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Editorial Review

Gastrointestinal side effects of mycophenolic acid in renal transplant patients: a reappraisal

Neal M. Davies[1], Josep Grinyó[2], Robert Heading[3], Bart Maes[4], Herwig-Ulf Meier-Kriesche[5] and Michael Oellerich[6]

[1]Washington State University, Pullman, WA, USA, [2]University of Barcelona, Barcelona, Spain, [3]Royal Infirmary, Glasgow, Scotland, UK, [4]Heilig Hartziekenhuis Roeselare-Menen, Belgium, [5]University of Florida, Gainesville, FL, USA and [6]George-August University, Goettingen, Germany

Abstract

Patient and graft survival following renal transplantation have improved markedly over the past decade, meaning that physician attention has turned more towards minimizing short- and long-term toxicities associated with immunosuppressive regimens. Gastrointestinal (GI) adverse events are common following renal transplantation and all immunosuppressive regimens have been associated with such events. Mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS) are potential components of immunosuppression regimens, and are associated with the most successful outcomes in kidney transplantation. The effects of MMF and EC-MPS are likely mediated via the active metabolite mycophenolic acid (MPA). The GI events caused by both MMF and EC-MPS may, in part, be related to MPA, independent of the formulation or route of administration. MPA may produce GI events either through direct action or through the action of it metabolites. However, many other factors may cause GI events observed following renal transplantation. These include the surgery itself and concurrent diseases such as diabetes, and bacterial, viral, fungal and parasitical infections. Additionally, numerous concomitant non-immunosuppressive agents, including antibiotics hypoglycaemic and proton-pump inhibitors, can be associated with GI events. In a recent trial in renal transplant patients with severe diarrhoea, approximately 50% of patients achieved resolution of diarrhoea through methods other than altering their immunosuppressive regimens. Indeed altering of the immunosuppressive regimen may lead to the risk of acute rejection. Thus, in order to reduce the risk of rejection and subsequent damage to the graft, it is important to consider other causes of GI events in renal transplant patients before altering immunosuppressive regimens

Keywords: adverse events; gastrointestinal; immunosuppression; mycophenolic acid; renal transplant; treatment

Introduction

Over the past decade, significant progress has been made in improving graft and patient survival within renal transplantation, such that as of 2002 1- and 5-year graft survival rates were 94% and 66%, respectively, and patient survival rates were 97% and 90% [1]. In the long term (10 years post-transplantation), graft survival rates are 36% and 55%, while patient survival rates are 58% and 77% for recipients of deceased and living donor kidneys, respectively [1]. This progress is in part thought to be due to combinations of anti-rejection agents with different mechanisms of action, allowing for individualized immunosuppressive regimens [2]. Such drugs include anti-interleukin-2 receptor antibodies, anti-lymphocyte antibodies, mycophenolate mofetil (MMF), everolimus, sirolimus, tacrolimus and cyclosporine [3–7]. Following the achievement of these excellent survival rates, physician attention has turned to minimizing the short- and long-term toxicities associated with these immunosuppressive drugs. Such adverse events can range from the mild (nausea, discomfort, appetite loss) through to the severe (severe diarrhoea, nephrotoxicity, hyperlipidaemia, diabetes), considerably increasing the morbidity of transplant recipients, decreasing patients' quality of life and increasing healthcare costs [8–10]. Furthermore, comorbidities linked to immunosuppressant regimens are a major cause of dose reductions or treatment cessations, which can have a detrimental effect on efficacy and survival [11,12]. While changes to immunosuppressant

Correspondence and offprint requests to: Dr Neal M. Davies, Department of Pharmaceutical Sciences, Washington State University, Pullman, WA 99164-6534, USA.
Email: ndavies@wsu.edu

regimens occur in the majority of patients, the proportion of patients changing over time is dependent upon the regimen employed [13].

Gastrointestinal (GI) adverse events are common in transplantation, occurring in up to 20% of renal transplant recipients [14,15]. Furthermore, such adverse events can extend along the entire GI tract, and can vary in severity from those which are mild and manageable, to those which are more severe [15]. It has recently been proposed that mycophenolic acid (MPA) is linked to GI disorders leading to the need for dose reduction and, thus, exposing the patient to the risk of acute rejection [11,12]. However, MPA-based (MMF or enteric-coated mycophenolate sodium [EC-MPS]) regimens are among the most commonly used, and are associated with the most successful outcomes in kidney transplantation [16,17], underscoring the need to better understand the aetiology of GI events, and the need to systematically evaluate GI events, so that unnecessary reduction of therapeutically effective agents can be prevented.

