Author’s response to reviews

Title: A systematic review of clinical guidelines on the management of acute, community-acquired CNS infections

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Version: 1 Date: 20 May 2019

Author’s response to reviews:

Dear editor/s.

Thank you for the review of the manuscript. We have updated and re-uploaded the manuscript using track-changes to address the reviewers comments. Please find an overview of the responses to the reviewers comments below, with a detailed description of the changes made at the end of this letter.

Following the reviewers' reports, we encourage you to state the objective more clearly the importance of your work, and to state how an approach of harmonisation / local adaptation could
apply broadly. Thanks for the review and comments, we have updated the introduction to emphasis the objectives and relevance of our work more clearly and as outlined below.

Reviewer #1: The authors present a systematic review of clinical guidelines on the management of CNS infections. The topic is of substantial interest given the heterogeneity in clinical practice and the importance of regional differences in the presentation and management of CNS infections. The methodology is quite sound and comprises both comprehensive database searches and an electronic survey, for which the response rate was adequate. The manuscript is overall well written and the tables, which allow for a rapid comparison of various guidelines, are quite informative. Helpful recommendations are offered for studies that scored below four per AGREE II criteria. In my opinion, this is a valuable contribution to the literature.

Thank you for your comments, please find responses to each point below.

Comments to address:

1) Some passages in the Results section belong in the Discussion. Page 21 line 438 "A Cochrane review from 2015 concluded that..." is a clear example of this. There are MANY other examples of statements made i.e. "MRI is useful for detection of early changes and for excluding alternative causes and is more sensitive and specific compared to CT", "Therefore bacterial meningitis cannot be ruled out based on the absence of classical signs and symptoms alone", etc. that should either be reworded (i.e. "it was found that, it was noted that, etc.) so that they are appropriate for Results or moved to Discussion.

   - Thanks for highlighting this. The results section has been reviewed and updated to clarify when it is a result, and any statements not derived from the guidelines moved to the introduction or discussion.

2) Boxes 1 and 2 are unnecessary, just include in the text

   - The boxes have been deleted. The search terms are now presented in the text.

3) Unclear exactly how overall quality score was ascertained from the domain scores, please clarify.

   - This has been clarified in the methodology.
4) Results-->
"The data showed good correlation between scores for the key domain 'rigour of development' and the overall quality scores". This statement is offered without any analysis. Please provide measures of quantification of correlation.

Thanks for this valid point, this particular statement has been deleted to avoid misinterpretation.

5) Table 6, I would remove the IEC study since it does not address treatment; otherwise this table may be misleading as the audience may come away with the impression that the IEC does not recommend acyclovir for encephalitis.

Thanks for highlighting, the IEC study has been removed from Table 6 to avoid misinterpretations.

6) The manuscript needs to be edited for language

The updated manuscript has been reviewed and edited throughout by an information specialist to address this point.

Reviewer #2: The authors have performed a systemic review of clinical guidelines on the management of community acquired CNS infections. Both bacterial and viral CNS infections are considered. The CMGs have been developed for different audiences in different countries in different time frames, which each may have a different population at risk. That the CMG’s vary in diagnostic and therapeutic guidelines is therefore not surprising. The added value of the comparisons presented in this review is limited in my view. The review does not aim to extract some sort of consensus of guidelines or common view on treatment of the diseases but identify the differences. These are relatively minor in my view.

Thank you for your comments, please find responses to each point below.

1. The introduction is unclear. The authors selected bacterial meningitis and viral encephalitis, while there are many other CNS infections. It is stated the rationale for performing this review is that CMGs are important tools identifying emerging infectious diseases but few of the guidelines focus on diagnostics. Most guidelines do not aim to provide case definitions, which is more important for instance for clinical trials than it is for treatment guidelines. It is
unclear how "harmonization of diagnostic and clinical management practices" can inform public health outbreak responses. The authors state the review is part of PREPARE's mission to provide clinical data to inform clinical and public health care responses, but I fail to see how this review facilitates this goal.

