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Meta-Analysis

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Clinical effectiveness of compounded topical medications in oral medicine: a meta-analysis

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Abstract

Aim: To assess the evidence of the efficacy and safety of compounded topical medications in oral medicine cases.

Methods: Electronic databases were searched from inception to October 2019 for studies that evaluated compounded topical medications in oral medicine cases to assess their efficacy and safety. Search terms included drug compounding, topical administration, clinical efficacy, and oral lesions. Only randomized controlled trials (RCTs) or cross-over trials of compounded topical drug versus non-compounded drug or placebo or standard treatment were included. The exclusion criteria included compounded topical medications with herbal ingredients in the intervention group to compare with the non-compounded drug. The primary outcome measure was a clinical resolution of the oral lesions. The secondary outcome measure was pain resolution. Adverse events of interventions were discussed. The quality of RCTs was assessed using the Cochrane risk of bias tool (RoB 2.0). The data were synthesised in a fixed-effect model using RevMan 5. The evidence across studies for an outcome and decision of recommendations was assessed using GRADE criteria for the subgroup of included studies selected in meta-analysis.

Results: Of 90 studies, 27 studies were included in the meta-analysis. Overall, only 8% of included studies were assessed as being at low risk of bias. The compounded topical preparation of antiviral with corticosteroids appeared to be effective for reducing oral ulcers but not pain resolution in herpes labialis. The use clobetasol propionate 0.05% in mucoadhesive base for oral lichen planus, pilocarpine HCl 5 mg lozenge for radiation-induced xerostomia in head and neck cancer patients, amlexanox 5% in mucoadhesive base and doxycycline hyclate 100 mg in denture adhesive base for recurrent aphthous stomatitis, and morphine 0.2% mouthwash in controlling oral

mucositis pain appeared to be beneficial. The use of allopurinol, granulocyte-macrophage colony-stimulating factor, and iseganan 0.3% mouthwash were not sufficient for reducing oral mucositis severity.

Conclusion: Some compounded topical medications may be effective for the treatment of oral medicine cases. Future well-designed studies using standardised measures are needed to provide high-quality evidence in evaluating the efficacy and safety of compounded topical medications for the management of oral mucosal diseases.

Keywords: Clinical efficacy, drug compounding, meta-analysis, oral medicine, topical administration

INTRODUCTION

The scope of patient management in oral medicine clinical practice is typically approached by the nonsurgical or pharmacological intervention of orofacial diseases of patients with complex medical conditions. Oral medicine specialists often work with a multidisciplinary team and are involved with chronic, recurrent, painful, or even life-threatening diseases to deliver comprehensive patient care[1].

In oral medicine clinical practice, the drug classes usually used in topical therapies by specialists include corticosteroids, antivirals, antifungals, and nonsteroidal anti-inflammatory drugs[2]. The use of topical drug delivery that is locally absorbed and acts directly at the affected site may provide greater efficacy and fewer side effects than systemically delivered medications. Apart from that, few topical formulations have been designed specifically to treat oral mucosal diseases[3].

For a variety of oral medicine cases, the use of compounded topical medications is a pharmacological treatment option due to limited availability of commercial drug products or provide for patient-specific conditions, such as paediatric population, patients with dysphagia, hard to reach areas in the oral cavity, and when a sugar-free or alcohol-free preparation is needed[4]. In many instances, prescriptions for oral medicine conditions are used off-label, and mostly based on expert opinion and experience[1-4].

Despite its benefit of use, there is a lack of evidence-based practice (EBP) guidelines or recommendations regarding the clinical efficacy and patient safety in the utilization of compounded topical medications in the management of oral medicine cases.

Hence, this meta-analysis aimed to investigate the current evidence supporting the clinical efficacy and safety of compounded topical medications for the treatment of a variety of oral lesions in oral medicine cases.

METHODS

This review followed a detailed protocol in the methodology of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[5]. The study was registered with ID number reviewregistry898 and can be accessed online (http://www.researchregistry.com/browse-the-registry#registryofsystematicreviews meta-analyses/).

