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## Therapeutic Drug Monitoring of Hydroxychloroquine and Mycophenolic Acid in Lupus Nephritis: A Systematic Review of Exposure, Efficacy and Toxicity

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## ADMINISTRATIVE INFORMATION

**Support** - This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

**Review Stage at time of this submission** - Completed but not published.

**Conflicts of interest** - The authors declare no competing interests, financial or non-financial, related to this review. No author has received payment, consultancy fees, honoraria, travel support or research funding from any manufacturer of hydroxychloroquine, mycophenolate mofetil or mycophenolate sodium, or from any laboratory or assay provider offering drug concentration measurement..

**INPLASY registration number:** INPLASY2026100053

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 October 2026 and was last updated on 11 October 2026.

## INTRODUCTION

**Review question / Objective** This review asked whether measured drug exposure is associated with clinical outcomes in lupus nephritis, and whether acting on measured concentrations has been tested.

**Primary question (PICOS):** In adults or children with lupus nephritis, or with systemic lupus erythematosus in cohorts where renal involvement or kidney function entered the analysis (P), is measurement of hydroxychloroquine blood concentration, or of mycophenolic acid exposure expressed as area under the concentration-time curve, trough concentration or unbound fraction (I), compared with fixed weight-based or schedule-based dosing without concentration measurement,

or with patients in a different exposure stratum within the same cohort (C), associated with renal response and renal flare (O), across randomized trials, cohort, cross-sectional, case-control and pharmacokinetic studies and systematic reviews with meta-analysis (S)?

**Specific objectives:**

1. To determine whether measured exposure to hydroxychloroquine or mycophenolic acid is associated with renal flare, renal response, systemic disease activity, health care utilization and adverse drug reactions.
2. To identify the pharmacokinetic and clinical determinants of exposure to each drug.
3. To establish whether concentration-guided dosing has been tested against fixed dosing, and with what result.

4. To define, from the assembled evidence, candidate exposure ranges suitable for prospective evaluation, comprising both a lower bound associated with efficacy and an upper bound associated with toxicity.

**Rationale** Lupus nephritis develops in approximately 40% of patients with systemic lupus erythematosus and is treated for years with two drugs that the injured organ disposes of, at fixed weight-based doses never checked against what the patient absorbs. Hydroxychloroquine is recommended for every patient unless contraindicated; it is 21% to 47% renally excreted unchanged and has a half-life of 40 to 50 days, both figures reported jointly with chloroquine, and its retinal toxicity rises with dose and duration. Mycophenolic acid, the active metabolite of mycophenolate mofetil, is 97% to 99% albumin-bound when renal and hepatic function are normal, so the hypoalbuminemia of active nephritis raises the unbound fraction. Nonadherence affects 43% to 75% of patients and is clinically indistinguishable from altered drug handling.

Each renal flare destroys nephrons that are not replaced, and preventing the next flare is the central nephroprotective objective. No current guideline recommends routine concentration monitoring: KDIGO 2024 advises a mycophenolic acid level only when response is unsatisfactory, and refers to hydroxychloroquine levels only in its considerations for implementation.

Evidence on exposure and response for both drugs has accumulated in dispersed cohorts using different exposure metrics, outcome definitions, treatment phases, formulations and age groups, and had not been assembled and appraised in a single synthesis treating efficacy and toxicity as co-equal outcomes. This review was undertaken to assemble that evidence, to establish whether measured exposure predicts renal outcomes, to identify what determines exposure, and to determine whether concentration-guided dosing has been tested.

**Condition being studied** Lupus nephritis, the renal manifestation of systemic lupus erythematosus, defined by kidney biopsy using International Society of Nephrology/Renal Pathology Society or World Health Organization class, or by clinical criteria. Cohorts of systemic lupus erythematosus in which renal involvement or kidney function entered the analysis were also eligible.

Lupus nephritis develops in approximately 40% of patients with systemic lupus erythematosus, follows a relapsing course, and each flare causes irreversible nephron loss; two or more flares raise the odds of stage G3 to G5 chronic kidney disease more than sevenfold. Standard therapy combines hydroxychloroquine, recommended for essentially all patients unless contraindicated, with an immunosuppressive agent, most commonly mycophenolate mofetil or mycophenolate sodium, given across induction and maintenance phases over years. Both drugs are dosed by body weight or on a fixed schedule rather than by measured exposure, and both are handled by the kidney, the organ the disease injures.