- We focused on viral and bacterial pathogens as these are the most likely type of pathogens that may present as (re-) emerging, community-acquired CNS infections with epidemic potential. We have adjusted the introductory text to make the rationale clearer.

2. The boxes providing some of the used definitions of encephalitis are not very helpful as they only reflect a minor part of the guidelines. The case definition in box 4 is also unhelpful as it provides no cut-offs for e.g. CSF white cell differential - but just mention "consistent with bacterial meningitis". What is consistent with bacterial meningitis? We know 10% of cases have less then 100 leukocytes/mm3 in their CSF. The clinical criteria also very vague.

- Thanks for the comment, we have deleted the examples case definitions as suggested to avoid misinterpretations.

3. Table 2 is quite unclear, is the purpose to show the number of guidelines that mention these common signs and symptoms or a very small set of patients in which the symptoms are described (8,10 and 10). if is the latter, the numbers are too small to be informative. Describing how many guidelines mention a symptom as 'common' is also not useful.

- Thanks for highlighting this, we have added a legend to the table and additional text in the table to clarify what the numbers refers to. The table shows the number of CMGs that cite specific signs and symptoms on presentation for different age-groups, to illustrate the most commonly described symptoms on presentation. The table also highlights the variations in information and complexity that exists between guidelines and as pointed out, the limited usefulness this means for clinicians, highlighting the need for CMGs to be evidence-based, comprehensive and ideally harmonized, both in regard to evidence, standard of development and quality.

4. Table 3, 4 and 5 are not very clear and again not very helpful.

- As per previous comment the tables are intended to give an overview of recommendations and illustrate the variations that exists between guidelines, in regard to recommendations and coverage. The variations identified, illustrated in the tables highlights the need for harmonization of guideline development, to ensure equity in access to best available,
evidence-based recommendations for clinicians and different populations across Europe. As other reviewers found the tables illustrative and useful, we have suggested to keep them but have added an explanatory legend to each. We have also reviewed and update the tables for clarification and consistency.

Reviewer #4: This is well executed, well written review of an important area of clinical guideline development which highlights relevant issues in a clinically relevant way. I do not have any suggestions for improvement of the manuscript.

- Thank you for the review and comment.

Detailed description of the changes made to the manuscript:

1. Language reviewed and edited throughout the manuscript by an information specialist.

2. Abstract section:

Line 40-41: edited to: "Twenty-six CMGs were identified, 146 addressing bacterial, ten viral and two both bacterial and 12 viral CNS infections."

3. Background section:

Line 54-68 added: "Endemic, epidemic and emerging infectious diseases, including antimicrobial resistant organisms, remain a serious, cross-border threat to health in Europe. The response to these threats needs to be evidence-based and coordinated, and whilst Europe-wide efforts have been made to link and harmonise public health responses, much less has been done in the clinical sphere. The EU-funded Platform for European Preparedness Against R(e-)emerging Epidemics (PREPARE) was established to promote harmonised clinical research studies on infectious diseases with epidemic potential in order to improve patient outcomes and inform public health responses. One issue identified by PREPARE was the lack of understanding of variations in clinical practice across Europe, which may hamper the interpretation of clinical and surveillance data on emerging infectious threats with epidemic potential and impede the implementation of cross-border clinical research. Central nervous system (CNS) infections continue to affect populations worldwide with high morbidity, mortality and risk of long-term
sequelae, and are also associated with a range of emerging and re-emerging viral threats to Europe, such as West Nile virus, Toscana virus, measles, and enteroviruses (1, 2).”

Added on line 76 – 77 (moved from results): “ Neonatal meningitis is associated with high morbidity and higher incidence compared to older age-groups (6).”

Line 101 – 106, moved this paragraph and incorporated it into the first part of the introduction.

“The EU-funded Platform for European Preparedness Against R(e-)emerging Epidemics (PREPARE) is a network for harmonised clinical research studies on infectious diseases with epidemic potential. This review is part of PREPARE’s mission to provide clinical data to inform clinical and public health responses to infectious disease outbreaks, by assessing current application of clinical case definitions and CMGs for community-acquired CNS infections across Europe.”

