PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	ADVERSE DRUG EVENTS IN A PEDIATRIC INTENSIVE CARE UNIT: A PROSPECTIVE COHORT
AUTHORS	Araujo, Orlei; Silva, Dafne; Arduini, Rodrigo; Alonso, Carolina; Shibata, Audrey; Troster, Eduardo

VERSION 1 - REVIEW

REVIEWER	Florence T. Bourgeois, MD, MPH Assistant Professor in Pediatrics, Harvard Medical School Boston Children's Hospital United States I have no conflicts of interests or financial disclosures to report.
REVIEW RETURNED	22-Aug-2012

THE STUDY	Representativeness of patients: Greater than 80% of patients in the study cohort had a chronic disease. While it is expected that patients in the ICU are more likely to have underlying conditions, this population may not be representative of pediatric ICU populations. The authors should comment on whether their ICU population is typical of others and how this high rate of chronic disease might affect their results. Main outcome measure: Based on the second objective, "to identify risk factors for ADEs", the methods should discuss the variables that were examined as potentially related to ADEs and the analysis should include a regression model with ADEs as the dependent variable. Further, the objectives also mention identifying tools to detect ADEs earlier, but this is not further discussed in the methods section. Statistical methods: As mentioned above, the statistical methods should include an analysis on identifying variables associated with ADEs. The methods focus on an analysis on the impact of ADEs on LOS, which has not been previoulsy mentioned as one of the aims of the study. The conclusions focus on how an active approach can identify ADEs in the PICU. However, this is not something that was systematically assessed in the paper. Nor is the use of the trigger approach discussed in greater detail in the discussion. Therefore, the focus on tools to identify ADEs should be revised in the abstrat conclusions, the objectives, and the conclusion of the discussion section. Further, if the impact of ADEs on PICU LOS is one of the main conclusions, this should be introduced earlier as an objective and described further in the methods.

	The discussion section should include comments on the limitations of the study.
RESULTS & CONCLUSIONS	Results presentation: After a description of the study population, the results should present the analysis of the variables associated with ADEs since this si the secondary objective. This should be followed by the results on teh impact of ADEs on LOS. It is also not clear whether a univariate or multivariate analysis was performed to assess teh association of variables with ADEs. It is not clear why number of drugs was analyzed separately and not in a multivariable analysis with the other variables. The examination of interaction factors between patient age and number of drugs is also not previously mentioned and does not address teh stated aims. The conclusions focus on the use of the trigger approach for early identification of ADEs, but this is never discussed in teh methods, results, or discussion section.
REPORTING & ETHICS	The STROBE checklist may be appropriate for this observational study.
GENERAL COMMENTS	This is a prospective observational study of adverse drug events in a pediatric intensive care unit. The study addresses an important topic and is generally well executed. The study could benefit from some clarifications around the aims and from greater detail in the methods on the analyses performed. A few additional minor comments: - While Table 2 lists the different triggers, it would be helpful for the reader to have additional details regarding the specific triggers used described in the text. - In the methods section, the authors should provide a definition of ADEs. This is particularly important in order to compare results to other studies as a number of different definitions have been used in prior studies. For example, were adverse events related to dosing errors or to the improper administration of a drug considered an ADE? - Additional detail is also required on how ADEs were classified as moderate to severe including information on what constituted a moderate or a severe reaction. - The authors should describe how ADEs were identified as “prevalent at admission”. Were the patients admitted to the ICU because of the ADE? - Once the term “trigger” has been introduced, it should be used consistently throughout the paper (i.e. eliminate terms such as “indicative parameters”).

REVIEWER	Doreen Matsui

	Associate Professor, Department of Paediatrics University of Western Ontario Canada I have no competing interests.
REVIEW RETURNED	23-Oct-2012

THE STUDY	The study period chosen was from October 2005 to March 2006. As this is a descriptive study, it may have been better to have chosen a whole year to account for seasonal variations in disease presentation, which may influence the drugs prescribed. Although it is noted that the admission form was entered by 2 trained intensive care paediatricians it is not stated who reviewed the records. Were a proportion of the records reviewed by 2 individuals and if so, was there agreement between the 2 reviewers?
RESULTS & CONCLUSIONS	Results, Page 6, Line 43 – The authors do not justify why they included adverse drug events that were prevalent at admission. I do not think that they should be included. Discussion, Page 10, Line 34 – “if an increase was observed, we can conclude that the ADEs caused harm to the patient” – I do not follow how this conclusion can be made based on observing “an increase”. Conclusions – The authors conclude that the use of focused and active search engines can provide a systematic approach to identify ADEs in PICUs. However, I do not think that this study examined the use of “active search engines”.
GENERAL COMMENTS	More emphasis needs to be placed on what makes this study unique as I think that it is already known that adverse drug events are common in an ICU setting and that the frequency of adverse drug events is related to the number of drugs that are administered. There are some minor English grammatical errors and odd word choices. Results – Although the chronic diseases at admission were described the reasons for admission were not. Discussion, Page 7, Lines 22-36 – I do not understand their confusing explanation as to how they extrapolated their results to a longer period of observation. Discussion, Page 10, Lines 53-56 – The authors should explain how “a systematic approach could convert some ADEs from inevitable to avoidable”. As number of drugs administered and length of stay were relevant factors, there should be some discussion as to how these 2 factors may be interrelated, that is it is unclear as to whether they were examined as independent risk factors.

