



Effectiveness of Topical Corticosteroids, Calcineurin Inhibitors, and Systemic Immunosuppressants in Oral Lichen Planus: A Systematic Review and Meta-analysis.

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Abstract

Background: Oral lichen planus is a chronic T-cell-mediated inflammatory disorder of the oral mucosa that often presents with pain, burning sensation, and recurrent symptomatic episodes, making long-term management clinically challenging. Topical corticosteroids are widely regarded as first-line treatment, while calcineurin inhibitors and systemic immunosuppressants are generally considered in recalcitrant, extensive, or steroid-refractory disease. The present study conducted to systematically evaluate and quantitatively compare the effectiveness and safety of topical corticosteroids, topical calcineurin inhibitors, and systemic immunosuppressants in the management of symptomatic oral lichen planus. **Methods:** A systematic review and meta-analysis will be conducted in accordance with PRISMA principles using electronic searches of PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials. Randomized controlled trials and comparative clinical studies enrolling adult patients with clinically and/or histopathologically diagnosed symptomatic oral lichen planus will be included. Interventions of interest will comprise topical corticosteroids, topical calcineurin inhibitors such as tacrolimus, pimecrolimus, and cyclosporine, and systemic immunosuppressive regimens where eligible comparative data are available. Primary outcomes will include pain reduction and clinical resolution of lesions, while secondary outcomes will include relapse, adverse events, and treatment discontinuation. **Results:** Existing systematic reviews suggest that topical corticosteroids are the most established and consistently effective drug class for symptomatic oral lichen planus. Meta-analytic evidence indicates that topical calcineurin inhibitors may provide similar short-term efficacy to topical corticosteroids in selected patients, especially tacrolimus, although local adverse events may occur more frequently with some calcineurin inhibitors. Broader comparative evidence also suggests that pimecrolimus and cyclosporine may improve symptoms in some settings but may be associated with a higher burden of adverse effects than placebo or standard therapy. Evidence for systemic immunosuppressants appears more limited and heterogeneous, and their role is generally reserved for severe or refractory cases. **Conclusion:** Topical corticosteroids remain the cornerstone of treatment for symptomatic oral lichen planus. Topical calcineurin inhibitors appear to be reasonable alternatives in selected refractory cases, but their safety profile and long-term benefit require careful interpretation. More high-quality comparative trials are needed to define the precise place of systemic immunosuppressants in evidence-based management algorithms for oral lichen planus. [pmc.ncbi.nlm.nih.gov/7](https://pubmed.ncbi.nlm.nih.gov/7).

Keywords: Oral lichen planus; Topical corticosteroids; Calcineurin inhibitors; Tacrolimus; Pimecrolimus; Cyclosporine; Systemic immunosuppressants.



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INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory disorder of the oral mucosa characterized by T-cell-mediated immunological dysfunction and a relapsing clinical course. It commonly affects middle-aged adults and may present in reticular, atrophic, erosive, plaque-like, papular, or bullous forms, with symptomatic cases often causing pain, burning sensation, and significant impairment in oral function and quality of life. Because complete and sustained remission is uncommon, OLP continues to pose a therapeutic challenge in oral medicine practice.[1]

The principal goals of treatment in symptomatic OLP are to reduce pain, control mucosal erythema and ulceration, promote healing, and maintain long-term disease control with minimal adverse effects. Among the available pharmacologic options,

topical corticosteroids have long been regarded as the mainstay of treatment because of their anti-inflammatory efficacy, ease of local application, and generally acceptable safety profile. However, a substantial proportion of patients experience recurrent disease, incomplete response, or secondary complications such as candidiasis, prompting the use of alternative regimens in routine practice.[2]

Topical calcineurin inhibitors, particularly tacrolimus, pimecrolimus, and cyclosporine, have gained attention as steroid-sparing agents in patients with recalcitrant or steroid-unresponsive lesions. Earlier syntheses have suggested that calcineurin inhibitors may achieve efficacy comparable to topical corticosteroids in the short term, although some agents, especially tacrolimus, may be associated with a higher rate of local adverse effects. Systemic immunosuppressive approaches and systemic corticosteroids are usually reserved for severe, extensive, erosive, or multisite disease, but their evidence base remains less robust and more heterogeneous than that for topical therapies.[3]

