

Are there symptoms for infection?⁽¹⁾

Fever (greater than 38°C), leukopenia, stool culture and/or *Clostridium difficile* toxin

YES

Infectious diarrhea

Treat accordingly

NO

Non-Infectious diarrhea

Stop diarrhea-causing drugs (other than immunosuppressants) and consider lifestyle and diet modification⁽²⁾

Mild Diarrhea: less than 4 stools/day, no weight loss, less than 10 days duration

Moderate-Severe Diarrhea: Continuous more than 10 days and weight loss

Give MMF with food and observe

If no improvement, split dose of MMF (e.g. from 1 gm bid to 500 mg qid)

If no improvement, reduce MMF dose (e.g. 1000 mg per day or 500 mg twice daily)⁽¹¹⁾

If no improvement, see **Moderate-Severe**

If improved, resume the dose of MMF to pre-reduction levels over a few weeks⁽¹⁰⁾

If patient can't tolerate at least 50 % of recommended MMF-EC-MPS dose, **switch to Azathioprine to avoid inadequate immunosuppression⁽⁵⁾** as it was reported AZA has less incidence of diarrhea than MMF especially in liver transplant patients^(3,4)

If patient tolerates, reduce the dose of MMF (e.g. 1000 mg per day or 500 mg twice daily)⁽¹¹⁾

If improved, Resume the dose of MMF to pre-reduction levels over a few weeks⁽¹⁰⁾

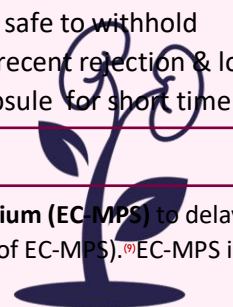
If no improvement, change two times daily dosing to three or four times daily while maintaining the same total daily dose.⁽⁴⁾
N.B; No data confirms the effectiveness of MMF therapy remains after splitting the daily so to three times daily.⁽¹⁰⁾

If no improvement and it is unsafe to withhold immunosuppression shortly (recent rejection or high rejection risk)

If no improvement and it is safe to withhold immunosuppression shortly (no recent rejection & low rejection risk) → Stop MMF capsule for short time .

If no improvement, switch to Azathioprine^(3,4)

If symptoms improve, begin **Enteric-coated mycophenolate sodium (EC-MPS)** to delay release of mycophenolate⁽⁹⁾ 1 g of MMF is equivalent to 720 mg of EC-MPS.⁽⁹⁾ EC-MPS is an effective and safe as MMF.⁽⁶⁾
N.B. Some studies found **a similar frequency of GI side effects with MMF and EC-MPS⁽⁵⁾**



General management of diarrhea

- First step to treat acute **diarrhea is rehydration, preferably oral rehydration** by Oral rehydration solution (ORS) 2-4 L/day.
- **IV rehydration** in case of severe diarrhea or if oral rehydration is not available (lactated ringer or normal saline 20 mL/kg if IV rehydration)
- Solid organ transplant recipients with diarrhea and mild to moderate dehydration should be **given reduced osmolarity rehydration fluids.** ⁽⁸⁾

Notes

- Recent publications suggested that patients exposed to Cyclosporine and MMF might be less susceptible to diarrhea than patients exposed to tacrolimus and MMF, through the differential effects of Cyclosporine and tacrolimus on P-glycoprotein activity and enterohepatic recirculation. ⁽¹⁾
- MMF may be administered with or without food (one hour before or 2 hours after a meal) as effects of food on bioavailability are minor on an empty stomach . However, in stable renal transplant patients, it may be administered with food. ⁽¹²⁾

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