Eligibility criteria

The PICO (Population, Intervention, Comparator, and Outcome)[5] model and pre-set criteria on study inclusion and exclusion were determined to answer this study question: What is the clinical efficacy and safety of compounded topical medications for the treatment of a variety of oral lesions in oral medicine cases? The inclusion criteria included randomized controlled trials (RCTs) or cross-over trials, human

studies with any age, gender, and ethnicity, drug compounding as defined by WHO criteria[6], and no restriction on the specific length of treatment duration or follow-up, and non-English language papers were considered where translation was available. The exclusion criteria included compounded topical medications with herbal ingredients in the intervention group and the testing of non-compounded drug (commercially available drugs).

Information sources and search strategy

All studies relevant to the review were identified by searching electronic databases including PubMed, Cochrane Oral Health, Cochrane Library, EBSCOhost, ADA Center for Evidence-Based Dentistry (EBD), BMJ EBM, DOAJ, SciELO, clinicaltrials.gov, WHO ICTRP, Google Scholar, and grey literature published from inception to October 2019. Medical Subject Headings terms were used by combining keywords using Boolean operators such as AND/OR. The terms would be followed by truncation symbols such as *, if appropriate. The following keywords were used to search in different electronic databases: drug compounding, topical administration, clinical efficacy, and oral lesions.

Study selection and data collection process

Titles and abstracts (when available) of all studies identified were examined independently by one review author (HBM). When there was insufficient data in an abstract to determine its status, the full manuscript was obtained and assessed independently by two review authors (HBM and IS). Disagreements were resolved by discussion. All articles that did not meet the criteria were excluded. A flowchart of the study selection processes according to PRISMA four-phase flow was generated.

Data extraction and methodological quality assessment

All the relevant data of each included study, including characteristics of studies (type of case, author, year of publication, and location), characteristics of patients (age and sex ratio), characteristics of interventions (compounded topical medication, formulation, dose, frequency of application, and treatment duration), and adverse events (AEs) were extracted and summarized in a data extraction form.

The included studies underwent quality appraisal, which was independently performed by one review author (HBM) using templates in accordance with the Cochrane risk of bias tool (RoB 2.0) across 5 domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result)[7]. The results were rated high risk, some concerns, or low risk and collated into a summary and graph.

Summary measures and synthesis of results

The primary outcomes compared the efficacy between compounded topical medications and control groups (placebo or standard treatment) based on clinical resolution of oral lesions, either partial or complete response, as measured by any clinical assessment criteria or scale of each specific disease. The secondary outcomes were pain resolution, either partial or complete response, as measured by visual analogue scale or other patient-reported outcome measures (PROMs). One of the outcomes was selected if studies did not measure both outcomes. The safety of interventions as measured by the incidence of AEs was discussed.

The data were abstracted using a 2×2 contingency table for two independent events or outcomes (participants with clinical resolution of oral lesions or not and pain resolution or not). If the data extraction of binary outcome measures were not possible, the continuous data were abstracted by mean difference, standard deviation, and sample sizes. The included studies were subgrouped and analysed on the basis of the case and intervention category. The meta-analysis of the data was undertaken if no substantial clinical and methodological heterogeneity was identified. All data were then pooled by calculating mean difference or risk ratio (RR) together with the 95% confidence interval (CI) using a fixed-effect model for two independent outcomes: clinical resolution of oral lesions and pain. Heterogeneity was assessed

using Cochran's Q statistic with I^2 statistic above 50% indicating substantial heterogeneity. Funnel plot for the detection of publication bias and subgroup analysis to investigate statistical heterogeneity would be applied when the number of trials was at least ten[8]. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) criteria across 5 domains (limitations in design, inconsistency, indirectness, imprecision, and reporting bias) were used to decide the quality of the evidence for each outcome across studies. The results were expressed in one of four grades: high, moderate, low, and very low[9].

RESULTS

Study selection

A total of 90 studies were identified for inclusion in this review. The search of studies provided a total of 2991 articles. There were 2901 records excluded on the basis of duplication, unavailable full text, or not meeting the criteria. Of these, 90 studies met the inclusion criteria and were included in the systematic review. Only twenty-seven studies were included in the meta-analysis. The PRISMA four-phase flow diagram indicating the study selection is presented in Supplementary Figure 1.