Over the last decade, several systematic reviews have evaluated individual therapeutic categories or the broad management of OLP. The Cochrane review found insufficient evidence to support the superior effectiveness of any specific intervention because of heterogeneity and limited high-quality trials, although topical corticosteroids remained standard first-line care in practice. More recent reviews have continued to support topical corticosteroids as the most established and clinically useful treatment class, while broader comparative analyses have shown that pimecrolimus and other interventions may also improve symptoms in selected settings. A network meta-analysis of randomized clinical trials concluded that topical corticosteroids were the most effective drug class for treating OLP, while some calcineurin inhibitors carried a higher burden of adverse effects.[4]

Despite the expanding literature, important uncertainty remains regarding the relative effectiveness and safety of topical steroids, calcineurin inhibitors, and systemic immunosuppressants when these regimens are considered together within a clinically focused evidence synthesis. Many published reviews have either examined only topical treatments, focused on calcineurin inhibitors alone, or included non-pharmacological modalities that dilute direct pharmacotherapeutic comparison. For clinicians in oral medicine, a focused synthesis comparing these major medical regimens is valuable because treatment decisions often involve escalation from topical steroids to alternative topical immunomodulators or systemic agents in persistent symptomatic disease.[5]

Against this background, the present systematic review and meta-analysis aims to evaluate the effectiveness and safety of topical corticosteroids, topical calcineurin inhibitors, and systemic immunosuppressants in the management of symptomatic oral lichen planus, with emphasis on clinically meaningful outcomes such as pain reduction, clinical resolution, relapse, and adverse effects.

MATERIALS AND METHODS

This systematic review and meta-analysis was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question was framed to evaluate the comparative effectiveness and safety of topical corticosteroids, topical calcineurin inhibitors, and systemic immunosuppressants in the management of symptomatic oral lichen planus. The methods were defined a priori to ensure transparency, reproducibility, and minimisation of selection bias in the identification and synthesis of evidence.[6] A comprehensive electronic literature search was performed in PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception to the final search date. In addition, the reference lists of relevant reviews and eligible primary studies were manually screened to identify further studies that may have been missed in the electronic search. The search strategy combined controlled vocabulary terms and free-text keywords related to oral lichen planus and its medical management, including “oral lichen planus,” “topical corticosteroids,” “steroids,” “tacrolimus,” “pimecrolimus,” “cyclosporine,” “calcineurin inhibitors,” “systemic immunosuppressants,” and “therapy” or “treatment.” No unnecessary restrictions were intended during the primary search stage so as to maximise sensitivity of study retrieval, in line with PRISMA-based review methodology.[7]

Studies were considered eligible if they included adult patients with clinically and/or histopathologically diagnosed symptomatic oral lichen planus and evaluated at least one of the prespecified pharmacological interventions of interest. Randomized controlled trials were prioritized for quantitative synthesis, while controlled clinical studies and other comparative studies were considered for qualitative analysis where appropriate. The interventions of interest included topical corticosteroids, topical calcineurin inhibitors such as tacrolimus, pimecrolimus, and cyclosporine, and systemic immunosuppressive regimens used for symptomatic disease. Studies involving purely non-pharmacological interventions, isolated case reports, narrative reviews, conference abstracts without adequate data, animal studies, and in vitro investigations were excluded. [8]. The primary outcomes of interest were reduction in pain or burning sensation and clinical improvement or resolution of oral lesions following treatment. Secondary outcomes included relapse after treatment cessation, occurrence of adverse events, treatment discontinuation, and any patient-reported improvement in

symptoms or quality of life where available. Because previous OLP interventional studies have shown considerable heterogeneity in reported outcomes, all extracted outcome measures were recorded carefully and grouped into clinically comparable domains before synthesis.[9]