This review was initiated to assess current information on GI disorders in renal transplant recipients, to evaluate the role of MPA-containing immunosuppressive regimens in such disorders, and to provide clinical evidence to support an approach aimed at reducing such disorders without unduly decreasing immunosuppressive therapy.

Assessment of GI problems

There is an inherent difficulty in assessing GI disorders in transplant patients. Not only can GI disorders arise through a number of different mechanisms (surgery, concomitant therapies/diseases, immunosuppressant therapy), but the symptoms that patients present with can overlap between disorders. In addition, there is a distinct lack of defined criteria to evaluate or describe GI disorders, especially in the transplant population [18,19]. As an example, there is no clear definition of diarrhoea, or a standardized approach to describe its severity [18,19]. Recently, efforts have been made to develop questionnaires to evaluate GI disorders in transplant recipients [20,21]. However, these evaluations depend on subjective evaluation by clinician and patient. A recent study found that the extent of symptom reporting in ulcerative colitis patients depended on a patient's subjective assessment [22]. In spite of these limitations, questionnaires may be a useful way to assess fluctuating and variable symptoms in individual patients. They can also give a good indication of an individual patient's subjective perception of the severity of their symptoms and the relative impact of the symptoms on their overall quality of life.

The lack of a validated, reproducible and uniform approach to the clinical evaluation of GI symptoms makes it difficult to compare GI effects of various regimens and has hampered attempts to evaluate the contribution of individual immunosuppressants to adverse GI events. In addition, making comparisons and contrasts between various studies is difficult because of the lack of standardized reporting.

Possible causes of GI problems

The aetiology of GI disorders following transplantation is not well understood. Each disorder is likely to involve a complex interplay of paracrine, immune and neuroendocrine factors [23]. Furthermore, as well as GI disorders that would be observed in the general population, transplant patients can suffer from GI events initiated or influenced by a number of factors including surgery, concurrent diseases (e.g. diabetes, infections) and immunosuppressive therapies [14,19,24–26].

Transplant procedure

It is thought that the transplant procedure itself can cause GI disorders. A retrospective review of 297 cadaveric kidney transplants examined the incidence, diagnosis and therapy of surgical complications following transplantation. GI disorders was one of the largest complications observed following kidney transplantation, representing 16% of post-operative complications, leading to increased morbidity and mortality [27].

Concurrent diseases

A large proportion of renal transplant recipients have concurrent diseases that can contribute to the GI disorders diagnosed in this patient population. Diabetes alone has been associated with an increased prevalence of GI disorders, with 75% of patients visiting diabetes clinics reporting significant GI symptoms [28]. The incidence and severity of these symptoms appear to be linked to autonomic neuropathy and poor glycaemic control [29]. Infections are an important cause of GI disorders in transplant patients [14,30]. The time to infection post-transplantation can be generally divided into 3 periods: early (post-surgery to <1 month post-transplantation); middle (1–≤6 months post-transplantation); late (>6 months post-transplantation). The aetiologies of infection are different between the periods with donor/recipient infections being more common during the early period, opportunistic infections during the middle period, and community-based infections during the late period [30]. The infectious agents commonly associated with GI complications in renal transplant patients can be seen in Table 1 [14,30].

Bacterial infections. Bacterial overgrowth of the small intestine has been documented in a substantial portion of patients with persistent diarrhoea following transplantation [31], and can be encountered early post-

Table 1. Infectious complications of the gastrointestinal tract of renal transplant recipients

Bacteria
  Clostridium difficile
  Campylobacter jejuni
  Helicobacter pylori
  Salmonella species
  Listeria monocytogenes
  Other enteric bacteria

Viruses
  Cytomegalovirus
  Other herpes virus infections

Fungi
  Candida
  Cryptococcus
  Aspergillus

Parasites
  Strongyloides stercoralis
  Cryptosporidium parvum

transplant [32]. The two main bacterial infections encountered among renal transplant recipients (6–10% of transplant population) are *Clostridium difficile* and *Campylobacter jejuni*. Both of these infections generally present, at least initially, as diarrhoea and abdominal pain. However, it should be noted that *C. difficile* can also present as intestinal obstruction, abscesses or toxic megacolon [14,33,34]. Other bacteria that have been associated with GI symptomology in transplant patients are *Salmonella* species, *Listeria monocytogenes* and *Helicobacter pylori* [15,30].