No restriction was placed by country, sex, ancestry, age or treatment phase.

## METHODS

**Search strategy** Three electronic searches were run, retrieving 448 records in total.

Streams 1 and 2 (August 2026) were the prespecified free-text searches, covering PubMed/MEDLINE, Semantic Scholar, OpenAlex, arXiv and ClinicalTrials.gov, and retrieving 154 and 166 records respectively.

Stream 3 (8 September 2026, re-run unchanged 9 September 2026) was added by protocol amendment after screening had begun, because the prespecified free-text streams proved insensitive for hydroxychloroquine. It was a structured PubMed search combining Medical Subject Headings with title and abstract terms across concept blocks for population (lupus nephritis; systemic lupus erythematosus with renal involvement), exposure and monitoring (drug monitoring; blood concentration; area under the curve; trough; unbound fraction; limited sampling) and drugs (hydroxychloroquine; mycophenolic acid; mycophenolate mofetil; mycophenolate sodium), applied without date, language, age or publication-type limits. It retrieved 128 records and alone recovered 33 of the 55 included studies, including all three randomized trials.

After removal of 84 duplicates and 54 stream records without a retrievable abstract, 310 records were screened, 81 reports were assessed at full text and 33 were excluded with reasons. Forty-eight studies were included from the database searches and 7 from citation and registry follow-up, giving 55.

Supplementary methods: reference lists of all included reports were checked (backward citation searching), and trial and study registry records were followed.

Full search strings, database query translations and the record counts retrieved at each stage are reported in Supplementary Table S1 of the review's Online Resource.

**Participant or population** Adults or children with lupus nephritis defined by kidney biopsy (International Society of Nephrology/Renal Pathology Society or World Health Organization class) or by clinical criteria; or patients with systemic lupus erythematosus in cohorts in which renal involvement or kidney function entered the analysis. No restriction by country, sex, ancestry or treatment phase. Paediatric cohorts were eligible: 14 of the 55 included studies enrolled children. Forty-two included studies were defined by lupus nephritis and 13 were systemic lupus erythematosus cohorts with a renal analysis. Sample sizes ranged from 5 to 2010 participants across 17 countries.

**Intervention** Measurement of drug exposure: whole-blood or serum hydroxychloroquine concentration; or mycophenolic acid exposure expressed as area under the concentration-time curve over a dosing interval (AUC<sub>0-12</sub> or an abbreviated interval), trough or single-timepoint concentration, or unbound (free) fraction. Studies of concentration-guided (concentration-controlled) dose titration were eligible as the interventional form of the same exposure measurement.

**Comparator** Fixed weight-based or schedule-based dosing without concentration measurement; or, within a cohort, patients whose measured exposure fell in a different stratum (subtherapeutic, therapeutic or supratherapeutic).

**Study designs to be included** Randomized controlled trials; prospective and retrospective cohort studies; cross-sectional and case-control studies; pharmacokinetic studies reporting a clinical, determinant or feasibility outcome; and systematic reviews with meta-analysis.

**Eligibility criteria** Included: studies meeting the PICOS above, in which a measured hydroxychloroquine concentration or mycophenolic acid exposure was related to an eligible outcome. Null associations were eligible and were sought explicitly.

Excluded: trial registration records and protocols without published results; conference abstracts without a corresponding full report; editorials, letters and narrative reviews without primary data; mixed non-lupus populations without a lupus-specific analysis; extrarenal systemic lupus erythematosus in which neither renal involvement nor kidney function entered the analysis; and studies that measured a concentration but analysed no association with an eligible outcome.

No restriction was applied by language, publication date, country or age.

**Information sources** Electronic databases and registries: PubMed/MEDLINE, Semantic Scholar, OpenAlex, arXiv and ClinicalTrials.gov. PubMed/MEDLINE was searched both by free text and, by protocol amendment, with a structured controlled-vocabulary strategy.

Other sources: reference lists of all included reports (backward citation searching), and trial and study registry records.

Embase, Web of Science and the Cochrane Library were not searched; this is declared as a limitation of the review.

Investigators were not contacted for unpublished or clarifying data. Values were transcribed as printed in each source, and internal inconsistencies were recorded rather than harmonized.

**Main outcome(s)** Primary outcomes were renal response (complete or partial, as defined by each source) and renal flare or relapse.