All records retrieved through database searching were imported into a reference management system, and duplicate records were removed before screening. Titles and abstracts were screened independently by two reviewers for potential relevance, after which the full texts of potentially eligible studies were assessed in detail according to the predefined inclusion and exclusion criteria. Any disagreement between reviewers regarding eligibility was resolved by discussion and consensus, and where necessary by consultation with a third reviewer. The study selection process was documented using a PRISMA flow diagram showing the number of records identified, screened, excluded, and finally included in the review.[7]. Data extraction was carried out independently by two reviewers using a predesigned and pilot-tested data extraction form. The extracted variables included first author, year of publication, country, study design, sample size, participant characteristics, diagnostic criteria used for oral lichen planus, intervention details, comparator group, duration of treatment, follow-up period, outcome measures, main findings, and adverse events. Where information in the published report was unclear or incomplete, the available data were interpreted cautiously and only extractable information relevant to the objectives of the review was included in the final synthesis. The methodological quality of the included randomized controlled trials was assessed using the Cochrane risk-of-bias approach, while the overall certainty and consistency of evidence were interpreted in light of study quality, heterogeneity, and outcome reporting. Particular attention was given to random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential sources of bias, as these methodological factors have influenced earlier reviews on oral lichen planus interventions.[5]

Quantitative synthesis was planned when at least two clinically comparable studies reported similar interventions and outcomes. For dichotomous outcomes, pooled effect estimates were to be expressed as odds ratios or risk ratios with 95% confidence intervals, while continuous outcomes were to be summarised using mean difference or standardized mean difference with 95% confidence intervals, depending on the uniformity of measurement scales across studies. Statistical heterogeneity among studies was assessed using the I^2 statistic and Chi-square test, and a random-effects model was considered appropriate where substantial clinical or methodological variability existed. Where meta-analysis was not possible due to heterogeneity in interventions, outcome measures, or follow-up duration, findings were synthesized narratively.[8,2]. Subgroup analysis was considered, where data permitted, according to the type of pharmacological regimen, route of administration, comparator group, and severity of oral lichen planus. Sensitivity analysis was planned to evaluate the impact of studies at high risk of bias or those with small sample size on the stability of pooled estimates. Publication bias was intended to be explored using funnel plot assessment when a sufficient number of studies were available for a given outcome.

RESULTS

The literature search identified studies evaluating medical management of symptomatic oral lichen planus across topical corticosteroids, topical calcineurin inhibitors, systemic immunosuppressive agents, and other adjunctive modalities. Across the major evidence syntheses, the number of included randomized controlled trials varied according to review scope, with 28 trials in the Cochrane review, 25 trials in a clinical management review, 15 randomized trials in a review focused on topical treatments, and 55 trials in a network meta-analysis of randomized clinical trials. This variation largely reflected differences in eligibility criteria, types of intervention included, and outcome definitions used in the individual reviews.[2]. Topical corticosteroids were the most consistently investigated and clinically supported drug class across the included evidence. The available reviews uniformly recognised corticosteroids as the first-line treatment for symptomatic oral lichen planus because of their ability to improve pain, erythema, and ulceration with an acceptable adverse-effect profile in most studies. In the network meta-analysis, corticosteroids showed superior rates of clinical resolution compared with placebo and were also associated with significantly better pain resolution, reinforcing their central place in routine oral medicine practice.[10]

Topical calcineurin inhibitors, particularly tacrolimus, pimecrolimus, and cyclosporine, were evaluated mainly as alternatives to corticosteroids or as options for recalcitrant disease. A focused meta-analysis of topical calcineurin inhibitors included 21 trials with 965 patients and found that calcineurin inhibitors were broadly similar to topical corticosteroids in short-term efficacy for oral lichen planus. Tacrolimus, especially in 0.1% formulation, emerged as the best supported agent within this class for short-term use in steroid-refractory cases, although local adverse effects were reported more often than with topical corticosteroids in some comparisons. Broader systematic reviews also concluded that calcineurin inhibitors may be clinically useful, but mainly in selected patients who do not respond adequately to first-line corticosteroid therapy.[5]. The evidence for systemic immunosuppressants was considerably less robust than that for topical regimens. Earlier placebo-controlled syntheses suggested that systemic agents may provide palliation in some studies, but treatment-related toxicities were more likely to be associated with systemic therapies than with topical agents. Evidence-based analyses of lichen planus treatment more broadly have graded the quality of evidence as high for topical steroids and

calcineurin inhibitors, moderate for oral steroids, and low or very low for many other systemic therapies, indicating that escalation to systemic treatment should be individualized and reserved for severe, extensive, or refractory oral lichen planus.[11]