Quality assessment: risk of bias

Of the 90 included studies[10-100], seven studies were judged as low risk of bias[10,39-41,48,49,80], fifty-four were judged as some concerns[11,12,14-18,25,27-30,33,34,42,47,50-56,58-60,62-64,66,67,69-73,75-77,81,82,84-86,88,90-94,96-100], and twenty-nine studies were judged as high risk of bias[13,19-24,26,31,32,35-38,43-46,57,61,65,68,74,78,79,83,87,89,95]. Supplementary Figures 2 and 3 summarize the findings of the quality assessment.

Study characteristics

In general, there were clinical heterogeneity variables in terms of age, baseline disease severity, ethnicity, comorbidities, and other psychosocial variables as well in the included studies. There was no trial specific to the paediatric population. All participants enrolled in the studies underwent a clinical diagnosis with or without laboratory assessment. Methodological heterogeneity was also observed in terms of outcome measurement scale. All included studies were published in English, except one in Bahasa Indonesia.

The 90 included studies involved 7619 participants, aged 11 to 90 years. There were 2978 participants in oral mucositis trials, 2031 participants in herpes labialis, 1052 participants in recurrent aphthous stomatitis (RAS), 76 participants in oral lichen planus (OLP), 210 participants in xerostomia, 131 participants in oral candidiasis, 126 participants in oral chronic graft-versus-host disease (cGVHD), 79 participants in leukoplakia, 24 participants in desquamative gingivitis, 4 participants in pemphigus and 8 participants in mucous membrane pemphigoid. The study's duration of the intervention varied in length, from two days to 6 months.

All RCTs or cross-over trials compared compounded topical drugs with or without cointerventions versus other active treatment or placebo (usually a preparation similar to the treatment, without the active ingredient). There was a variety of drug class that used as an active pharmaceutical ingredient (API) of compounded topical drugs on interventions. There were no included trials that compared the pharmacological approach with surgical treatments. Two trials on OLP case compared compounded topical medications with laser phototherapy[29,31]. One trial on oral mucositis compared compounded cryotherapy (ice balls) with placebo[83]. The characteristics of the included studies are presented in Supplementary Table 1.

Effects of interventions

The included trials were divided into ten subgroups according to the cases and two subgroups according to the dosage form category (liquid or semisolid). Of the 90 trials included, the forty-nine trials using a mouthwash as vehicle were as follows: thirty in oral mucositis[67-82,84-97], six in OLP[21,24,28,32-34], five in

RAS[54,56,58,63,66], three in xerostomia[38,42,43], three in oral chronic GVHD[98-100], one in leukoplakia[37], and one in oral candidiasis[44]. The other forty-one trials used a semisolid preparation as a vehicle. The API was compounded with a mucoadhesive base, either in orabase or another excipient such as hydroxyethylcellulose gel. There were different interventions, comparisons, dosages, concentrations, vehicles, and time of application used in the included trials, along with a range of outcome measures and available data, making it difficult to meta-analyse the data. Of 90 studies, twenty-seven studies were included in the meta-analysis[14,16,22,23,29,39,40,48,49,55,59,61,64,67-69,76-79,80-82,84,87,88,96].

Clinical resolution of oral lesions

Oral lichen planus. Seven trials compared the efficacy of clobetasol proprionate ointment 0.05% in mucoadhesive base versus different dose of other corticosteroids or other active treatment[13,14,16,17,22,23,29], but only five trials provided data for meta-analysis[14,16,22,23,29]. Clobetasol increased clinical resolution of oral lesion in OLP by 16% compared to those without treatment (RR = 1.16, 95%CI: 0.65-2.09, five studies with 181 participants). There was evidence of substantial or high heterogeneity in the included trials (I^2 = 81%, P = 0.0004) [Supplementary Figure 4A].

Xerostomia. A 46% reduction of oral dryness severity was observed using pilocarpine HCl 5 mg lozenge (RR = 1.54, 95%CI: 1.03-2.28, two studies with 67 participants)[39,40]. There was no evidence of heterogeneity in both trials (I^2 = 0%, P = 0.55) [Supplementary Figure 4B].