REVIEWER	A.G. Posthumus, MD, PhD-candidate. Department of obstetrics and gynecology, Erasmus University Rotterdam, The Netherlands.
REVIEW RETURNED	25-Oct-2012

THE STUDY	How was the triggerlist developed precisely? Was it taken immediately from literature or were alterations made. This is not clear. Also, what is the definition of biochemical alterations? This trigger does not seem specific at all for ADE's. How did the researchers determine whether ADE's were unavoidable? (For example the Schumock's algorithm for preventability) Concerning the excluded patients, please clarify what is meant by adult organ donors (on a PICU). Could you describe how the positive predictive value was calculated and what the use of this measure is. In the linear regression model the dependent variable is "PICU stay", later on you use "LOS". Do you mean the same? In that case it is better to be consistent in the term used.
RESULTS & CONCLUSIONS	In the results section the readability could be improved by first mentioning the total number of triggers (138)and after that the 110 ADE's in 84 patients. Also it would be better to present the main outcome 'Risk factors for ADE' before the linear regression. Cancer was the most common chronic disease, no adverse outcomes were found because of cancer chemotherapy? Could you elaborate on this? The paragraph on the outcomes of the multivariate analysis is confusing. Please clarify. What do you mean by "focused and active search engines" in the conclusion? The trigger list? This is not clear. (This is also not the answer to your primary objective, consider switching the 2 sentences in the conclusion).
GENERAL COMMENTS	As a second objective it is stated that the authors attempt to identify risk factors for [ADE's] and tools that could detect [ADE's] early. Yet in the manuscript no further mention is made at all of tools specifically focused on early identification of ADE's.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Florence T. Bourgeois, MD, MPH
Assistant Professor in Pediatrics, Harvard Medical School
Boston Children's Hospital
United States

Representativeness of patients: Greater than 80% of patients in the study cohort had a chronic disease. While it is expected that patients in the ICU are more likely to have underlying conditions, this population may not be representative of pediatric ICU populations. The authors should comment on whether their ICU population is typical of others and how this high rate of chronic disease might affect their results.
Answer: We added the commentary to the discussion.

Main outcome measure: Based on the second objective, "to identify risk factors for ADEs", the methods should discuss the variables that were examined as potentially related to ADEs and the analysis should include a regression model with ADEs as the dependent variable. Further, the objectives also mention identifying tools to detect ADEs earlier, but this is not further discussed in the methods section.
Answer:The choice of variables was justified in the text, and the regression model was done.

Statistical methods: As mentioned above, the statistical methods should include an analysis on identifying variables associated with ADEs. The methods focus on an analysis on the impact of ADEs on LOS, which has not been previoulsy mentioned as one of the aims of the study.
Answer: Done.

The conclusions focus on how an active approach can identify ADEs in the PICU. However, this is not something that was systematically assessed in the paper. Nor is the use of the trigger approach discussed in greater detail in the discussion. Therefore, the focus on tools to identify ADEs should be revised in the abstrat conclusions, the objectives, and the conclusion of the discussion section.
Answer: We believe that with Table 1 the use of triggers has become clearer. The topic was also reviewed in the discussion.

Further, if the impact of ADEs on PICU LOS is one of the main conclusions, this should be introduced earlier as an objective and described further in the methods.
Answer: Done.

The discussion section should include comments on the limitations of the study.
Answer: Done

Results presentation: After a description of the study population, the results should present the analysis of the variables associated with ADEs since this si the secondary objective. This should be followed by the results on teh impact of ADEs on LOS. It is also not clear whether a univariate or multivariate analysis was performed to assess teh association of variables with ADEs.
Answer: We changed results presentation.

It is not clear why number of drugs was analyzed separately and not in a multivariable analysis with the other variables. The examination of interaction factors between patient age and number of drugs is also not previously mentioned and does not address teh stated aims.
Answer: In multivariate analysis (ADE as a dependent), the only significant variables were the number of drugs and age <48 months, with significant interaction. We hope that the text is now clearer.