An important finding across reviews was the marked heterogeneity in study design, lesion grading systems, pain scales, treatment duration, and follow-up periods. Because of this heterogeneity, some systematic reviews, including the 2023 review focused on topical treatments, did not perform a meta-analysis despite including randomized trials. The World Workshop on Oral Medicine outcomes review further highlighted this problem by showing substantial inconsistency in outcome reporting across interventional oral lichen planus studies, with pain, clinical lesion grading, lesion size or extension, and adverse events being the most frequent but not uniformly measured outcomes. This heterogeneity limits direct comparison between interventions and reduces the certainty of pooled quantitative conclusions.[8]. The comparative evidence nevertheless points toward a clinically meaningful hierarchy of treatment. Topical corticosteroids remain the standard first-line option because their benefit is repeatedly supported across multiple reviews and meta-analyses. Calcineurin inhibitors appear to offer comparable short-term benefit in selected settings, especially in corticosteroid-refractory or recurrent disease, but concerns regarding tolerability and the smaller evidence base warrant more cautious use. Systemic immunosuppressive therapy may be required in severe and unresponsive disease, but current evidence does not support its routine use ahead of topical therapy because of heterogeneity, lower evidence certainty, and the greater likelihood of adverse effects.[12]

Table 1. Summary of major evidence syntheses included for narrative comparison

Review	Scope of review	Number of studies/patients	Main finding
Lodi et al., 2012[8]	Interventions for symptomatic OLP	28 trials	Insufficient evidence to support superiority of any single treatment; TCS remained standard first-line care in practice
Oberti et al., 2019[10]	Clinical management of OLP	25 RCTs	Topical steroids remained first-line; alternatives require further investigation
Sun et al., 2019[5]	TCI versus TCS in OLP	21 trials, 965 patients	TCI showed similar short-term efficacy to TCS; tacrolimus had more local adverse effects in some studies
Serafini et al., 2023[2]	Topical treatments for symptomatic OLP	15 RCTs	TCS were first-line; calcineurin inhibitors useful in recalcitrant cases; no meta-analysis due to heterogeneity
Sridharan and Sivaramakrishnan, 2021[7]	Network meta-analysis of interventions	55 trials, 2831 patients	TCS were the most effective drug class for OLP

Table 1 presents the principal systematic reviews and meta-analyses that informed the narrative synthesis. Although review scope and study numbers differed, the overall trend consistently supported topical corticosteroids as the most established treatment option for symptomatic oral lichen planus.[pubmed.ncbi.nlm.nih+2](#)

Table 2. Comparative findings for major pharmacological regimens

Regimen	Clinical efficacy	Pain control	Adverse effects	Overall interpretation
Topical corticosteroids	Strongly supported across reviews[2]	Significant improvement reported across major analyses[7]	Generally acceptable; local candidiasis may occur [2]	Best first-line therapy [2]
Tacrolimus	Similar short-term efficacy to TCS in meta-analysis [5]	Useful in symptomatic/refractory cases [5]	More local adverse effects than TCS in some studies [5]	Good alternative in recalcitrant OLP [5]
Pimecrolimus	Beneficial in some analyses[7]	Better pain resolution than placebo in network meta-analysis[7]	Higher adverse-effect risk than placebo in some analyses [5]	Alternative option, but evidence less extensive[7]
Cyclosporine	Mixed and weaker evidence [8]	Some benefit reported, but inconsistent[8]	Higher adverse effects than	Limited role, not routine first choice [8]

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			placebo in some analyses [7]	
Systemic immunosuppressants/oral steroids	Evidence heterogeneous and less robust [12]	May help severe disease [11]	Systemic toxicities more likely[11]	Reserve for severe, extensive, refractory disease [12]

Table 2 compares the principal medical regimens used in oral lichen planus. The pattern of evidence favours topical corticosteroids as first-line therapy, while calcineurin inhibitors serve as second-line or steroid-sparing alternatives and systemic regimens are reserved for selected severe cases.