Cytomegalovirus. All transplant patients are at risk of developing CMV, but CMV-seronegative patients who receive an organ from a seropositive donor are at the highest risk [35]. CMV is causative in 10–15% of transplant patients suffering GI disease [36,37]. CMV disease of the GI tract should be strongly suspected in a patient with GI disturbances, in association with fever, and evidence of CMV infection [38]. CMV can affect all segments of the GI tract and the major presenting clinical symptoms are abdominal pain, diarrhoea, fever, anorexia, and weight loss [39,40]. However, GI CMV infection can also occur while patients are asymptomatic [41,42]. A definitive diagnosis of CMV-induced GI toxicity can be made from tissue biopsy.

Fungal and parasitic infections

The main fungal infections encountered in renal transplant patients are *Aspergillus* (0–5% of renal transplant population), *Candida* (16–19%) and *Cryptococcus* (0–8%) [43], with both *Aspergillus* and *Candida* being associated with GI disorders including abdominal infection and abscesses [43]. In addition, because of increased international travel and immigration, physicians need to be aware of the symptoms

and clinical consequences of parasitic infections in transplant patients [44]. Two of the most common parasites infecting the GI tract are *Strongyloides stercoralis* and *Cryptosporidium parvum*, with their main presenting symptoms being haemorrhagic enterocolitis and severe diarrhoea, respectively [30,44].

Concomitant medications. Patients with concurrent diseases receiving renal transplants will most likely be receiving a number of non-immunosuppressant drugs, some of which have been associated with GI adverse events. Some of the more common of these drugs include antibiotics, hypoglycaemics and proton-pump inhibitors, the use of which has been associated with an increased incidence of diarrhoea, nausea and vomiting [45–47].

All immunosuppressive drugs have been associated with GI complications [3–5,48–65]. For example, in several 6-month trials, diarrhoea and nausea were experienced by 12–28% and 4–14% of patients receiving MMF, cyclosporine and corticosteroids [5,48,51], 16–18% and 38–42% of those receiving sirolimus, cyclosporine and corticosteroids [3,52,53], 41 and 36% of those receiving cyclosporine and corticosteroids [4], 44 and 38% of those receiving tacrolimus and corticosteroids [4] and 45 and 16% of those receiving MMF and corticosteroids [55]. GI events in patients treated with EC-MPS and cyclosporine were around 29% [66]. The wide range of incidence for similar events makes comparisons between studies difficult and supports the contention that a more rigorous approach to diagnosis and management is warranted.

Mechanisms of GI complications associated with mycophenolic acid

Of all the immunosuppressants currently available, MPA is the only one that has been thoroughly investigated with regard to mechanism of action for causing GI toxicities. A *post hoc* analysis suggested that the effects of MPA on GI events appear to be likely independent of the initial route of administration used [67]. The authors of this article hypothesized that conversion of MMF to MPA after oral administration may be required to induce GI events. However, this study was performed in the immediate period post-transplant and may not reflect GI events that occur in stable patients on long-term maintenance immunosuppression. Furthermore, the IV group also received more anti-thymocyte globulin (ATGAM) that could have contributed to more diarrhoea in this group obscuring the difference. Further studies with diarrhoea as a primary endpoint and powered to show a difference in diarrhoea are needed to clarify these GI events.

Both MPA and its metabolites may cause GI effects. The direct action of MPA is related to its antiproliferative properties, as it is a selective inhibitor of inosine monophosphate dehydrogenase (IMPDH),

an enzyme key to the *de novo* production of purines for T and B cells. [68] The *de novo* pathway for purine synthesis is not confined to T and B cells, however, and other cells in the body, including GI epithelial cells, are partially dependent upon the pathway for growth and replication [68]. The presence of MPA could inhibit the replication of GI epithelial cells, leading to disruption of fluid absorption and diarrhoea. In an animal study, administration of MPA post-surgery reduced the reparative capacity of the GI tract following colonic anastomoses [69]. While no such effects have been observed in humans, there have been case reports of villous atrophy following MPA exposure in patients with severe diarrhoea [70,71]. In both studies, the villous atrophy resolved following withdrawal of MPA-containing therapy.