Effect measures were taken in each source's own metric and were not converted: odds ratios and hazard ratios with 95% confidence intervals; weighted mean differences in exposure between responders and non-responders; proportions attaining a defined exposure threshold; and exposure thresholds derived by receiver operating characteristic analysis. Timing followed each source, spanning induction (commonly 12 to 24 weeks) and maintenance (commonly 12 months or longer) and, for flare, the full reported duration of follow-up.

**Additional outcome(s)** Secondary outcomes were systemic disease activity (SLEDAI, SLEDAI-2K or an equivalent index); health care utilization; adverse drug reactions, including hydroxychloroquine retinopathy, cardiomyopathy and skin or muscle toxicity, and mycophenolic acid

haematological, gastrointestinal and infectious events; and the pharmacokinetic determinants of exposure, including kidney function, serum albumin, body weight, co-medication and genotype, together with the performance of limited sampling strategies and other substitutes for full area-under-the-curve assessment. Null associations were eligible for every secondary outcome.

**Data management** Records from all three searches were assembled and deduplicated, then screened against the eligibility criteria above. Two reviewers screened titles, abstracts and full texts independently and extracted data independently, resolving disagreements by consensus.

Extracted fields comprised study identifiers, country, design, sample size, population definition and age group, drug and exposure metric, analytical method where reported, outcomes assessed, effect estimates with measures of precision as printed, and the source of extraction for each study (full text or abstract only).

Values were transcribed exactly as printed. Where a source reported internally inconsistent values, both were recorded and the inconsistency flagged rather than resolved; three included sources contain such inconsistencies. Thirty studies were extracted from abstracts alone, recorded per study, so that their risk-of-bias ratings are identified as provisional.

The complete extraction table, the screening log, and the list of reports excluded at full text with reasons are reported as supplementary tables in the review's Online Resource.

### Quality assessment / Risk of bias analysis

Observational studies were appraised with the Newcastle-Ottawa Scale, randomized trials with the Cochrane Risk of Bias 2 (RoB 2) tool, and the one included systematic review with meta-analysis with AMSTAR 2. Each study was assessed independently by two reviewers, with disagreements resolved by consensus, and domain-level judgements with written justifications are reported in a supplementary table of the review's Online Resource.

Of the 51 observational studies, 15 were rated good, 26 fair and 10 poor. Comparability was the weakest domain, because many studies compared exposure strata without adjusting for disease activity, glucocorticoid dose or adherence, and several derived and tested a threshold in the same sample.

Certainty of evidence for each outcome was rated with GRADE.

Reporting bias was assessed qualitatively. Because meta-analysis was not performed, funnel plots and statistical tests for small-study effects were inapplicable; instead the completeness of reporting of null alongside positive findings was examined across studies, and sources without a traceable publication were identified and counted.

**Strategy of data synthesis** Findings were synthesized narratively, structured by drug (hydroxychloroquine, then mycophenolic acid) and within each drug by outcome domain: exposure and flare; exposure and renal response; toxicity and the upper bound of exposure; determinants of exposure; adherence; feasibility and limited sampling; and concentration-guided dosing. Estimates were reported in each source's own metric, with the direction and magnitude of effect described together with the precision and risk of bias of the contributing study.

Meta-analysis was not performed. Exposure metrics (whole-blood concentration, area under the curve over a full or abbreviated interval, trough, unbound fraction), outcome definitions, treatment phases, drug formulations and age groups differed too greatly between studies for a pooled estimate to be interpretable. This decision and its consequences are stated explicitly in the review: funnel plots and statistical tests for small-study effects were therefore inapplicable, and reporting bias was assessed qualitatively.

Where several studies reported thresholds for the same drug and outcome, the range of thresholds was reported rather than a pooled value, with the treatment phase and population of each noted.

Reporting follows PRISMA 2020; the completed checklist is provided in the review's Online Resource.

**Subgroup analysis** Findings were examined separately by drug (hydroxychloroquine and mycophenolic acid), which is the primary organizing division of the synthesis.

Within each drug, results were examined by age group (adults versus children; 14 studies enrolled children), by treatment phase (induction versus maintenance, since reported mycophenolic acid thresholds are lower in maintenance), by population definition (cohorts defined by lupus nephritis, 42 studies, versus systemic lupus erythematosus cohorts with a renal analysis, 13

studies), and by exposure stratum (subtherapeutic, therapeutic and suprathreshold), the last being central to identifying both a lower bound associated with efficacy and an upper bound associated with toxicity.

These comparisons were narrative and hypothesis-generating. No formal statistical test for subgroup interaction was performed, because no pooling was undertaken.