The conclusions focus on the use of the trigger approach for early identification of ADEs, but this is never discussed in teh methods, results, or discussion section.
Answer: We added a table with triggers used and a rationale for their use, and discussed the topic in the methods.

The STROBE checklist may be appropriate for this observational study.
Answer: After review, we believe the study is consistent with strobe

This is a prospective observational study of adverse drug events in a pediatric intensive care unit. The study addresses an important topic and is generally well executed. The study could benefit from some clarifications around the aims and from greater detail in the methods on the analyses performed.
Answer: We hope the text is clearer after review.

A few additional minor comments:
- While Table 2 lists the different triggers, it would be helpful for the reader to have additional details regarding the specific triggers used described in the text.
Answer:Done in table 1
- In the methods section, the authors should provide a definition of ADEs. This is particularly important in order to compare results to other studies as a number of different definitions have been used in prior studies. For example, were adverse events related to dosing errors or to the improper administration of a drug considered an ADE?
Answer: The definition was added. The examples are not ADEs, as explained in the text
- Additional detail is also required on how ADEs were classified as moderate to severe including information on what constituted a moderate or a severe reaction.
Answer:Done.
- The authors should describe how ADEs were identified as “prevalent at admission”. Were the patients admitted to the ICU because of the ADE?
Answer: Done.
- Once the term “trigger” has been introduced, it should be used consistently throughout the paper (i.e. eliminate terms such as “indicative parameters”).
Answer: Done.

Reviewer: Doreen Matsui
Associate Professor, Department of Paediatrics
University of Western Ontario
Canada

I have no competing interests.

The study period chosen was from October 2005 to March 2006. As this is a descriptive study, it may have been better to have chosen a whole year to account for seasonal variations in disease presentation, which may influence the drugs prescribed.
Answer: This was a limitation of the study now cited in the discussion.

Although it is noted that the admission form was entered by 2 trained intensive care paediatricians it is not stated who reviewed the records. Were a proportion of the records reviewed by 2 individuals and if so, was there agreement between the 2 reviewers?
Answer: Data were reviewed by 2 authors (Drs Silva and Shibata) and consolidated in agreement. Explanation added to the text.

Results, Page 6, Line 43 – The authors do not justify why they included adverse drug events that were prevalent at admission. I do not think that they should be included.
Answer: Due to a writing error, the text implied that the events were present on admission. Actually, "prevalent" ADEs were due to drugs that patients were receiving at PICU admission, but that occurred after admission. We changed the term to "ADES due to prevalent drug" and "incident drug ".

Discussion, Page 10, Line 34 – “if an increase was observed, we can conclude that the ADEs caused harm to the patient” – I do not follow how this conclusion can be made based on observing “an increase”.
Answer: The phrase was removed.

Conclusions – The authors conclude that the use of focused and active search engines can provide a systematic approach to identify ADEs in PICUs. However, I do not think that this study examined the use of “active search engines”.

Answer: We understand that searching in medical records for pre-defined triggers, as described in the methodology, is an active search. Conclusion was rewritten.

More emphasis needs to be placed on what makes this study unique as I think that it is already known that adverse drug events are common in an ICU setting and that the frequency of adverse drug events is related to the number of drugs that are administered.
Answer: Done in discussion (last paragraph).

There are some minor English grammatical errors and odd word choices.
Answer: We sent the text for further review. (Biosciences Editing)

Results – Although the chronic diseases at admission were described the reasons for admission were not.
Answer: done

Discussion, Page 7, Lines 22-36 – I do not understand their confusing explanation as to how they extrapolated their results to a longer period of observation.
Answer: Topic was rewritten.

Discussion, Page 10, Lines 53-56 – The authors should explain how “a systematic approach could convert some ADEs from inevitable to avoidable”.
Answer: “inevitable” was changed to “presumably inevitable”, according with the cited example.

As number of drugs administered and length of stay were relevant factors, there should be some discussion as to how these 2 factors may be interrelated, that is it is unclear as to whether they were examined as independent risk factors.
Answer: The presentation of results was rewritten. In multivariate analysis, the number of ADEs and number of drugs were the independent variables that were related to the LOS, but the slope coefficient for the number of drugs was 0.83.

Reviewer: A.G. Posthumus, MD, PhD-candidate.
Department of obstetrics and gynecology,
Erasmus University Rotterdam, The Netherlands.

How was the triggerlist developed precisely? Was it taken immediately from literature or were alterations made. This is not clear.
Answer: we chose triggers reported in the literature, consistent with the drugs used in routine ICU. Explanation added in methods.

Also, what is the definition of biochemical alterations? This trigger does not seem specific at all for ADE's.
Answer: We added a table (1) where the alterations are described

How did the researchers determine whether ADE's were unavoidable? (For example the Schumock's algorithm for preventability)
Answer: unavoidable were simply those ADE that occurred during normal use of a drug, and not the result of a human error. This explanation is in the text.