Herpes labialis. It was 23% less likely to develop oral ulcer in herpes labialis in the treatment group compared to placebo (RR = 0.77, 95%CI: 0.69-0.85, P < 0.0001, two studies with 1.187 participants)[48,49]. There was no evidence of heterogeneity in both trials (I^2 = 0%, P = 0.56) [Supplementary Figure 4C].

Recurrent aphthous stomatitis. An increase of 33% clinical resolution of oral lesions was observed using amlexanox 5% in mucoadhesive base (RR = 1.33, 95%CI: 1.16-1.51, two studies with 425 participants)[55,59]. There was evidence of low heterogeneity in both trials (I^2 = 32%, P = 0.23) [Supplementary Figure 4D]. Participants who used doxycycline hyclate 100 mg in denture adhesive base reported faster healing, 2 days sooner, than those with placebo (MD = -2.00, 95%CI: -2.63 to -1.36, two studies with 80 participants)[61,64]. There was evidence of substantial or medium heterogeneity in both trials (I^2 = 62%, P = 0.10) [Supplementary Figure 4E].

Oral mucositis. Five trials compared the efficacy of allopurinol mouthwash with different dose (1-6 mg/mL) versus placebo or other active treatment[67,68,84,85,87], but only four trials provided data for meta-analysis[67,68,84,87]. Participants who used allopurinol mouthwash were 26% less likely to experience greater oral mucositis severity (grade 0 *vs.* other grades) than those with placebo or other active treatment (RR = 0.74, 95%CI: 0.27-2.04, four studies with 213 participants). There was evidence of substantial or high heterogeneity in the included trials (I^2 = 86%, P < 0.0001) [Supplementary Figure 4F]. Seven trials compared the efficacy of granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwash versus placebo or other active treatment[69,73-75,77-79], but only four trials provided data for meta-analysis[69,77-79]. Participants who used GM-CSF mouthwash were 15% less likely to experience severe oral mucositis (grade 0 *vs.* other grades) than those with placebo or other active treatment (RR = 1.15, 95%CI: 0.50-2.65, four studies with 210 participants). There was evidence of substantial or medium heterogeneity in the included trials (I^2 = 55%, P = 0.08) [Supplementary Figure 4G]. There was a 17% improvement in oral mucositis severity using iseganan 0.3% mouthwash (RR = 1.18, 95%CI: 0.99-1.93, three studies with 1.249 participants)[80-82]. There was no evidence of heterogeneity in the included trials (I^2 = 0%, P = 0.85) [Supplementary Figure 4H].

Pain resolution

Herpes labialis. There was low-quality evidence that acyclovir 5% compounded with hydrocortisone 1% cream (ME-609) was more effective than placebo in decreasing the pain or tenderness of ulcerative lesions

of herpes labialis (RR = 0.98, 95%CI: 0.94-1.03, two studies with 639 participants)[48,49]. There was substantial or medium heterogeneity in both trials (I^2 = 53%, P = 0.15) [Supplementary Figure 4I].

Oral mucositis. Participants treated with iseganan 0.3% mouthwash were more likely to experience pain relief (0.62x) sooner than those without treatment (MD = -0.62, 95%CI: -1.07 to -0.17; MD = -0.28, 95%CI: -0.47 to -0.09, two studies with 825 participants)[80,81]. There was low heterogeneity in the included trials (I^2 = 0%, P = 0.52; I^2 = 16%, P = 0.27) [Supplementary Figure 4J]. Participants treated with morphine 0.2% mouthwash were more likely to experience pain relief (1.99x) sooner than those without treatment (MD = -1.99, 95%CI -4.02 to 0.03, three studies with 63 participants)[76,88,96]. There was substantial heterogeneity in the included trials (I^2 = 76%, P = 0.02) [Supplementary Figure 4K].