4. Methods section

Search strategy: Deleted Box 1 and Box 2 and incorporated the search terms with the text.

Added to line 121-124: Search terms: (central nervous system infection [MeSH Terms]) AND (clinical guideline OR clinical practice guideline OR physician guideline OR bedside clinical guideline OR clinical management guideline OR clinical practice protocol OR physician protocol OR clinical management protocol) AND (“last 10 years” [PDat]).

Added to line 128 – 133: Search terms: ("Central Nervous System Infections"[Mesh]) OR meningitis [Title/Abstract]) OR meningoencephalitis [Title/Abstract]) OR encephalitis[Title/Abstract]) AND (guideline[Title]) OR guidelines[Title]) OR guidance[Title]) OR protocol[Title]) OR protocols[Title]) OR ("Guideline" [Publication Type] OR "Guidelines as Topic"[Mesh]) OR "Practice Guideline" [Publication Type]).

Line 170 – 183 edited to: “ Efforts were made to find additional information online on associated webpages for CMGs with limited information about the methodology used. Within each domain there were a number of sub-criteria to score from one to seven. (Supplement 1). A score of one was assigned if there was no information or the criteria was not met; a score of seven when the criteria were met. These scores were summarised for each domain, and the total score for the domain calculated as the percentage of the total possible score for that domain. The final score for each domain was calculated as the average of the reviewers’ scores. Each CMG was also given a total overall quality assessment score based on the average score for all the domains (seven being the highest quality) together with a recommendation for use with or without further modifications.
5. Results section:

Line 215-215, deleted: “The data showed good correlation between scores for the key domain ‘rigour of development’ and the overall quality scores.”

Line 251 – 252 and

Line 258 – 259, deleted: The case definition examples in Box 3 and Box 4 and the references to these in the text.

Table 2, explanatory text added: “The table shows the proportion of CMGs that each specific signs or symptoms was described in.”

and in the table- added “CMG” after the numbers showing the number of guidelines that presented clinical signs and symptoms on presentation for each of the age-groups presented.

Line 296 – 300, paragraph moved, re-phrased and incorporated on line 302 – 308 to clarify that this relates to results/information identified in the CMGs.

Table 3, explanatory text added: “The table shows the diagnostic methods recommended (shaded cells) for patients with suspected viral or bacterial aetiologies.”

Line 365 – 369, this paragraph has been moved to the background section.

Table 5, explanatory text added and the legend keys updated to make sure they are consistent across the tables.

Line 393 – 399, this paragraph has been rephrased to clarify that the statements relates to results identified in the guidelines. Edited to: “Early treatment using acyclovir (I.V.) pending diagnosis, was recommended by the CMGs focused on viral CNS infections that included treatment recommendations (7, 22, 26-33) since early treatment with acyclovir has been associated with a lower risk of sequelae and death from the most commonly diagnosed cause, HSV (7) (Table 6).”

Line 466 – 470, paragraph deleted as not part of the results: “A Cochrane review from 2015 concluded that there was a small reduction in mortality in all patients with pneumococcal meningitis treated with corticosteroids and a small reduction in hearing loss and neurological sequelae for all causes. In children, corticosteroids only reduced the rate of hearing loss when Hib meningitis (45).”

Line 475 – 479, this paragraph has been re-phrased to clarify that it is results: “It was highlighted that corticosteroids can reduce inflammation and brain oedema and has in some studies shown benefits of reducing rates of complications and improving outcomes in patients with meningitis, but also that some studies have raised concerns about potential side effects (2).”
Table 7, added: “The table shows empirical treatment recommendations for different risk groups. And updated the legend keys for consistency across the tables.

Please let me know if you require any further information.

Kind regards,

Dr. Louise Sigfrid on behalf of all the co-authors.

University of Oxford

20 May 2019