Effects of mycophenolic acid acyl glucuronide

MPA is primarily metabolized to 7-O-MPA-β-glucuronide (MPAG) and mycophenolic acid acyl glucuronide (AcMPAG) [72]. MPAG is thought to be pharmacologically inactive, but acyl glucuronides are in general toxic molecules and can display pro-inflammatory effects. AcMPAG forms adducts with plasma proteins, (Figure 1) [73] and causes the release of cytokines both *in vitro* and *in vivo* [74,75]. These effects may be linked to the inflammatory symptoms observed in renal transplant patients. Indeed, the plasma levels of both AcMPAG and the pro-inflammatory molecule interleukin-6 (IL-6) have been correlated in renal transplant patients [76].

In addition, AcMPAG may also be generated within the GI tract, produced from MPA by intestinal and hepatic glucuronidases [77,78]. In the GI tract, AcMPAG inhibits IMPDH II [79] and so may affect GI epithelial cells directly to promote diarrhoea by affecting replication as described previously. However, it should also be noted that epithelial cells in the GI tract may not be wholly dependent on *de novo* purine synthesis, and may be permeable to purines that are released into the intestine during digestion [80], thus bypassing the IMPDH dependent pathway. Therefore, while IMPDH inhibition may play a role, additional processes may be involved in mediation of the GI effects.

AcMPAG also forms protein adducts that can directly interfere with cell function or trigger the immune system, leading to hypersensitivity and auto-immune reactions, or cause glutathione depletion [81,82]. A recent preclinical study identified proteins from rat liver and colonic homogenates that react with AcMPAG. The α and β chains of ATPase/ATP synthase, selenium-binding protein 2 and protein disulphide isomerase from liver homogenates formed adducts with AcMPAG [81]. However, while ATPase/ATP synthase and protein disulphide isomerase are known to be involved in the control of the energy and redox states of cells, the role of selenium-binding protein 2 is not yet understood. How these mechanisms
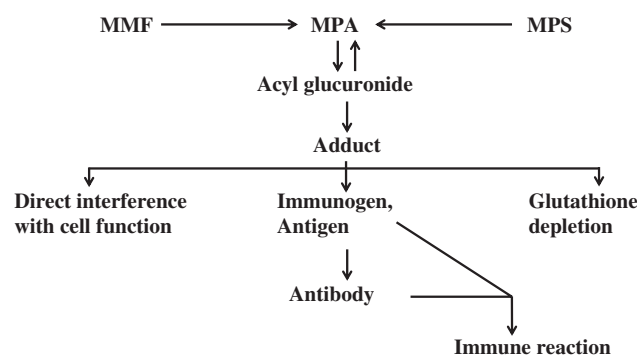
Fig. 1. Possible mechanisms by which acyl glucuronidation of mycophenolic acid induces gastrointestinal toxicity [78]. Adapted with permission from: Shipkova M, Armstrong VW, Oellerich M et al. Acyl glucuronide drug metabolites: toxicological and analytical implications. Ther Drug Monit 2003; 25: 1–16

contribute to the toxic effects of AcMPAG is unknown. In another study, cDNA microarray analysis was used to identify genes whose expression was altered by MPA [83]. Among these genes from rat intestine, three were down-regulated by MPA and linked possibly to GI effects: polymeric immunoglobulin receptor (increasing susceptibility of GI tract to bacteria and reactive drug molecules), catalase (increasing sensitivity to oxidative stress) and CCAAT/enhancer-binding proteins (affecting defence against free radicals) [83].

Recently, the relation of plasma concentrations of MPA, MPAG and AcMPAG to GI adverse events were assessed as part of an open, prospective, randomized, controlled, multi-centre study comparing fixed dose (1 g bid) *vs* concentration-controlled MMF (target MPA-AUCs of 30–60 mg h/l) regimens combined with cyclosporine or tacrolimus in renal transplant recipients [84]. Proportionally more patients treated with MMF and tacrolimus than those treated with MMF and cyclosporine experienced diarrhoea (34 and 16%, respectively, in the fixed-dose arm, and 30 and 16%, respectively, in the concentration-controlled arm). Patients who received tacrolimus had significantly higher exposure to MPA than those who received cyclosporine, which could account for the higher incidence of diarrhoea. However, tacrolimus by itself is also associated with diarrhoea. In contrast, plasma MPAG and AcMPAG concentrations were significantly higher in patients who received cyclosporine. The higher plasma MPAG and AcMPAG concentrations in cyclosporine-treated patients are consistent with inhibition of biliary excretion of these metabolites by cyclosporine. However, it is possible that tacrolimus-treated patients may be subjected to greater intestinal exposure to the metabolites of MPA due to the greater enterohepatic recirculation in addition to being exposed to tacrolimus.