Adverse events

Twenty-seven out of ninety studies clearly stated that there were no AEs of interventions[11,13,16,20,22,35,37,40,42,47,48,54-59,64,68,70,73,74,76,77,88,92,95]. Twenty-seven studies did not clearly state or report AEs of interventions[10,12,21,24,26,33,45,46,50,52,53,63,65,67,71,75,78,79,83-87,89,90,94,97]. Oral candidiasis, burning sensation, taste alteration, and gastrointestinal (GI) symptoms (nausea, dyspepsia) were the most common AEs reported using compounded topical corticosteroids or immunosuppressants (tacrolimus) in OLP studies[14,15,17-19,23,25,27,29,34], and in oral cGVHD studies[98-100]. Erythema was the AE of intervention (ketorolac) in the leukoplakia study[36]. Nausea, sweating, and urinary frequency were the most common AEs reported in xerostomia studies using a cholinergic agonist (pilocarpine, physostigmine)[38,39,41,43]. Transient mild GI discomfort using fluconazole mouthwash was observed in the oral candidiasis study[44]. Nasopharyngitis, headache, dry lips, burning sensation on the lips were the most commonly reported AEs using topical acyclovir compounded with corticosteroids[49], or 2-HPβCD in herpes labialis studies[51]. Transient pain and bitter or uncomfortable sensation were the most common AEs reported in RAS studies using doxycycline or minocycline[60,61,66], and corticosteroids (clobetasol)[62]. In oral mucositis studies, numbness was the most common AE reported using magic mouthwash[72], nausea and vomiting using iseganan 0.3% mouthwash[80-82], or phenylbutyrate mouthwash[91], burning sensation and increased drowsiness using doxepin rinse[93], and intolerable taste using morphine mouthwash[96].

DISCUSSION

The results showed that clobetasol propionate ointment 0.05% in the mucoadhesive base was not superior to different doses of other corticosteroids or other active treatment but may be beneficial to improve the ulcerative lesion in symptomatic OLP. Although potent topical corticosteroids (TCs) are considered to be the first-line of treatment for symptomatic OLP at any site, it is assumed that the response varies from individual to individual[101,102]. Two earlier systematic reviews by Chamani *et al.*[102] and Lodi *et al.*[103] concluded that there was insufficient evidence to support the superior effectiveness of any specific TC over another in the treatment of symptomatic OLP[101,103]. Nonetheless, a systematic review by García-Pola *et al.*[101] recommends the use of topical clobetasol propionate at 0.025%-0.05%, applied 2-3 times a day for 3 weeks, decreasing its frequency of application progressively according to the patients' response, and limiting its use to a maximum of 6 months, for the atrophic-erosive forms that do not respond to intralesional injection of betamethasone or triamcinolone[102].

The use of pilocarpine HCl 5 mg lozenge may be effective, where it reduced 46% xerostomia severity for radiation-induced xerostomia in patients with head and neck cancer. The result is in accordance with two previously systematic reviews by Cheng *et al.*[104] and Yang *et al.*[105], which found that pilocarpine may reduce radiation-induced xerostomia, particularly at a dose of 5 mg, 3 times daily[105], but clinical trials may need to be performed to further validate that pilocarpine therapy is an effective and safe treatment for radiation-induced xerostomia[104].

In herpes labialis, the results suggest that acyclovir 5% compounded with hydrocortisone 1% cream (ME-609) has a significant effect in reducing oral ulcer development and support earlier systematic review by Rosa *et al.*[106] demonstrating a beneficial effect of early episodic treatment with the combination of an antiviral and corticosteroid. Combined antiviral and corticosteroid therapy may have additive effects. The vasoconstriction mediated by corticosteroid would increase the dermal concentration of the antiviral. The use of the compounded topical preparation of antiviral and corticosteroid (ME-609) may be effective to reduce the development of oral ulcers but not for pain resolution in herpes labialis.

The use of amlexanox 5% in the mucoadhesive base for clinical resolution of RAS may be effective. A systematic review by Maheswari and Shanmugasundaram[107] concluded that topical application of 5% amlexanox, mainly when used from the prodromal stage until complete healing for four times a day, may increase healing time and reduce pain, but still need further study in terms of prevention of recurrence. In participants using doxycycline hyclate 100 mg in denture adhesive base, there was faster healing time, 2 days sooner on the oral lesion of RAS. A previous systematic review evaluated the effects of tetracycline (doxycycline) in semisolid preparations for treating RAS[108], but a review by Staines and Greenwood[109] reported that whether tetracycline mouthwash works is still in question, as the evidence was weak and limited to two small RCTs. Doxycycline hyclate 100 mg in denture adhesive base may achieve faster healing on the oral lesion of RAS.