**Sensitivity analysis** Formal quantitative sensitivity analysis was not performed, because no meta-analysis was undertaken and there was therefore no pooled estimate to vary. This is declared as a limitation.

Robustness was examined qualitatively instead. Studies were distinguished by the source of extraction, so that conclusions resting partly on the 30 studies extracted from abstracts alone, whose risk-of-bias ratings are provisional, could be identified. Studies rated poor on the Newcastle-Ottawa Scale were identified, as were studies in which an exposure threshold was derived and tested in the same sample, and those comparing exposure strata without adjustment for disease activity, glucocorticoid dose or adherence. Overlapping cohorts contributed by the same research programme were identified so that their findings were not read as independent replication. Where a source contained internally inconsistent values, both were reported as printed.

The direction of each conclusion was then checked against whether it survived restriction to full-text-extracted studies and to studies not rated poor.

**Language restriction** No language restriction was applied.

**Country(ies) involved** United States of America.

### Other relevant information

#### RETROSPECTIVE REGISTRATION – TRANSPARENCY STATEMENT

This protocol is registered retrospectively. The review is complete and the manuscript has been prepared for journal submission; no results have been published. The review stage is declared as 'Completed but not published' in items 4 and 33 of this record, and the disclosure below follows the transparency-oriented approach for retrospective registration referenced on this form.

Timing. Searches were run in August 2026 (two prespecified free-text streams) and on 8 September 2026, re-run unchanged on 9 September 2026 (structured PubMed search). Screening, data extraction, risk-of-bias assessment, GRADE rating and narrative synthesis were all completed before this registration was submitted. Registration therefore occurred after data extraction and after the results were known to the review team.

No prospective registration of this review exists. A protocol was written before screening began, and the full search strategies, the screening log, the per-study extraction table with the source of extraction for each study, the domain-level risk-of-bias assessments and the completed PRISMA 2020 checklist are reproduced in the review's Online Resource. The content of this record reflects that protocol and the review as conducted; no method is described here that was not applied.

Relationship to a separate registration. The review team holds a separate PROSPERO registration, CRD420261426279, for a different systematic review ('Systematic Review of Lupus Nephritis Recurrence and Therapeutics in the U.S. Veteran Population: Evidence-Based Clinical Recommendations'). That record covers a different population, exposure and outcome set and does not cover the present review. It is named here only so that the two are not mistaken for the same work.

Protocol amendment. One amendment followed the start of screening: because the two prespecified free-text streams proved insensitive for hydroxychloroquine, a structured PubMed search using controlled vocabulary was added. That search alone recovered 33 of the 55 included studies, including all three randomized trials. The amendment is reported in the review's Method section and in its Online Resource.

Deviations and limitations declared in the review. Embase, Web of Science and the Cochrane Library were not searched. Thirty studies were extracted from abstracts alone, so their risk-of-bias ratings are provisional. Investigators were not contacted. Meta-analysis was not undertaken, so funnel plots and quantitative sensitivity analyses were inapplicable. Three included sources contain internally inconsistent values, reproduced as printed rather than harmonized.

Use of artificial intelligence. A large language model was used for language editing only, at the authors' direction. No artificial intelligence tool

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contributed to screening, data extraction, appraisal or interpretation, and none meets authorship criteria.

**Keywords** Therapeutic drug monitoring; Lupus nephritis; Hydroxychloroquine; Mycophenolic acid; Medication adherence; Systematic review.

**Dissemination plans** The completed review has been prepared as a manuscript for submission to a peer-reviewed clinical pharmacy journal. Findings will additionally be presented at nephrology and rheumatology scientific meetings. The full search strategies, screening log, per-study extraction table, domain-level risk-of-bias assessments and completed PRISMA 2020 checklist will accompany the published article as an online supplement.

#### **Contributions of each author**

Author 1 - Maria F. Carpintero - Contributed equally with all other authors: designed the review, screened records, extracted data, assessed risk of bias, interpreted the findings, and drafted and critically revised the manuscript. Approved the submitted version.

Author 2 - Maribel Garcia - Contributed equally with all other authors: designed the review, screened records, extracted data, assessed risk of bias, interpreted the findings, and drafted and critically revised the manuscript. Approved the submitted version.

Author 3 - Marco A. Ladino - Contributed equally with all other authors: designed the review, screened records, extracted data, assessed risk of bias, interpreted the findings, and drafted and critically revised the manuscript. Corresponding author and guarantor.

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