Thus, based on the mechanisms proposed above, MPA, regardless of its drug of origin (MMF or EC-MPS) probably contributes to some GI disorders

in transplant patients, and controlled, randomized double-blind studies have shown that neither formulation is superior to the other in avoiding GI effects [49,66]. In a large 12-month trial comparing MMF and EC-MPS in 423 *de novo* renal transplant patients, there was no significant between-group difference in the proportion of patients experiencing adverse GI events, or in the proportion of patients discontinuing treatment because of such events [49].

In an open-label experience of patient-reported GI events, renal transplant patients ($n=278$) with GI adverse events, who switched from MMF to EC-MPS, had improved scores on the Gastrointestinal Symptom Rating Scale and Gastrointestinal Quality of Life Index after 4–6 weeks [85]. However, rather than using an appropriate control arm where patients with the same symptoms continuing treatment with MMF were followed, this study used a comparison group where the investigators followed a group of patients that did not have symptoms and did not require intervention. In the case of potentially self-limiting conditions like GI symptoms, the absence of a suitable control group means that there is no way of determining whether the condition treated would have resolved as rapidly with standard treatment. In fact the findings of that study are contrary to those from a controlled, blinded, randomized study, in which

stable renal transplant patients ($n=322$) were randomized to continue MMF or receive EC-MPS [66]. In this trial, a similar incidence of GI adverse events was observed in each group at 3 months (20.9% *vs* 26.4% [MMF *vs* EC-MPS]) and at 12 months (24.5% *vs* 29.6%) [66].

Treatment of GI disorders in renal transplant patients

While GI disorders occur commonly after renal transplant and have been ascribed to immunosuppressants [86–88], a measured approach to reducing these medications is necessary because of the risk of rejection and subsequent damage to the graft [11,12]. Since the presenting symptoms of GI disorders are usually non-specific and overlapping among aetiologies, a systematic and individualized approach to optimizing patient management is required. Figure 2 outlines a suggested algorithm for the management of diarrhoea in renal transplant patients [19,89–91].

Unless a patient is seriously ill, a wait-and-see approach may be warranted to determine whether the problem will spontaneously resolve without intervention. In a study of 130 renal transplant recipients, diarrhoea resolved spontaneously in 65% of patients
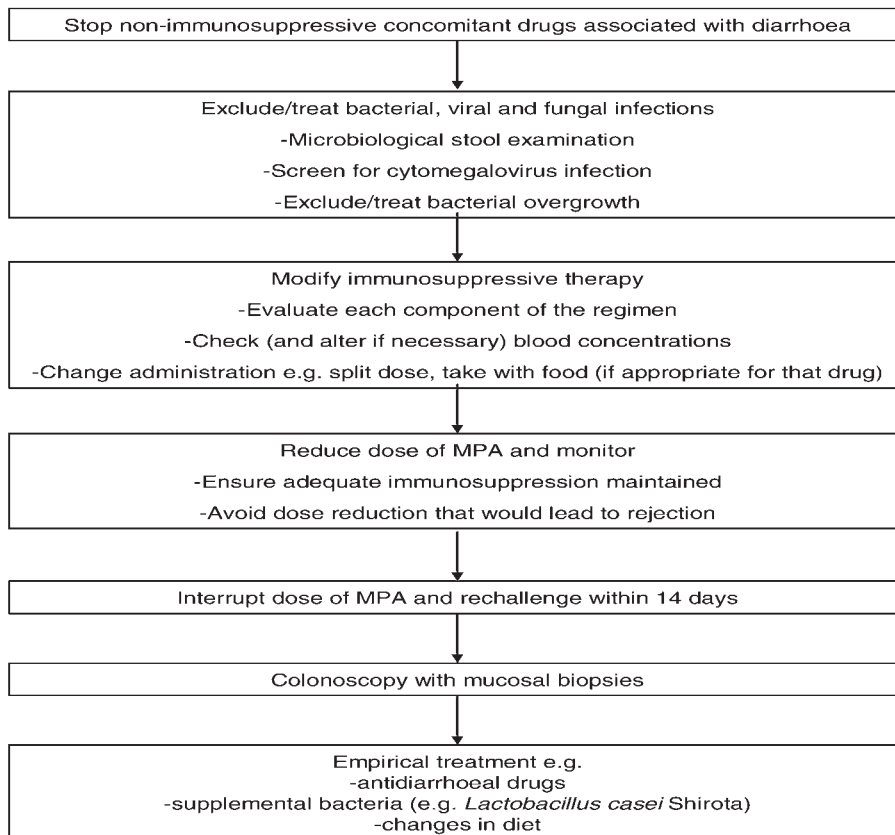
Fig. 2. Suggested approach to treating gastrointestinal adverse events in renal transplant patients [19,89–91]. Adapted with permission from: Maes B, Hadaya K, de Moor B et al. Severe diarrhea in renal transplant patients: results of the DIDACT study. Am J Transplant 2006; 6:1466–72

