

Review Form 1.8

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| Journal Name: | Journal of Advances in Medicine and Medical Research |
| Manuscript Number: | Ms_JAMMR_120115 |
| Title of the Manuscript: | Prototheca spp. Infections in the Central Nervous System: Systematic Review and Drug Therapeutic Approaches |
| Type of the Article | Original Research Article |

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<https://www.journaljammr.com/index.php/JAMMR/editorial-policy>)

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PART 1: Review Comments

| Compulsory REVISION comments | Reviewer's comment | Author's Feedback <i>(Please correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i> |
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| <p>Is the manuscript important for scientific community? <i>(Please write few sentences regarding this manuscript to justify your answer)</i></p> | <p>Yes, the manuscript is important to the scientific community for several reasons:</p> <p>Clinical and Scientific Relevance: The study addresses rare and severe <i>Prototheca</i> spp. infections of the Central Nervous System (CNS), a topic that is not widely explored in the scientific literature. This contributes to a better understanding of a little-known but potentially fatal medical condition. Identification of Risk Factors: The identification of underlying conditions, such as immunocompromise and hydrocephalus in children, as risk factors for <i>Prototheca</i> spp. infections in the CNS provides important insights for clinicians and researchers into vulnerable populations. Evaluation of Drug Therapies: The detailed analysis of resistance profiles and discussion of the most effective therapeutic options, such as the combination of amphotericin B with tetracyclines or isavuconazole, provides valuable information for clinical practice and the development of treatment protocols. Basis for Future Research: The manuscript lays a solid foundation for future investigations, encouraging further studies into the pathogenesis, epidemiology and treatment of <i>Prototheca</i> spp. infections in the CNS. Contribution to Public Health: By increasing knowledge about rare infections and the best practices for their treatment, the study can contribute to the improvement of health care and to the development of strategies for the prevention and management of these infections. Therefore, the manuscript is a valuable contribution to the scientific community, offering new insights and potential advances in the treatment of rare CNS infections.</p> | |
| <p>Is the title of the article suitable? <i>(If not please suggest an alternative title)</i></p> | <p>The title "Prototheca spp. Infections in the Central Nervous System: Systematic Review and Drug Therapeutic Approaches" is clear and informative, reflecting well the content and objectives of the manuscript. However, to make it even more precise and attractive, some improvements could be considered. An alternative title suggestion would be:</p> <p style="padding-left: 40px;">"Systematic Review of <i>Prototheca</i> spp. Infections in the Central Nervous System and Evaluation of Therapeutic Drug Approaches".</p> <p>This alternative title highlights the systematic nature of the review and the evaluation of therapeutic approaches, providing a clear understanding of the focus of the study.</p> | |

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| <p>Is the abstract of the article comprehensive?</p> | <p>The article summary is comprehensive and covers the main aspects of the study, including the context, objectives, methodology, results and conclusions. However, some minor improvements can be made to ensure that all relevant information is clearly presented in a concise manner. Here is a slightly revised version:</p> <p>Background and Aim: Prototheca is a genus of unicellular, non-photosynthetic microalgae found in diverse environments, including water, soil, and the intestinal microbiota of animals and humans. They are the only algae pathogenic to humans. Infections of the Central Nervous System (CNS) by Prototheca spp. are rare but severe. This research aims to systematically review the pathogenic potential of Prototheca spp. as CNS infectious agents in humans, identify underlying conditions that contribute to disease development, and evaluate the most suitable drug therapy alternatives for this clinical condition.</p> <p>Methods: A systematic review was conducted using PubMed, SciELO, and Google Scholar databases. Search terms included "Prototheca," "Central Nervous System," "meningitis," "encephalitis," "meningoencephalitis," and "brain." Manuscripts published in English, Portuguese, Spanish, and Russian from 1981 to 2024 were reviewed.</p> <p>Results: The review identified 15 case reports of CNS infections by Prototheca spp. described in 14 scientific articles. Three species were implicated: Prototheca wickerhamii, Prototheca zopfii, and Prototheca trispora, with Prototheca wickerhamii being the most prevalent (66.6%). Only four patients were immunocompromised. A significant association was found between hydrocephalus in children and vulnerability to CNS protothecosis, accounting for 20% of cases. All fatal cases occurred in immunocompromised patients. Resistance profile analysis showed 88.9% susceptibility to amphotericin B and susceptibility to two triazoles (voriconazole and isavuconazole) that cross the blood-brain barrier.</p> <p>Conclusion: Immunodeficiency is not a prerequisite for susceptibility to CNS infections by Prototheca spp., but it predicts an unfavorable prognosis. The most promising treatments are combinations of amphotericin B with tetracyclines or isavuconazole. Dosage adjustments are necessary due to the toxicity of long-term algicidal antifungal treatments, posing a challenge in managing drug therapy.</p> | |
| <p>Are subsections and structure of the manuscript appropriate?</p> | <p>Yes, they are.</p> | |
| <p>Do you think the manuscript is scientifically correct? (Please write few sentences regarding this manuscript to justify your answer)</p> | <p>The manuscript presents a well-founded scientific analysis of the infection of the Central Nervous System (CNS) by <i>Prototheca</i> spp. in humans. Clarity and Objectivity in Presentation: The introduction clearly defines the aim of the research, which is to analyze the pathogenic potential of <i>Prototheca</i> spp. in the human CNS, identify underlying conditions involved in the disease and evaluate therapeutic alternatives. This demonstrates a precise and relevant orientation of the study. Detailed Methodology: The systematic review method is comprehensively described, including the databases used, the search terms, and the inclusion criteria for the manuscripts. The temporal (1981-2024) and linguistic (English, Portuguese, Spanish and Russian) scope reinforces the robustness of the review. Complete and Relevant Results: The review of 14 articles identifying 15 cases of CNS infection by <i>Prototheca</i> spp. provides a comprehensive and detailed overview of the incidence and species involved, with <i>Prototheca wickerhamii</i> being the most prevalent. The identification of cases in immunocompromised patients and the association with hydrocephalus in children is valuable information for clinical understanding. Resistance Profile Analysis and Drug Therapy: The analysis of susceptibility to different antifungals and the discussion of promising therapies (such as the combination of amphotericin B with tetracyclines or isavuconazole) are well-founded, based on resistance and clinical efficacy data. Consideration of the challenges of dosage adjustment due to toxicity reinforces the seriousness of the therapeutic discussion. Conclusions Consistent with the Data Presented: The conclusions drawn about CNS infection by <i>Prototheca</i> spp. consistently reflect the data presented. The relationship between</p> | |

