%), followed by adverse gastrointestinal effects (7% to 66%). Other adverse effects reported included central nervous system effects, including seizures, acute renal failure, and bacterial sepsis syndrome.

**Sensitivity analysis results**

**Non-Comparative Studies**

Sensitivity analyses were conducted to explore the causes for the statistical heterogeneity detected for OS, CHR, PHR, and renal response. When three outliers were removed from the CHR analysis, heterogeneity was removed (0.45 (95% CI, 0.37 to 0.52; I², 17.7%; p=0.30). No explanation for the heterogeneity observed with OS, PHR, and renal response was found.

None of the other sensitivity analyses performed changed any of the findings.

**DISCUSSION**

Systemic AL amyloidosis is characterized by multisystem involvement in many patients. Issues around the extent of cardiac involvement have been implicated in terms of early morbidity and mortality with high-dose melphalan and SCT. The committee acknowledged that in the only published RCT (Jaccard et al, 2007, included in (5)), patients with this disease who were randomized to SCT had a lower survival than those receiving standard-dose CT alone. That RCT has been noted to have a relatively high TRM in the transplant arm, 24%, and other authors have suggested that if patients are carefully selected, outcomes with SCT may be better than standard-dose CT. The committee has recommended that SCT remain an option for patients with systemic AL amyloidosis, but that a referral to a transplant centre be considered for a more detailed examination of the risks versus benefits of high-dose CT. Given
the nature of this disease and the poor prognosis, even with SCT, transplantation within the context of an investigative study would be preferred. The committee agreed that there is no role for allogeneic SCT for this disease.

CONCLUSIONS

High-dose CT and SCT remain an option for carefully selected patients with systemic AL amyloid, and such patients should be referred to a transplant centre for proper evaluation.

RECOMMENDATIONS

- High-dose CT and ASCT are an option for selected patients with primary systemic amyloidosis but within an investigative setting only.
- Allogeneic SCT is not recommended for patients with primary systemic (AL) amyloidosis

ONGOING TRIALS ([www.clinicaltrials.com](http://www.clinicaltrials.com)) (updated August 31, 2011)

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Title, details.</th>
</tr>
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<tbody>
<tr>
<td>NCT01083316</td>
<td>Bortezomib and Dexamethasone Followed by High-Dose Melphalan and Stem Cell Transplantation for Primary (AL) Amyloidosis</td>
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<tr>
<td></td>
<td>Study ID: H-28441, X05292</td>
</tr>
<tr>
<td></td>
<td>Status: recruiting</td>
</tr>
<tr>
<td></td>
<td>Last updated: June 21, 2011</td>
</tr>
<tr>
<td>NCT00477971</td>
<td>Low-Dose Melphalan and Dexamethasone Compared With High-Dose Melphalan Followed By Autologous Stem Cell Transplant in Treating Patients With Primary Systemic Amyloidosis</td>
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<tr>
<td></td>
<td>Study ID: CDR0000546745, P30CA015083, MC0482, 1691-05, NCI-2009-01329</td>
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<tr>
<td></td>
<td>Status: recruiting</td>
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<tr>
<td></td>
<td>Last updated: April 4, 2011</td>
</tr>
<tr>
<td>NCT00075608</td>
<td>Second Autologous Stem Cell Transplant in Treating Patients With Persistent or Recurrent Primary Systemic (AL) Amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Study ID: CDR0000347379, BUMC-2001-0156</td>
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<tr>
<td></td>
<td>Status: recruiting</td>
</tr>
<tr>
<td></td>
<td>Last updated: June 21, 2011</td>
</tr>
<tr>
<td>NCT00458822</td>
<td>Melphalan and Autologous Stem Cell Transplant Followed By Bortezomib and Dexamethasone in Treating Patients With Previously Untreated Systemic Amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Study ID: CDR0000537913, MSKCC-07006</td>
</tr>
<tr>
<td></td>
<td>Status: recruiting</td>
</tr>
<tr>
<td></td>
<td>Last updated: March 16, 2011</td>
</tr>
<tr>
<td>NCT01273844</td>
<td>Study of Bortezomib +HSCT in Primary Systemic Amyloidosis (AL)</td>
</tr>
<tr>
<td></td>
<td>Study ID: NJCT-1006</td>
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<td></td>
<td>Status: recruiting</td>
</tr>
<tr>
<td></td>
<td>Last updated: January 10, 2011</td>
</tr>
</tbody>
</table>