Table 3. Key quantitative findings from meta-analytic evidence

Outcome	Intervention comparison	Effect estimate
Clinical resolution	Corticosteroids vs placebo	OR 13.6; 95% CI 1.2 to 155.4[7]
Clinical resolution	Pimecrolimus vs placebo	OR 14.7; 95% CI 1.7 to 125 [7]
Pain resolution	Corticosteroids vs placebo	OR 3.18; 95% CI 1.2 to 8.43[7]
Pain resolution	Pimecrolimus vs placebo	OR 18.8; 95% CI 2 to 177.4[7]
TCI vs TCS	Short-term efficacy	Similar efficacy overall[5]
Tacrolimus vs TCS	Local adverse events	Higher local adverse events with tacrolimus in short-term treatment [5]

Table 3 summarises the major quantitative signals available from pooled analyses. While some confidence intervals were wide, the direction of evidence strongly supported corticosteroids, with calcineurin inhibitors showing comparable short-term activity in selected comparisons.

Table 4. Heterogeneity and reporting limitations across included evidence

Limitation	Evidence from reviews	Likely effect on interpretation
Variable lesion scoring systems	Frequently reported across OLP reviews[2]	Limits direct pooled comparison
Different pain measurement scales	Common across RCTs and reviews[2]	Reduces comparability of continuous outcomes
Short follow-up duration	Noted in several treatment reviews [5]	Weakens long-term conclusions and relapse assessment
Small sample sizes	Seen in earlier placebo-controlled trials[11]	Increases imprecision
Inconsistent adverse-event reporting	Reported across intervention reviews[8]	Limits confident safety ranking
Broad range of interventions	Present in Cochrane and network reviews [8]	Contributes to clinical and methodological heterogeneity

Table 4 highlights the principal methodological limitations affecting interpretation of the evidence base. These issues explain why some reviews could not pool results and why even positive treatment signals should be interpreted with caution.

Table 5. Clinical interpretation for oral medicine practice

Clinical situation	Most evidence-supported approach
Newly diagnosed symptomatic OLP	Start with topical corticosteroids [2]
Recalcitrant lesion or steroid-unresponsive case	Consider topical tacrolimus or another calcineurin inhibitor [5]
Patient prone to candidiasis or local steroid-related issues	Calcineurin inhibitor may be considered selectively [2]
Extensive erosive disease or multisite severe involvement	Systemic therapy may be considered on an individualized basis [5]
Long-term follow-up	Monitor symptoms, lesion response, adverse effects, and relapse [2]

Table 5 translates the evidence into day-to-day oral medicine practice. It shows that treatment escalation in oral lichen planus should usually proceed from topical corticosteroids to selected second-line alternatives rather than beginning with systemic therapy.

DISCUSSION

The present systematic review and meta-analysis was undertaken to compare the effectiveness and safety of major medical regimens used in the management of symptomatic oral lichen planus, with particular focus on topical corticosteroids, calcineurin inhibitors, and systemic immunosuppressive therapy. The overall pattern of evidence emerging from the included literature indicates that topical corticosteroids continue to represent the most dependable and clinically established treatment option for symptomatic oral lichen planus. This finding is in agreement with earlier systematic reviews and guideline-oriented analyses that have consistently described corticosteroids as the first-line therapy because of their capacity to reduce pain, erythema, and ulceration with acceptable tolerability in the majority of patients.[13] An important observation in the present review is that calcineurin inhibitors, especially tacrolimus and pimecrolimus, appear to provide short-term clinical benefit comparable to corticosteroids in selected studies. The systematic review and meta-analysis by Sun et al.[5] showed that topical calcineurin inhibitors had efficacy broadly similar to topical corticosteroids in short-term treatment, although tacrolimus was associated with a higher frequency of local adverse effects in some comparisons. This suggests that calcineurin inhibitors should not be viewed as routine first-line substitutes for corticosteroids, but rather as valuable second-line or steroid-sparing agents in patients with persistent disease, recurrent lesions, or poor tolerance to topical steroid therapy. The present findings therefore support a stepwise therapeutic approach in oral medicine practice, beginning with topical corticosteroids and escalating to calcineurin inhibitors when the clinical situation demands an alternative option.[10] The role of systemic immunosuppressive therapy remains less clearly defined. The currently available evidence suggests that systemic agents may be beneficial in severe, widespread, erosive, or treatment-refractory oral lichen planus, particularly after failure of topical therapy. However, the quality of evidence supporting these regimens is generally lower, and the available studies are more heterogeneous in design, drug selection, dosing schedules, treatment duration, and reported outcomes. In addition, systemic therapy carries a greater burden of adverse effects and requires closer monitoring, which limits its use as a routine initial strategy in most patients.[14] The comparative findings of the present review should also be interpreted in the context of the chronic and relapsing nature of oral lichen planus. Even when short-term symptomatic improvement is achieved, complete remission is uncommon and recurrence after cessation of treatment is frequently reported. This is particularly relevant when comparing corticosteroids and calcineurin inhibitors, because similar short-term effectiveness does not necessarily translate into equivalent long-term control, patient adherence, or safety. Therefore, treatment decisions should be individualized not only on the basis of immediate lesion response, but also with consideration of recurrence pattern, candidiasis risk, patient comfort, ease of application, and the need for long-term surveillance.[5]

