Effective treatment of Madura foot: a systematic review protocol

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Review question/objective: The objective of this review is to determine the best available evidence on the effective treatment of Madura foot. More specifically, the objectives are to identify:

1. The most effective antibiotics for treatment of actinomycetoma.
2. The most effective antifungal agents for treatment of eumycetoma.
3. The most appropriate stage or timing for surgical intervention for eumycetoma.

Keywords actinomycetoma; eumycetoma; Madura

Background

Madura foot or mycetoma is a chronic granulomatous soft-tissue infection caused by either true fungi (eumycetoma) or gram-positive aerobic bacteria (actinomycetoma).[1-3] Although data on the global burden of this disease is lacking, the infection is known to be endemic to equatorial, tropical or sub-tropical regions of the world.[1] As such, the highest reported prevalence of the disease is in Mauritania in the northwestern part of Africa with 3.49 cases per 100,000 inhabitants whereas Sudan has the highest number of cases reported per year (106 cases reported annually).[4] Nonetheless, sporadic cases have been reported in the Western world mostly in migrant populations.[1,5] The disease affects individuals of all ages but is common among adult males aged 20–50 years.[3,5] Owing to its socio-economic impact, the WHO now considers Madura foot as one on its list of neglected tropical diseases.[6]

Madura foot develops after traumatic inoculation of subcutaneous tissues with contaminated soil and the infection thereafter progresses to adjacent tissues or bone. The foot, hand and lower leg regions are the most commonly affected areas.[4] The disease follows a slow progression from the time of traumatic inoculation to presentation of symptoms. Although this period is variable, it may be as long as 12 years.[7] Affected patients typically present with a chronic indurated swelling on the affected site, draining sinuses and discharging granules. The granules are diagnostic as they represent collections of fungal hyphae or bacterial filaments.[1] An adequate diagnostic procedure is essential to guide on appropriate choice of therapy. A deep biopsy for histology appears to give a more substantial contribution to identification of the causal organism than culture.[8]

Patients with actinomycetoma are treated with an antibiotic and can expect to have clinical cure with little chance of recurrence. There appears to be no standards in choice of antibiotics and duration of treatment, although, admittedly, considerations in therapy may be tampered by the apparent extent of the disease.[9] If not identified and treated early enough, actinomycetoma may have a rapid course and can lead to amputation or death secondary to systemic spread. In contrast, eumyecetoma has a more insidious course, is less responsive to even the new antifungal agents, has a high recurrence rate, and often results in amputation.[10] It is not clear whether the choice of antifungal agents and the duration of treatment can alter the subsequent need for surgical amputation. Indeed, surgical intervention (early wound debridement) at the outset of disease, backed by antifungal therapy, may have a better outcome. This combined mode of therapy also limits the extent of amputation and leads to shorter hospital stay, both

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of which are associated with greater cost-effectiveness.[11,12]

There is unclear guidance on the most appropriate treatment strategy for Madura foot. A search of the Cochrane Library and the *Joanna Briggs Institue Database of Systematic Reviews and Implementation Reports* showed no reviews addressing the issue of treatment of Madura foot. Therefore in this systematic review, we aim to examine the best available evidence on the most effective antimicrobial choices for Madura foot, their dosage, duration and frequency of administration as well as the most appropriate sequence and timing of surgical interventions for eumycetoma and actinomycetoma.

Inclusion criteria

Types of participants

The review will consider studies that include individuals of all ages with Madura foot (actinomycetoma or eumycetoma) as confirmed by histological studies.

Types of intervention(s)/phenomena of interest

The review will consider studies that evaluate antibiotic and antifungal regimens (any drug, dosage, frequency, duration) as well as surgical interventions (wound debridement,advanced excision or limb amputation) for Madura foot. Studies in which any drug combinations are used or combinations of drugs and surgery are used will also be considered.

Outcomes

The review will consider studies that assess antimicrobial regimens and/or surgical intervention for Madura foot using the following outcomes:

1. Resolution of disease (absence of symptoms following intervention as determined by a health professional at the time of follow-up)
2. Recurrence of disease (recurrence of symptoms after a period of resolution as determined by a health professional at the time of follow-up)
3. Amputation
4. Mortality.

Types of studies

The review will consider both experimental and epidemiological study designs, including randomized controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies for inclusion. This review will also consider descriptive epidemiological study designs including case series, individual case reports and descriptive cross-sectional studies for inclusion.

Search strategy

The search strategy aim will to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and EMBASE will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies.

The primary databases to be searched will be MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library and Embase. Other databases to be searched will include Current Controlled Trials, The Trials Register of Promoting Health Interventions (TRoPHI), Australian Clinical Trials Registry (ACTR), Clinical Medicine Net Prints Collection, Bandolier Evidence-basedHealth Care and The Center for Clinical Trials and Evidence-based Healthcare at Brown Medical School. The search for unpublished studies and grey literature will include WHO, UNHCR and International Organization of Migration (IOM) records, CDC reports, Dissertation Abstracts International, WHO Library, Agency for Healthcare Research and Quality, Grey Literature Report, National Library of Medicine, Theses Canada Portal, Proquest Digital Theses, Australasian Digital Theses Program and the British Library. Studies published in the English language will be considered for inclusion in this review. Studies published from 1 January 1950 [being the first date of systematic indexing in the primary search database (MEDLINE)] will be considered for inclusion in this review.

Assessment of methodological quality

Studies selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-analysis of Statistics Assessment and

Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data collection

Data will be extracted from studies included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, where possible be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard $\chi^2$and also explored using subgroup analyzes based on the different study designs included in this review. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Acknowledgements

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Appendix I: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix II: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

