INPLASY PROTOCOL

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Conflicts of interest:
None declared.

A meta-analysis of topical antifungal drugs to treat atopic dermatitis

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Review question / Objective: **Various bacteria and fungi colonize the skin surface of patients with AD. The colonized fungi mainly include Malassezia, non-Malassezia yeasts, and molds. Among them, Malassezia occupies 63%~86% of the fungal colonization community on the skin surface of AD patients. Although the relationship between the level of Malassezia on the skin surface and disease severity remains controversial, many studies have shown that the level of serum anti-Malassezia-specific immunoglobulin E (IgE) antibodies in AD patients is related to the disease severity, especially in patients with AD in the head and neck. The specific mechanism by which Malassezia causes or aggravates AD is unclear, but damage to the skin barrier in AD patients is a key component of the mechanism. The presence of Malassezia on the skin also seems to change its barrier function, resulting in more Malassezia and its antigens colonizing the skin surface area that is exposed to the immune system. This produces a large number of specific IgE antibodies and cytokines to aggravate the disease.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 December 2021 and was last updated on 13 December 2021 (registration number INPLASY2021120062).

INTRODUCTION

Review question / Objective: **Various bacteria and fungi colonize the skin surface of patients with AD. The colonized fungi mainly include Malassezia, non-Malassezia yeasts, and molds. Among them, Malassezia occupies 63%~86% of the fungal colonization community on the skin surface of AD patients. Although the relationship between the level of Malassezia on the skin surface and disease severity remains controversial, many studies have shown that the level of serum**

anti-Malassezia-specific immunoglobulin E (IgE) antibodies in AD patients is related to the disease severity, especially in patients with AD in the head and neck. The specific mechanism by which Malassezia causes or aggravates AD is unclear, but damage to the skin barrier in AD patients is a key component of the mechanism. The presence of Malassezia on the skin also seems to change its barrier function, resulting in more Malassezia and its antigens colonizing the skin surface area that is exposed to the immune system. This produces a large number of specific IgE antibodies and cytokines to aggravate the disease.

Condition being studied: Since it was first discovered that fungi, especially Malassezia, play a role in the progression of AD, many clinical studies have been performed worldwide to explore the efficacy of topical antifungal treatment of AD. However, the quality, type, and conclusions of the studies that have been conducted on the treatment of AD using topical antifungal drugs are inconsistent. Foreign studies have shown that the efficacy of topical antifungal drugs in AD patients is consistent with that of topical glucocorticoids, and Wong et al6 showed that adding antifungal drugs to glucocorticoid therapy does not improve the efficacy. However, domestic studies in China have also reported that that the curative effect of topical antifungal drugs was better than that of topical glucocorticoids, and adding antifungal drugs to glucocorticoid therapy can significantly improve its efficacy.

METHODS

Search strategy: Embase, Pubmed, Cochrane Library, CBM, CNKI, VIP and Wanfang databases were searched, and all Chinese or English publications on treating AD with topical antifungal drugs before May 27, 2021 were retrieved. Chinese and English search terms are combined with free words and combined according to Boolean logic.

Participant or population: The research objective was any patient who was diagnosed with AD by a doctor in accordance with the Hanifin and Rajka (1980) diagnostic criteria and the British revised Williams (1994) diagnostic criteria. Age and gender were not limited.

Intervention: The treatment group used topical antifungal drugs as intervention measures, including the comparison of topical antifungal drugs with placebo and other drugs, comparison of topical antifungal drugs with other drugs, and comparison with corresponding other drugs. On the basis of different intervention measures, the data were divided into three subgroups (topical antifungal drugs vs placebo, topical antifungal drugs vs topical glucocorticoids, and topical antifungal drugs + topical glucocorticoid vs topical glucocorticoids).

Comparator: On the basis of different intervention measures, the data were divided into three subgroups (topical antifungal drugs vs placebo, topical antifungal drugs vs topical glucocorticoids, and topical antifungal drugs + topical glucocorticoid vs topical glucocorticoids). NoteExpress document manager and Review Manager5.3.

Study designs to be included: RCTs of topical antifungal drugs in the treatment of AD were included.The treatment group used topical antifungal drugs as intervention measures.The primary outcome was the effective rate,and the secondary outcomes were the condition scores and adverse reactions. The research objective was any patient who was diagnosed with AD by a doctor in accordance with the Hanifin and Rajka (1980) diagnostic criteria and the British revised Williams (1994) diagnostic criteria. Age and gender were not limited.