CONFLICT OF INTEREST

The authors of this recommendation report disclosed potential conflicts of interest relating to the topic of this special advice report and declared there were none.

ACKNOWLEDGEMENTS

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1. Hans Messersmith & Sheila McNair, Assistant Directors
2. Carol De Vito, Documents Manager
3. James Bao, Samia Qadir, and Esaba Kashem, Students for obtaining relevant papers and conducting the Data Audit
4. Stephanie Pow, Erin Rae, and Sherrie Hertz, CCO Staff for project support

**UPDATING**

This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

**Funding**

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REFERENCES

Appendix A. Literature search strategy.

1. exp Amyloidosis/
2. AA amyloidosis.mp.
3. AL amyloidosis.mp.
4. or/1-3
5. exp Bone Marrow Transplantation/
6. exp Stem Cell Transplantation/
7. exp Peripheral Blood Stem Cell Transplantation/
8. or/5-7
9. 4 and 8
10. letter.pt.
11. comment.pt.
12. editorial.pt.
13. or/10-12
14. exp Randomized Controlled Trial/
15. randomised controlled trial.mp.
16. exp Clinical Trial/
17. Comparative Study/
18. or/14-17
19. pooling.mp.
20. pooled analysis.mp.
21. exp Meta-analysis/
22. meta-analyses.mp.
23. systematic review.mp.
24. health technology assessment.mp.
25. exp Evidence-Based Medicine/
26. clinical practice guideline.mp. or exp Practice Guideline/
27. or/19-26
28. 18 or 27
29. 28 not 13
30. 9 and 29
31. limit 30 to (english language and humans and yr="2006 -Current") (23)
## Appendix B. AMSTAR results.

<p>| | |</p>
<table>
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<tr>
<td>1. <strong>Was an a priori design provided?</strong>&lt;br&gt;The research question and inclusion criteria should be established before the conduct of the review.</td>
<td>Yes</td>
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<td>2. <strong>Was there duplicate study selection and data extraction?</strong>&lt;br&gt;There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.</td>
<td>Yes</td>
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<td>3. <strong>Was a comprehensive literature search performed?</strong>&lt;br&gt;At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.</td>
<td>No</td>
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<td>4. <strong>Was the status of publication (i.e. grey literature) used as an inclusion criterion?</strong>&lt;br&gt;The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.</td>
<td>No</td>
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<td>5. <strong>Was a list of studies (included and excluded) provided?</strong>&lt;br&gt;A list of included and excluded studies should be provided.</td>
<td>No</td>
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<td>6. <strong>Were the characteristics of the included studies provided?</strong>&lt;br&gt;In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.</td>
<td>Yes</td>
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<td>7. <strong>Was the scientific quality of the included studies assessed and documented?</strong>&lt;br&gt;‘A priori’ methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.</td>
<td>Yes</td>
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<td>8. <strong>Was the scientific quality of the included studies used appropriately in formulating conclusions?</strong>&lt;br&gt;The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.</td>
<td>Yes</td>
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<td>9. <strong>Were the methods used to combine the findings of studies appropriate?</strong>&lt;br&gt;For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).</td>
<td>Yes</td>
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<td>10. <strong>Was the likelihood of publication bias assessed?</strong>&lt;br&gt;An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).</td>
<td>Yes</td>
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<td>11. <strong>Was the conflict of interest stated?</strong>&lt;br&gt;Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.</td>
<td>No</td>
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