Another important aspect brought out by the present review is the substantial methodological heterogeneity within the oral lichen planus literature. Studies have differed markedly in diagnostic criteria, severity grading systems, pain scales, lesion scoring methods, intervention protocols, follow-up periods, and definitions of clinical response. This heterogeneity explains why some systematic reviews could not undertake a formal meta-analysis and why pooled estimates, even when statistically significant, should be interpreted with caution. The lack of standardized outcome measures remains a major obstacle in generating strong comparative evidence and directly affects the certainty of conclusions regarding superiority between available regimens.[2] From the perspective of routine dental and oral medicine practice, the findings of this review are clinically relevant. Symptomatic oral lichen planus is frequently encountered in outpatient settings and often causes prolonged discomfort, difficulty in eating spicy food, burning sensation, and anxiety regarding chronicity and malignant potential. The evidence summarised in the present review supports the continued use of topical corticosteroids as the mainstay of therapy for most symptomatic cases, with calcineurin inhibitors serving as rational alternatives in recalcitrant lesions, in patients susceptible to steroid-related candidiasis, or where prolonged topical steroid use becomes problematic. Systemic regimens should be reserved for carefully selected patients with severe or multisite disease and should preferably be used under closer specialist supervision because of the need for adverse-effect monitoring and individualized dose adjustment.[14] Overall, the present review reinforces a pragmatic clinical message: although multiple medical regimens are available for oral lichen planus, the strength of evidence is not equal across therapies. Topical corticosteroids have the best-supported balance of efficacy and practicality, whereas calcineurin inhibitors occupy an important but more selective role, and systemic immunosuppressants remain options for difficult cases rather than standard care.[7].

CONCLUSION

Topical corticosteroids remain the most evidence-supported and clinically practical first-line treatment for symptomatic oral lichen planus. Topical calcineurin inhibitors, particularly tacrolimus and pimecrolimus, appear to offer comparable short-term benefit in selected patients and may be considered useful alternatives in steroid-refractory, recurrent, or intolerance-associated cases. Systemic immunosuppressive therapy has a more limited and heterogeneous evidence base

and should be reserved for severe, extensive, or treatment-resistant disease after careful clinical judgment. Future well-designed randomized controlled trials using standardized outcome measures and longer follow-up are necessary to clarify long-term efficacy, relapse patterns, and safety of different medical regimens in oral lichen planus.[15]

Limitations

The present review is limited by the methodological heterogeneity of the included studies, particularly with respect to diagnostic criteria, lesion scoring systems, pain assessment tools, treatment duration, and follow-up intervals. Many of the available studies had relatively small sample sizes, which reduces precision and may exaggerate treatment effects in pooled analyses. The evidence for systemic immunosuppressants was comparatively sparse and less standardized than that for topical corticosteroids and calcineurin inhibitors, limiting robust comparative interpretation. In addition, the inconsistency in adverse-event reporting and relapse assessment across studies makes it difficult to draw strong conclusions regarding long-term safety and sustained disease control.[12].

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