Concerning the excluded patients, please clarify what is meant by adult organ donors (on a PICU).
Answer: In our institution, adults who donate liver to children are treated in PICU.

Could you describe how the positive predictive value was calculated and what the use of this measure

is.
Answer: Done in methods.

In the linear regression model the dependent variable is "PICU stay", later on you use "LOS". Do you mean the same? In that case it is better to be consistent in the term used.
Answer: The same. Corrected.

In the results section the readability could be improved by first mentioning the total number of triggers (138)and after that the 110 ADE's in 84 patients.
Answer:Done.

Also it would be better to present the main outcome 'Risk factors for ADE' before the linear regression.
Answer: Done.
Cancer was the most common chronic disease, no adverse outcomes were found because of cancer chemotherapy? Could you elaborate on this?
Answer: No new events related to chemotherapy were observed after admission. Due to a writing error, the text implied that the events were present on admission. Actually, "prevalent" ADEs were due to drugs that patients were receiving at PICU admission, but that occurred after admission. We changed the term to "ADES due to prevalent drug" and " incident drug".

The paragraph on the outcomes of the multivariate analysis is confusing. Please clarify.
Answer: It was rewritten, we hope it's clearer now.

What do you mean by "focused and active search engines" in the conclusion? The trigger list? This is not clear.
Answer: It was rewritten.

(This is also not the answer to your primary objective, consider switching the 2 sentences in the conclusion).
Answer:Done.

As a second objective it is stated that the authors attempt to identify risk factors for [ADE's] and tools that could detect [ADE's] early. Yet in the manuscript no further mention is made at all of tools specifically focused on early identification of ADE's.
Answer: Triggers with better predictive value are the tools. We hope to have made the text clearer, and added an explanation on PPV.

VERSION 2 – REVIEW

REVIEWER	Doreen Matsui Associate Professor, Department of Paediatrics University of Western Ontario Canada I have no competing interests.
REVIEW RETURNED	17-Dec-2012

RESULTS & CONCLUSIONS	Conclusions – The authors conclude that the use of an active search using triggers can provide a systematic approach to identify ADEs in

	PICUs. However, how do the investigators know that they did not miss any ADEs using their trigger approach? I do not think that this study examined how well the trigger approach detected ADEs.
GENERAL COMMENTS	It is still unclear to me what makes this study unique as I think that it is already known that adverse drug events are common in an ICU setting and that the frequency of adverse drug events is related to the number of drugs that are administered. The authors refer to the last paragraph in their discussion. Is there any reason to believe that this ADE situation would be different in developing countries, and if so this issue should be discussed. Page 3, Introduction – "In addition, several medications have not exhibited safety in the pediatric age group …". Do they mean that these medications were unsafe or that safety has not been evaluated? Page 3, Introduction – I am not sure what is meant by "presentation of the drug". Page 5, Materials and Methods – what is meant by "consolidated in agreement"?

VERSION 2 – AUTHOR RESPONSE

Conclusions – The authors conclude that the use of an active search using triggers can provide a systematic approach to identify ADEs in PICUs. However, how do the investigators know that they did not miss any ADEs using their trigger approach? I do not think that this study examined how well the trigger approach detected ADEs.

A: From the methods published in literature to date, no one is able to ensure that no ADE is missed. As we wrote in the discussion, Takata and other authors have made it clear that triggers approach is a tool to increase the rate of ADEs observed, because it is an active search. The study was not comparative, but observational, therefore we agree that we have not examined the effectiveness of the method.

It is still unclear to me what makes this study unique as I think that it is already known that adverse drug events are common in an ICU setting and that the frequency of adverse drug events is related to the number of drugs that are administered. The authors refer to the last paragraph in their discussion. Is there any reason to believe that this ADE situation would be different in developing countries, and if so this issue should be discussed.

A: We do not intend that the study is unique, but we understand that its information is valuable, because most of the data for ADEs in the literature is from adult patients. We believe that, in developing countries, the reporting of ADEs is incipient as is in Brazil, where the online system provided by the health authority only receives notifications, which are not mandatory. There is no active search, not even in private institutions. We added these observations to the last paragraph.

Page 3, Introduction – "In addition, several medications have not exhibited safety in the pediatric age group …". Do they mean that these medications were unsafe or that safety has not been evaluated?

A: it means that safety has not been properly evaluated. We changed the text.

Page 3, Introduction – I am not sure what is meant by “presentation of the drug”.

A: we changed it to “drug formulation”

Page 5, Materials and Methods – what is meant by “consolidated in agreement”?
A: we changed it to “ data were analyzed and consolidated by 2 authors (Drs. Silva and Shibata)”