Eligibility criteria: The inclusion criteria were as follows. (1) RCTs of topical antifungal drugs in the treatment of AD were included. (2) The research objective was any patient who was diagnosed with AD by a doctor in accordance with the

Hanifin and Rajka (1980) diagnostic criteria and the British revised Williams (1994) diagnostic criteria. Age and gender were not limited. (3) The treatment group used topical antifungal drugs as intervention measures. (4) The primary outcome was the effective rate (where the symptom improvement was ≥ 50%, or the patient's symptoms resolved, or the treatment was markedly effective, the effective rate was classified as effective; other results were classified as ineffective). The secondary outcomes were the condition scores and adverse reactions (see the appendix for more details). The exclusion criteria were as follows. (1) The study was not a randomized controlled trial. (2) The intervention group and the control group were incomparable. (3) The study was not in either Chinese or English. Two researchers independently extracted the data on the basis of the data extraction table that was drawn up in advance. The basic content that was extracted was as follows. (1) First author, year of publication, country, and region. (2) Characteristics of the research objectives. (3) Intervention measures, including the drug name, route of administration, dosage, and course of treatment. (4) Outcome indicators and research results.

Information sources: Embase, Pubmed, Cochrane Library, CBM, CNKI, VIP and Wanfang databases were searched, and all Chinese or English publications on treating AD with topical antifungal drugs before May 27, 2021 were retrieved. Two researchers independently extracted the data on the basis of the data extraction table that was drawn up in advance. The basic content that was extracted was as follows: (1) first author, year of publication, country, and region; (2) characteristics of the research objectives; (3) intervention measures including the drug name, route of administration, dosage, and course of treatment; (4) outcome indicators and research results.

Main outcome(s): Because the intervention control measures used in the RCTs that were included in this meta-analysis were not verified in multiple studies and most of the studies were poor quality and had incomplete data, it is currently not possible to accurately evaluate the efficacy and safety of external antifungal drugs to treat patients with AD. The clinical application of external antifungal drugs requires more high-quality large-sample prospective randomized controlled studies to confirm the results. In future clinical research, the randomization methods, allocation concealment, and blinding methods should be fully described to minimize patient drop out or to properly analyze and handle patients who are lost to follow-up. The severity and location of the study patients should be fully described to analyze different subgroups. Additionally, the effective rate, clinical symptom scores, and adverse reactions should be fully reported, and the international and commonly used SCORAD or EASI scores should be used to describe the results and provide a more reliable theoretical basis for clinical use.Nine studies were included, comprising 785 subjects. On the basis of different intervention measures, the data were divided into three subgroups (topical antifungal drugs vs placebo, topical antifungal drugs vs topical glucocorticoids, and topical antifungal drugs + topical glucocorticoid vs topical glucocorticoids). The bias risk results showed that the random distribution methods and allocation concealment were imperfect, and some studies had incomplete data and selectively reported research results. Quantitative analysis results showed that topical antifungal drugs were better than topical glucocorticoid (P = 0.003), topical antifungal drugs + topical glucocorticoid was better than topical glucocorticoid (P = 0.001), but no significant difference in adverse reactions compared with three subgroups (P > 0.05).

Quality assessment / Risk of bias analysis: The risk of bias was assessed using the "risk of bias assessment" tool that is recommended by the Cochrane Collaboration. Any disagreements between the two researchers were discussed and resolved between the two researchers or handed over to a third party for a ruling.

Strategy of data synthesis: Binary variables are presented as the relative risk (RR) and the 95% confidence interval (CI), while numerical variables are presented as the mean difference (MD) and the 95%CI. Research data with the same intervention type were merged, and the heterogeneity was evaluated before merging the data. If the heterogeneity test results showed P > 0.1 and I2 ≤ 50%, the fixed-effects model was used to calculate the merged statistics. However, if the heterogeneity test showed P ≤ 0.1 and I2 > 50%, the random-effects model was used. The Z test or the CI method was used to test whether the combined results were statistically significant. If P ≤ 0.05 using the Z test, the upper and lower limits of the 95%CI for the RR do not include one or the upper and lower limits of the 95%CI of the MD. If zero is not included, the combined result is statistically significant. However, if P > 0.05 using the Z test, the 95%CI of the RR contains one, or the 95%CI of the MD contains zero, then the combined result is not statistically significant. When the number of studies for which the data could be merged was not less than ten, a funnel chart was used to analyze the publication bias. If the data could not be merged, they were described qualitatively.

Subgroup analysis: On the basis of different intervention measures, the data were divided into three subgroups (topical antifungal drugs vs placebo, topical antifungal drugs vs topical glucocorticoids, and topical antifungal drugs + topical glucocorticoid vs topical glucocorticoids). The primary outcome was the effective rate (where the symptom improvement was ≥ 50%, or the patient's symptoms resolved, or the treatment was markedly effective, the effective rate was classified as effective; other results were classified as ineffective). The secondary outcomes were the condition scores and adverse reactions.

Sensitivity analysis: None.

Language: The study was in Chinese or English.

Country(ies) involved: China.

Keywords: Topical antifungal; Malassezia; AD; Efficacy and safety; Meta-analysis.

Contributions of each author:

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