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| | immunodeficiency and unfavorable prognosis, as well as the treatment suggestions, are in line with the evidence discussed. Considering these points, the manuscript appears to be scientifically sound, presenting a well-designed systematic review and a critical analysis of the available data. | |
| <p>Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form.</p> | <p>The manuscript considers publications from 1981 to 2024 in various languages, which demonstrates a comprehensive search. However, it is crucial to check that the most recent and relevant studies have been included, especially in the last five years, to ensure that the findings are up to date with current clinical and research practices. The use of databases such as PubMed, SciELO and Google Scholar is appropriate, but including other specific medical and microbiology databases, such as Embase and Web of Science, can enrich the review. Considering that only 15 cases were found, it is important that all references are of high quality and relevant. Case studies, systematic reviews and meta-analyses should be prioritized.</p> <p>Suggestion: To strengthen the manuscript, consider adding the following ideas:</p> <ul style="list-style-type: none">. Recent Studies on <i>Prototheca</i> spp. and CNS: Search for articles from the last five years that explore <i>Prototheca</i> spp. infections, especially those focused on the CNS, immunocompromised individuals and drug therapies.. Clinical Guidelines and Treatment Protocols: Including recent clinical guidelines on the treatment of fungal infections and algacides can provide valuable context for the therapeutic options discussed.. Systematic Reviews and Meta-Analyses: If available, systematic reviews and meta-analyses on rare CNS infections and antifungal treatments can enrich the discussion and conclusions of the manuscript. | |

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| <p>Minor REVISION comments</p> <p>Is language/English quality of the article suitable for scholarly communications?</p> | <p>The quality of the article's English, based on the abstract provided, seems appropriate for academic communications. The text is clear, well-structured and uses terminology appropriate to the scientific context. However, as scientific language needs to be precise and free of ambiguities, here are some suggestions for further improving the quality of the language:</p> <p>Suggestions:</p> <p>Consistency and Precision: Maintain consistency in scientific nomenclature and medical terms. For example, when referring to the "Central Nervous System", use "CNS" consistently after the first mention. Avoid repeating terms. For example, "Central Nervous System infections by Prototheca spp." can be simplified to "CNS infections by Prototheca spp." after the first mention.</p> <p>Clarity and Fluidity: Use sentence constructions that flow logically and naturally. Make sure there is a smooth transition between sentences and paragraphs.</p> <p>Grammatical correctness: Make sure all sentences are grammatically correct and avoid fragmented or excessively long sentences. Use the active voice when possible, as it is usually more direct and clear.</p> <p>Proofread spelling and punctuation: Proofread the text to correct any spelling and punctuation mistakes. Use commas appropriately to separate ideas and improve readability.</p> | |
| <p>Optional/General comments</p> | <p>Relevance of the Study: The study addresses a rare and important topic in medicine, providing a comprehensive review of Central Nervous System infections by Prototheca spp. The clinical and scientific relevance of the work is clear, especially considering the severity of CNS infections.</p> <p>Quality of Research: The methodology employed in the systematic review is robust and well described, which increases the credibility of the results. The inclusion of publications in several languages and the wide time range (1981-2024) are positive points that demonstrate the comprehensiveness of the research.</p> <p>Discussion and Clinical Implications: The discussion of the results is well-founded and contextualized with the existing literature. The identification of clinical associations, such as the vulnerability of children with hydrocephalus and the relationship between immunocompromise and unfavorable prognosis, is valuable information for clinical practice.</p> <p>Suggestions for improvement:</p> <p>Updating References: Although the review period is extensive, ensuring that the most recent and relevant references are included is crucial. The addition of recent systematic reviews and meta-analyses can further strengthen the manuscript.</p> <p>Case details: Including more detailed descriptions of the clinical cases reviewed can enrich the results section, offering specific insights into the presentation and clinical management of these infections.</p> <p>Future Implications: Expand the conclusions section to include a broader discussion of the future implications of the research, both in terms of scientific investigation and clinical application.</p> <p>Structure and Organization: The structure of the manuscript is logical and well organized, with clearly defined sections that make the study easy to read and understand. The inclusion of subheadings within the main sections can help guide the reader through the manuscript.</p> | |

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PART 2:

| | Reviewer's comment | Author's comment <i>(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i> |
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| Are there ethical issues in this manuscript? | <i>(If yes, Kindly please write down the ethical issues here in details)</i> | |

Reviewer Details:

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| Name: | Rubens Barbosa Rezende |
| Department, University & Country | Federal University of São Paulo, Brazil |