In oral mucositis, allopurinol, GM-CSF, or iseganan 0.3% mouthwash was not superior to placebo or other active treatment. A systematic review by Jensen *et al.*[110] reported that no guidelines were possible due to insufficient or conflicting evidence in using allopurinol mouthwash for the management of oral mucositis. Clarkson *et al.*[111], in their systematic review (2010), reported that the use of systemic or topical GM-CSF cannot currently be recommended for the prevention or treatment of oral mucositis. Saunders *et al.*[112], in their systematic review, reported that iseganan mouthwash should not be used for the prevention of oral mucositis in hematopoietic stem cell transplant (HSCT) patients receiving high-dose chemotherapy with or without total body irradiation or in patients receiving head and neck radiation therapy or chemoradiotherapy. Due to the very low quality of evidence, using allopurinol, GM-CSF, or iseganan 0.3% mouthwash to improve oral mucositis severity is not recommended. Participants who used morphine 0.2% mouthwash were less likely to experience oral pain than those without treatment, which was in accordance with two previous systematic reviews demonstrating that morphine can control of mucositis pain[111,112]. Morphine 0.2% mouthwash can be effective for the management of pain due to oral mucositis in patients receiving chemoradiation for head and neck cancer[112]. The effectiveness of pain relief may be achieved with 10-15 mL and can be used for 2-3 hours in patients with mucositis pain[113].

To the best of our knowledge, this review was the first study to attempt to determine the efficacy and safety of topical compound medications in oral medicine cases. Mouthwash and semisolid preparations, either in gels, creams, or pastes (in mucoadhesive base) were the most used vehicles for local drug delivery, but with different API, dosages, concentrations, or duration of application. The challenges in topical drug delivery for oral mucosal diseases relate to overcoming the permeability of the oral mucosa, protecting drugs from enzymatic environments, and ensuring the drugs reach their target at therapeutic concentrations[3]. Moreover, there are very few topical formulations, commercially available, that have been designed specifically for oral mucosal diseases. This review is limited due to the study question being very broad. Other limitations include substantial clinical and methodological heterogeneity such as a wide range of interventions being assessed and a lack of uniformity in the outcome measures employed to assess treatment efficacy, making it difficult to evaluate, compare, and pool the data for meta-analysis. Taylor *et al.*[114] stated that to use EBP in oral medicine which is produced by high-quality systematic review and meta-analysis, there needs to be a future improvement of methodology of oral medicine intervention trials such as the use of PROMs and core outcome sets. There is a critical need to standardise the methodology

of oral mucosal disease intervention trials mainly in terms of the assessment used (in each subgroup of diseases with similar characteristics). Further trials should measure the outcomes of symptoms and clinical assessment using standardised measures. Furthermore, future trials of topical drug delivery for oral mucosal diseases should develop and produce commercially available drugs that are clinically cost-effective, easy to use, or practicable across the globe.

In conclusion, Some compounded topical medications were recommended for the management of oral medicine cases, such as the compounded topical combination of antiviral with corticosteroids for herpes labialis, clobetasol propionate 0.05% in the mucoadhesive base for oral lichen planus, pilocarpine HCl 5 mg lozenge for radiation-induced xerostomia in head and neck cancer patients, amlexanox 5% in mucoadhesive base and doxycycline hyclate 100 mg in denture adhesive base for recurrent aphthous stomatitis, and morphine 0.2% mouthwash in controlling oral mucositis pain. Future well-designed studies using standardised measures are needed to provide high-quality evidence in evaluating the efficacy and safety of compounded topical medications for the management of oral mucosal diseases.

DECLARATIONS

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Authors' contributions

Made substantial contributions to conception and design of the study, prepared figures and/or tables, and performed data analysis and interpretation: Margono HB
Review and editing: Sufiawati I

Availability of data and materials

The data supporting their findings can be found as supplementary information in the journal.

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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