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# Pharmacomicrobiomics of classical immunosuppressant drugs: a systematic review

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**ADMINISTRATIVE INFORMATION**

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

**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 August 2023 and was last updated on 31 August 2023.

## INTRODUCTION

**Review question / Objective** 1 Does the intestinal microbiota affect classical immunosuppressive drug pharmacology (pharmacokinetics, efficacy or tolerability)? 2 Do classical immunosuppressive drugs modify the composition of intestinal microbiota?

**Rationale** The clinical response to classical immunosuppressant drugs (glucocorticoids , cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolic acid and its prodrug mycophenolate mofetil) is highly variable among individuals. A new factor, only recently identified, that could be responsible for the interindividual variability in drug response is the patient's microbiota, i.e. the whole population of microorganisms living in a commensal status in humans (or animals). Patient's microbiota can both metabolize drugs to inactive or toxic compounds or accumulate them, preventing their systemic absorption. Conversely, some drugs can alter the composition of the intestinal microbiota. Evidence has been accumulated that these mechanisms may also affect the response to classical immunosuppressive drugs.

**Condition being studied** Conditions requiring the treatment with classical immunosuppressive drugs: organ tranplatation (kidney, heart, hemopoietic stem cells) or autoimmune diseases. Experimental models in animals involving the administration of classical immunosuppressants either to healthy animals or to animals with experimental autoimmune disorders or receiving organ transplatation.

## METHODS

**Search strategy** Electronic databases: PubMed and Scopus; Search terms: cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolic acid, mycophenolate mofetil, prednisone, methylprednisone, pharmacomicrobiomics,

gastrointestinal microbiome, drug metabolism, microbes, bioaccumulation.

**Participant or population** Human patients treated with classical immunosuppressive drugs because recipients of organ transplantation or because affected with autoimmune diseases.

**Intervention** Treatment with classical immunosuppressant drugs (glucocorticoids, cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolic acid and its prodrug mycophenolate mofetil) given orally either alone or in various combinations.

**Comparator** Either a control group (vehicle treated animals in preclinical experimentations or age-matched healthy controls in clinical studies) or the same patients (or animals) before the treatment with classical immunosuppressive drugs.

**Study designs to be included** Both randomized clinical trials and observational studies were included in the review.

**Eligibility criteria** Original studies performed in animal, in humans or in vitro; Studies evaluating metagenomic characterization of faecal or ileal microbiota and/or pharmacokinetics analysis of the administered immunosuppressive drugs, and/or analysis of their efficacy and/or toxicity; Studies in English; No publication time time limit; narrative reviews, systematic reviews, metanalyses, guidelines, consensus papers, case reports, editorials and commentaries were all excluded.

**Information sources** PubMed and Scopus.

**Main outcome(s)** Changes in the efficacy/tolerability of cIMDs and/or in their pharmacokinetic parameters. Changes in the composition of the intestinal microbiota.

**Additional outcome(s)** None.

**Data management** Records were stored and classified by using the endnote online library.

**Quality assessment / Risk of bias analysis** For animal studies the risk of bias of animal studies was evaluated using the SYRCLE's risk of bias tool, which is and adaption to animal studies of the RoB2 tool (Hooijmans et al., 2014). The Grade Criteria for observational and for randomized clinical trials, as appropriate, were used to evaluate the risk of bias human studies.

**Strategy of data synthesis** The main findings of the selected studies were summarized in a narrative form in the text of the article and in two tables, the first (Table 1) concerning the papers on the effect of the intestinal microbiota on cIMDs, and the second (Table 2) concerning the papers on effect of cIMDs on intestinal microbiota. The following variables were extracted and included in Table 1: 1-lead author and year of publication, 2- the experimental model used, 3- the drugs tested, 4- the presence/absence of changes in the pharmacokinetic properties of the tested drugs, 5- a detailed description of the effect of intestinal microbiota on cIMD pharmacokinetics. The variables extracted to prepare Table 2 were: 1-lead author and year of publication, 2- the species (human, mice, rats) object of the experimentation, 3- the condition/disease either spontaneous or experimental that was treated with cIMDs, 4- the specific cIMDs that were used with doses, administration modalities and duration of treatment, 5-the presence or absence of intestinal microbiota modifications upon treatment with cIMDs, 6- a detailed description of the changes occurring in intestinal microbiota including, when available, data on alpha- and beta-diversity and taxonomic information at the level of phylum, class, order, family, genus, and species.

**Subgroup analysis** Data concerning the effect of drugs on microbiota were stratified according to the specific immunosuppressive drug used and subgroup analysis was performed.

**Sensitivity analysis** Not performed.

**Language restriction** English language.

**Country(ies) involved** Italy.

**Other relevant information** None.

**Keywords** corticosteroids; cyclosporine; everolimus; microbiota; methylprednisolone; mycophenolic acid; prednisolone; prednisone; sirolimus; tacrolimus.

**Dissemination plans** Publication in a well reputed scientific journal.

**Contributions of each author**

Author 1 - Annalaura Manes - performed literature search and collaborated in paper screening.
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