[20]. Once a GI disorder has become prolonged or severe enough to warrant treatment, a detailed medical history should be taken and a clinical review should be initiated in order to identify the underlying cause. As much as possible, the severity and inconvenience to the patient should be ascertained. The time from transplant needs to be considered as different aetiologies are more typical of different post-transplantation periods. If the GI disorder has occurred at a sufficient time post-transplantation such that any possible effects of surgery can be eliminated, patients' non-immunosuppressant co-medications (antibiotics, diuretics) and concurrent diseases (diabetes) should be considered to eliminate the possiblity that they are causative. Following this, the patient should be investigated for an infectious origin of their complaint and treated appropriately. A microbiological stool examination and viral screen should be performed and bacterial overgrowth should be excluded. A recent study prospectively examined the effects of various treatment options in 108 renal transplant patients with severe diarrhoea (≥3 stools/day for ≥7 days) [19]. Resolution of diarrhoea was achieved by ~50% of patients through empirical treatment (anti-diarrhoeal agents, diet changes) or treatment of identified GI infections (bacterial, viral, protozoal) through blood/stool examinations, bacterial overgrowth tests or biopsies.

Finally, if no other cause for the GI symptoms can be found, the patients' immunosuppressive therapy should be modified in a controlled manner (i.e. not assuming without some consideration that one drug is more responsible for the symptoms than another), limiting the risk to the patient. Thus, each component of the treatment regimen should be carefully evaluated. Blood concentrations of tacrolimus and sirolimus especially should be ascertained, and if found to be at or above the therapeutic range, dosages of these drugs could be reduced. If the levels of these drugs are acceptable, or otherwise should not be adjusted, then changes in how MPA is administered should be tried before lowering the dose. For MMF, the drug should be taken with food which does not alter the pharmacokinetics of MMF-derived MPA in a clinically significant way [92]. If MPA is delivered as EC-MPS, the option to alter the fed–fasted state of the patient is restricted because of a substantial change in the pharmacokinetics of EC-MPS-derived MPA when administered with or without food [93]. If symptoms persist, the dose of MMF should be split, with the drug taken three or four times a day rather than twice a day, maintaining drug exposure throughout the day [14]. If dose splitting is undertaken with EC-MPS, careful attention to keeping a consistent timing of dose in relation to meals is required. If other causes as outlined above have been ruled out and if intolerable GI side-effects still persist, then the dose of MMF should be reduced. The required dose of MMF may differ between individual patients. For example, a study of 79 renal transplant patients found that those with low pre-transplant IMPDH levels were more likely to suffer MPA-related adverse events, and were more suited to a lower MPA dose [94]. In contrast, those with high pre-transplant IMPDH levels required higher MPA doses to prevent rejection [94].

Conclusions

GI symptoms and complications remain a substantial burden for both transplant patients and physicians, and are commonly, but not exclusively, associated with the majority of immunosuppressive regimens. Before altering the patient's immunosuppressive regimen, consideration to non-iatrogenic causes should be sought. MMF in particular has been blamed for many GI toxicities, and while some toxicities have been associated with MPA (related to MMF and EC-MPS), it is likely in many cases that another aetiology is present. Increased awareness and clinical vigilance for GI symptoms within the renal transplant community remains a priority.

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