

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Systematic evidence review of rates and burden of harm of intravenous admixture drug preparation errors in healthcare settings
AUTHORS	Beer, Idal; Hedlund, Nancy; Hoppe-Tichy, Torsten; Trbovich, Patricia

VERSION 1 - REVIEW

REVIEWER	Joseph Boullata, PharmD, RPh, BCNSP, FASPEN, FACN Hospital of the University of Pennsylvania and Drexel University Philadelphia, Pennsylvania, USA
REVIEW RETURNED	24-Feb-2017

GENERAL COMMENTS	<p>SPECIFIC CONSIDERATIONS FOR THE AUTHOR(S)</p> <p>INTRODUCTION –</p> <ul style="list-style-type: none"> • To help the reader, consider referring to the “medication use process” and/or redesign Figure 1 to represent a cyclical process with the step of “assessment” falling between “monitoring” and “prescribing”. The transcription step is a site of significant error (a step to be avoided as much as practical in the drug-use process). For the figure, consider inserting (perhaps combine with transcription step) the step of (IV drug) order review by the pharmacist. This critical step that includes review of indication, dosing, diluent etc seems to be missing. Additionally, potential errors in preparation will also include unrecognized incompatibility and instability. • Page 5, Line 28 – consider further defining “patient-specific dose” in terms of indication, body weight, organ function, etc. • Page 5, Line 38-40 – excellent point on unreported errors • Page 6, Line 11 – consider including parenthetically after “near-miss” the term “near-hit” which is being used at least as frequently <p>METHODS –</p> <ul style="list-style-type: none"> • Unfortunate not to have been able to include (few studies probably captured) the wrong sequence of mixing for multiple component orders (e.g., parenteral nutrition) • Page 8, Line 19 – parenteral nutrition is a medication, in fact a “high alert medication” per ISMP, so could revise as “(medication including parenteral nutrition)” • Please clarify whether the term “composite errors” would include multiple errors occurring in a single preparation ... assuming any of the studies described such <p>DISCUSSION–</p> <ul style="list-style-type: none"> • Suggest addressing the ISMP guidelines for safe IV admixture preparation which define numerous steps in the preparation process (Rich DS et al. Hosp Pharm 2013)
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	<p>REFERENCES–</p> <ul style="list-style-type: none"> • #4 “delivery” is misspelled • Rich DS, et al. Guidelines for the safe preparation of sterile compounds: results of the ISMP sterile preparation compounding safety summit of October 2011. Hosp Pharm. 2013;48(4):282-294,301.
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REVIEWER	Jehad Almasri Mayo Clinic, Rochester, MN, US
REVIEW RETURNED	27-Feb-2017

GENERAL COMMENTS	<p>As I am a specialist in systematic review methodology, my review is focused on the methods part, not on the clinical part. Hedlund and colleagues present a systematic review to give evidence about the incidence and the frequency of Intravenous admixture preparation errors (IAPEs) published in the literature in patients who had incorrect preparation of IV admixtures within an institutional health care setting by a licensed health care professional. They included 26 articles. The study is well done and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The manuscript is good written and meets the stated objectives. Here are my comments:</p> <ol style="list-style-type: none"> 1) I suggest adding to the abstract the total number of the population reported on the included articles. 2) The search restricted to the English published articles. I recommend expanding the search to include non-English articles, especially, the majority of listed countries that representing the included studies are non-English speakers. 3) I suggest to discuss the reason behind choosing “2005” as a starting year for the search, particularly, the authors highlighted the paucity of the eligible studies in their limitations. 4) In terms of the used tool for methodological quality appraisal purpose. I highly recommend using the more commonly used ones like Cochrane tool, instead of Hawker method which doesn't differentiate between different study designs and makes it less reliable tool as the authors already agreed on that in the limitations section. 5) I recommend adding a brief description of the used quality assessment tool and the results of using it to the abstract. 6) In page 11, lines 4-5. The authors mentioned that they included 26 articles in the final analysis, but no mention in the method section about what kind of analysis they did and in addition to that they stated in the limitation that doing meta-analysis is not appropriate. I highly recommend clarifying this point in method and explaining what the nature of reported data in the results section (i.e. range, 95% CI...etc) and the origin of them if possible. <p>Overall, and to make the manuscript better and easier for the journal readers, I suggest to add some figures to highlight and replace the text in results and maybe table 3 which can be moved to the appendix then.</p>
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VERSION 1 – AUTHOR RESPONSE

Comment #1: The search is old (September 2015) – please update it.

