# PRACTITIONER TECH SHEET | Mycophenolic Acid



Mycophenolic acid (MPA) is not a mycotoxin. It's a secondary mold metabolite that's excreted during the spore's growth phase. Wherever there's living, metabolizing mold, there's MPA, but not necessarily mycotoxins.

MPA affects multiple body organs, including the gastrointestinal, cardiovascular, respiratory, endocrine, genitourinary, neuromuscular, hematologic, and central nervous systems, as well as skin, liver, and kidneys.

MPA is a potent immunosuppressant that leads to susceptibility to bacterial, viral, and fungal infections.

The pharmaceutical derivative, Mycophenolate, mitigates organ rejection in transplant patients by preventing the body's immune system from rejecting a foreign substance — the new organ. This comes at a cost, including increased risk of certain infections and cancers, and impeding immune responses to certain vaccines.

MPA itself was trialed as a topical treatment for psoriasis, but abandoned due to side-effects and carcinogenicity. Instead, a derivative was developed and is in use today for certain dermatological issues. Due to its toxicity, therapeutic drug monitoring is required, even when using the safer derivatives. Monitoring free MPA in the serum poses additional challenges, as MPA strongly binds albumin, so disproportionate increases in free MPA occur in patients with uremia, hypoalbuminemia, and hepatic dysfunction.

Its function as a transplant rejection drug has to do with its inhibition of the enzyme Inosine Monophosphate Dehydrogenases (IMPDH). This enzyme impacts purine synthesis in both B and T lymphocytes. Lymphocytes are highly dependent on this de novo pathway of purine synthesis and cannot efficiently use the salvage pathway, so inhibition of IMPDH arrests cell proliferation as a result of DNA and RNA biosynthesis blocking. The net effect is immune impairment, and possible adverse reactions to treatments that also inhibit this enzyme.

Additional immunosuppressive effects are reduced secretory IgA, leading to mucositis and increased risk of mucosal colonization with non-commensal species.

MPA induces intestinal barrier dysfunction mediated by mitochondrial function impairment, oxidative stress, and reducing the expression of tight junction proteins.

MPA also has genitourinary effects, such as urinary frequency and dysuria. In pregnancy, MPA increases the risk of miscarriage and birth defects.

### MOLD SOURCES
Aspergillus spp, Penicillium spp, Eurotium repens

### COLOR
Typically light green, but can change color depending on substrate

### FAVORITE BUILDING MATERIAL
Wallpaper, wood, drywall, carpet, linoleum, insulation paper, ceiling tiles, crawl spaces, attics, heating ducts

### SIGNS
Leukopenia
Thrombocytopenia
Electrolyte imbalance (*sodium)

### SYMPTOMS
Anemia
Frequent, reactivated, chronic infections
Delayed or non-healing wounds
Aphthous ulcers
Abdominal pain, nausea, vomiting, diarrhea
Loss of appetite
Food sensitivities
Weight changes
Palpitations
Short of breath
Hypertension
Urinary frequency
Dysuria
Peripheral neuropathy
Peripheral edema
Breast implant illness
Miscarriage, birth defects
Photosensitivity
Cancer: skin, leukemia

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Based on a small study which detected MPA in initial and follow-up urine samples of office workers exposed to a water-damaged building at rates higher than controls, inhalational absorption, hematologic distribution, and urinary excretion is suggested.

If ingested, MPA is rapidly absorbed and undergoes enterohepatic recirculation. Microbial β-glucuronidases participate in the enterohepatic recirculation of MPA, and interestingly it is cleared more rapidly after antibiotic administration.

MPA is metabolized by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the liver, gut, and kidneys to its inactive metabolite, phenyl mycophenolic acid glucuronide (MPAG). MPA and MPAG are extensively bound to serum albumin. Due to their aqueous solubility, all metabolites are excreted in the kidneys.

It's common in the initial phase of detoxification for excretion to peak and fall rapidly once the patient is removed from the exposure. MPA will persist if the patient is still being exposed or is significantly colonized with invasive fungal species secreting endogenous MPA, as in the case of breast implant illness due to fungi.

## HEALTH IMPACTS

Myelosuppression. Leading to blood dyscrasias and immune suppression. MPA increases the likelihood of tissue-invasive CMV disease. In vitro, MPA directly upregulated Hepatitis B viral (HBV) replication and expression, necessitating antiviral therapy when the drug form of MPA must be used in patients with a risk of HBV reactivation.

Gastrointestinal. MPA exposure is associated with intestinal dysbiosis characterized by a decrease in density and diversity of the microbiome in the main bacterial phyla (Firmicutes and Bacteroidetes). These bacterial phyla are known for their metabolic role in maintaining the homeostasis of the digestive tract, particularly through the production of short-chain fatty acids (SCFA) that could contribute to the pathophysiology of mycophenolate-induced enteropathy.

Neuropathy. There are case reports of dose-dependent acquired sensory-motor axonal polyneuropathy with MPA's drug counterpart. The effects appear to be reversible.

Cardiovascular. MPA can reduce metabolic activity and cellular respiration in cardiomyocytes, while increasing mitochondrial reactive oxygen species production. While the exact mechanism is not completely clear, studies suggest that the drug form of mycophenolic acid may affect blood pressure regulation through its impact on the renin-angiotensin system.

## TREATMENT OPTIONS

*Note: the doses listed are intended for when each item is used as a standalone therapy. When multiple items are combined, they often work synergistically, meaning lower doses can typically achieve similar effectiveness due to their complementary effects.

Recommendations below are generally intended to be short in duration, and withdrawn once MPA is cleared.

Coffee enema. 1-2 weekly for 4-6 weeks. (MPA clearance increases without gut microbial β-glucuronidation.)

Therapeutic Diet:

Cruciferous vegetables (broccoli, cauliflower, cabbage, kale, Brussels sprouts, radish, mustard, and watercress).
Citrus.
Green tea.

Sensitivities:

Negative reaction to milk thistle or Chinese skullcap (potential UGT inhibitors) may indicate a high MPA toxic load.

Probiotics. Bifidobacterium longum, Lactobacillus acidophilus, and Enterococcus faecalis
Mouse study: ameliorated MPA-induced colitis by enhancing intestinal barrier function and improving intestinal microbiota dysbiosis.

Binder. Aloe polysaccharides.
Protection of intestinal mucosa and regulation of microbiota and immune system. Promotes mucosal healing and reduces inflammation in intestinal mucositis, immune modulator, reduced secondary infections.
Cholestyramine has been used for acute oral toxicity.

Schisandra chinensis. 600mg once to twice daily.
Protects intestinal epithelial cells from MPA-induced intestinal toxicity and barrier breakdown.

NAC. 500mg daily.
The antioxidant NAC effectively restored ZO-1 and occludin expressions, reduced apoptosis in intestinal epithelial cells after MPA increased intracellular and mitochondrial ROS production to promote oxidative stress.

Grape seed extract. 100mg up to three times daily.
Rich in phytochemicals that are substrates for UGT enzymes.

Green tea EGCG. 300mg twice daily.
A study in rats showed that consumption of green tea extract for four weeks enhanced hepatic glucuronidation.

Hawthorn. (Crataegus oxycantha). ½ tsp solid extract up to three times daily.
Support glucuronidation and cardioprotective.

Resveratrol. Minimum therapeutic dose: 1000mg daily, best divided.
Support glucuronidation. Alleviates intestinal injury and enhances the mitochondrial function in animal models of induced oxidative stress.

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