Response #1: An update to the literature search through April 25, 2017 has been completed and added to the manuscript. The data from the eight new articles that met the search criteria add further

support to the original conclusions of the manuscript; namely, that there is a lack of standardization of error definitions across studies and that rates of errors vary widely.

Comment #2: You assessed study quality using the Hawker method – this needs better explanation and tabulation of the findings reported in the Results.

Response #2: A supplemental table (new Table S2) has been added to provide more detail about the results of the Hawker analysis.

Reviewer 1 comments:

Comment #1: To help the reader, consider referring to the “medication use process” and/or redesign Figure 1 to represent a cyclical process with the step of “assessment” falling between “monitoring” and “prescribing”. The transcription step is a site of significant error (a step to be avoided as much as practical in the drug-use process). For the figure, consider inserting (perhaps combine with transcription step) the step of (IV drug) order review by the pharmacist. This critical step that includes review of indication, dosing, diluent etc seems to be missing. Additionally, potential errors in preparation will also include unrecognized incompatibility and instability.

Response #1: Please see revised Figure 1 to take into account the recommended changes (page 4).

Comment #2: Page 5, Line 28 – consider further defining “patient-specific dose” in terms of indication, body weight, organ function, etc.

Response #2: This has been added as recommended (page 5, line 12).

Comment #3: Page 6, Line 11 – consider including parenthetically after “near-miss” the term “near-hit” which is being used at least as frequently

Response #3: This terminology has been included, as recommended (page 6, line 6).

Comment #4: Unfortunate not to have been able to include (few studies probably captured) the wrong sequence of mixing for multiple component orders (e.g., parenteral nutrition)

Response #4: Incorrect sequence of mixing was not one of the pre-defined error categories for this systematic review. It also was not part of the definition of an IAPE in any of the studies identified in this systematic review.

Comment #5: Page 8, Line 19 – parenteral nutrition is a medication, in fact a “high alert medication” per ISMP, so could revise as “(medication including parenteral nutrition)”

Response #5: This change has been made as recommended (page 8, line 2).

Comment #6: Please clarify whether the term “composite errors” would include multiple errors occurring in a single preparation ... assuming any of the studies described such

Response #6: Some studies specified that the unit of measurement was errors per total opportunities for error (see Table 3), which would allow for multiple errors in the same preparation. We have added a sentence to this paragraph to clarify this point (page 10, lines 20-21).

Comment #7: Suggest addressing the ISMP guidelines for safe IV admixture preparation which define numerous steps in the preparation process (Rich DS et al. Hosp Pharm 2013)

Response #7: Thank you for the suggestion to address these guidelines. We’ve added a sentence to the discussion section as it relates to the complexity of IV admixture preparation and error reporting in the US (page 26, lines 16-18).

Comment #8: References - #4 “delivery” is misspelled

Response #8: This has been corrected (page 33, line 10).

Reviewer #2 comments:

Comment #1: I suggest adding to the abstract the total number of the population reported on the included articles.

Response #1: Unfortunately, it is not possible to add the total population number of the studies included in this review. Many studies reported only the number of IV preparations or preparation steps and not the number of patients.

Comment #2: The search restricted to the English published articles. I recommend expanding the search to include non-English articles, especially, the majority of listed countries that representing the included studies are non-English speakers.

Response #2: While it would be of great interest to be able to include results of studies in the languages of non-English speaking countries, it would be logistically challenging to translate and screen these studies. It would also potentially introduce bias into the systematic review process, as search terms would need to be standard across languages, and subtle differences in meaning would impact the results. Given the industry and academic standard of publishing in English, we feel that this English-only search is sufficient for gaining a broad, global understanding of the issue of IAPEs, and other researchers may wish to conduct searches in other languages for local audiences.

Comment #3: I suggest to discuss the reason behind choosing “2005” as a starting year for the search, particularly, the authors highlighted the paucity of the eligible studies in their limitations.

Response #3: This date was selected to include a sufficiently long period to capture the studies of interest, while remaining relevant to current practice in terms of technology and guidelines. We have included this language in the methods section to clarify our rationale (page 8, lines 3-5).

Comment #4: In terms of the used tool for methodological quality appraisal purpose. I highly recommend using the more commonly used ones like Cochrane tool, instead of Hawker method which doesn't differentiate between different study designs and makes it less reliable tool as the authors already agreed on that in the limitations section.

Response #4: While Cochrane is a well-respected and rigorous system, its strength is in evaluating clinical studies rather than observational studies. With this in mind, we chose the Hawker criteria, which is more adaptable across study types with varying methodologies, and better fit the needs of this systematic review.

Comment #5: I recommend adding a brief description of the used quality assessment tool and the results of using it to the abstract.

Response #5: The Hawker analysis has been added to the methods and the results, as recommended (page 2, lines 7-8).

Comment #6: In page 11, lines 4-5. The authors mentioned that they included 26 articles in the final analysis, but no mention in the method section about what kind of analysis they did and in addition to that they stated in the limitation that doing meta-analysis is not appropriate. I highly recommend clarifying this point in method and explaining what the nature of reported data in the results section (i.e. range, 95% CI...etc) and the origin of them if possible.

Response #6: The “analysis” in this sentence referred to the Hawker analysis of article quality in the following sentence. The main results of the systematic review are purely descriptive. The data in the results section are rates of errors as reported in the original papers, and no pooling across studies or statistical testing was done. We have changed this phrase to “final synthesis,” which does not imply a statistical analysis (page 11, line 5).

Meta-analysis was inappropriate to summarize the results of the literature search because methodology and error definitions varied so widely among articles. This is addressed in the limitations section of the discussion (page 30, lines 9-11).

Comment #7: Overall, and to make the manuscript better and easier for the journal readers, I suggest

to add some figures to highlight and replace the text in results and maybe table 3 which can be moved to the appendix then.

Response #7: We agree with the reviewer that the current Table 2 is extensive, and should be moved to supplemental content. However, we have found it is not very informative to present this information in a figure. Instead, we have prepared a shorter summary table and will refer readers to the supplemental content for more information. In addition, we have reduced the amount of text describing the characteristics of the studies in the results section, as this is now summarized in the table.

VERSION 2 – REVIEW

REVIEWER	Joseph Boullata Drexel University and Hospital of the University of Pennsylvania USA
REVIEW RETURNED	05-Jul-2017

GENERAL COMMENTS	SPECIFIC CONSIDERATIONS FOR THE AUTHOR(S)
	<ul style="list-style-type: none"> • Page 9, Line 17 – double-check whether the citation is [24] or should be [23] • Page 27, Line 16 – 34 studies were included rather than 26

VERSION 2 – AUTHOR RESPONSE

Comment #1: Page 9, Line 17 – double-check whether the citation is [24] or should be [23]

Response #1: This citation is correct as written. We cite Green et al. to provide additional support for our choice of the Hawker appraisal tool. While the systematic literature review by Green et al. focused on a different therapeutic area from the present study, the authors justified their choice of the Hawker method as the most flexible solution to the challenge of assessing studies with varying research methodologies, which was also the case with the present study.

Comment #2: Page 27, Line 16 – 34 studies were included rather than 26

Response #2: We thank the reviewer for his careful attention. This sentence been corrected to state that 34 studies were included.