UC DAVIS HEALTH | CHILDREN'S HOSPITAL

Post Renal Transplant Diarrhea Management Guidelines

I. PURPOSE

To outline the approach to the evaluation and management of children with severe diarrhea after renal transplantation

II. SETTING

In-patient and outpatient settings

III. POLICY

Diarrhea is a common infectious complication after pediatric renal transplantation and can also result from non-infectious causes. Many complications can result from severe diarrhea including acute kidney injury from dehydration. Other unique complications in transplant recipients include tacrolimus toxicity and acute rejection (from changes in immunosuppressive pharmacokinetics or dosing in response to the diarrhea). Therefore, a thorough evaluation is recommended for all pediatric patients with severe diarrhea to ensure that appropriate interventions are instituted, and risks of complications minimized.

DEFINITIONS
Severe diarrhea: Recurrent diarrhea, persistent diarrhea (lasting for > 2 weeks but < 4 weeks), chronic diarrhea (lasting for > 4 weeks) or large volume diarrhea

IV. PROCEDURE

1) In pediatric renal transplant recipients with severe diarrhea, in addition to ensuring that adequate hydration is being achieved (either enterally or parenterally), the following first line tests should be performed to evaluate the etiology:

a) GI (BioFire) multiplex PCR panel for bacterial, viral, and protozoal pathogens (the lab will reflexly perform a culture if a bacterial pathogen is detected on the Biofire)
b) Stool for C difficile toxin and PCR
c) In situations where the diarrhea persists and the above tests are unrevealing, consideration should be given to other infectious causes such as CMV etc. that may not be included in the Biofire. (a full list of pathogens detected by BIOFIRE® FILMARRAY® Gastrointestinal (GI) Panel (biomerieux.com) can be found here) Consider consulting the pediatric infectious disease service in such instances.

At UC Davis, if you order a GI panel (Biofire) in the in-patient setting, organisms from all of the above pathogenic groups will get detected and reported, with the exception of C difficile (this is tested on the Biofire but not reported out). Testing for this has to be

ordered separately since the preferred testing is a two-tiered testing process (PCR followed by antigen testing) while the BioFire is a PCR test only.

2) In all patients with severe diarrhea, consider whether medications could be a contributor such as oral magnesium or phosphorus (which are commonly used after transplant) or immunosuppressive agents especially Mycophenolate mofetil (MMF) but also tacrolimus. No confirmatory testing is available for medication induced diarrhea short of medication withdrawal or dose reduction; MPA and MPAG levels and/or endoscopy with biopsies may be of some value as supportive evidence and to rule out other causes of diarrhea unrelated to transplantation (such as celiac disease, inflammatory bowel disease, irritable bowel syndrome etc.). Consider consulting the pediatric gastroenterology team in instances where the infectious work-up is unrevealing and diarrhea persists.

3) Management:

a) **General measures**

i) Ensure adequate hydration (enterally or parenterally) and monitor renal function and serum electrolytes at least on a daily basis

ii) Tacrolimus levels: severe diarrhea is associated with elevations in tacrolimus exposure, with the potential for tacrolimus nephrotoxicity, because of decreased metabolism of tacrolimus by the intestinal P-glycoprotein and CYP3A4 systems that become dysfunctional in the context of diarrhea. Tacrolimus metabolism can take as long as 1 month after the resolution of diarrhea to normalize (1). Frequent monitoring of tacrolimus levels, not only during, but after the resolution of diarrhea, are essential to avoid either overexposure leading to toxicity or underexposure from dose reduction, leading to rejection.

iii) MMF dose adjustment: since MMF has been associated with diarrhea or its exacerbation even when other causes of diarrhea are identified, MMF dose reductions or discontinuation are sometimes practiced in the context of severe diarrhea. This approach is fraught with risks, and therefore must be done thoughtfully. Retrospective studies indicate a higher risk of rejection, faster decline in renal function and the appearance of donor specific antibodies in the context of MMF dose reductions (2,3).

iv) The use of probiotics (4) and antimotility agents (5,6) remains sub optimally studied, and they continue to be used by clinicians, In the absence of good evidence suggesting a high risk of sepsis or other complications . Consideration should be given to their use, as an alternative to immunosuppressive dose reductions or withdrawal, or as an adjunct therapy to both reduce stool output and improve hydration allowing earlier discharge, and to reduce risk of recurrence of diarrhea. Patients with central lines, and those who are neutropenic, maybe at higher risk of complications with the use of probiotics, but the evidence even in these instances is not robust (4).

b) **Specific measures:** specific therapies must be targeted to the underlying etiology of diarrhea, and are beyond the scope of this policy with the exception of a few notable new developments and considerations. Appropriate pharmacotherapy for infectious etiologies must be instituted in conjunction with the pediatric infectious disease and transplant infectious disease services.

i) MMF associated diarrhea: MMF use is frequently associated with the occurrence of

gastrointestinal side effects such as diarrhea. GI symptoms of MMF include nausea, vomiting, diarrhea, and abdominal pain mostly in the first six months from the initiation of the therapy but can be delayed beyond that (7). These side effects have been attributed to the observation that enterocytes are dependent to a substantial extent on the metabolic pathway inhibited by MMF. MMF use has also been associated with the development of colitis. The most recognized mechanism of pathogenesis of MMF-induced colitis is the production of acyl glucuronide, a metabolite of MPA that directly promotes the release of cytokines like interleukin-6, tumor necrosis factor -alpha, and messenger RNA as well as its binding to plasma proteins, nucleic acids, and the lipids to form a neoantigen that subsequently triggers the immune system to cause inflammation in the form of colitis by hypersensitivity and autoimmunity pathways (7). Management of MMF associated diarrhea can include dose reductions of MMF (to be used with extreme caution due to the above-mentioned risks of rejection and graft dysfunction), or substitution with other agents such as everolimus (7), azathioprine or even delayed release enteric coated mycophenolic acid (8).

ii) C difficile colitis: A variety of therapies are available; use of a particular treatment modality is dependent on severity of illness, the number of recurrences of infection, tolerability of adverse effects, and cost (as outlined in the Red Book). The first line agent for first episode of in children should be oral vancomycin or metronidazole. Fidaxomicin has less data in peds and is costly, and so should be reserved for multiple recurrences or patients >=18. Up to 20% of patients experience a recurrence after discontinuing therapy, but infection usually responds to a second course of the same treatment. Metronidazole should not be used for treatment of a second recurrence or for prolonged therapy, because neurotoxicity is possible.

Bezlotoxumab is a new-generation fully humanized monoclonal antibody approved by the FDA in 2016 that abrogates recurrent C difficile diarrhea by neutralizing cytotoxin b and so should be strongly considered in transplant patients with recurrent infections. Per the IDSA CDI guidelines (updated 2021) as well as the American Society of Transplantation guidelines, bezlotoxumab is recommended even with primary infection in patients who are immunocompromised, including post solid organ transplant. It is administered as a one-time IV infusion while the patient is still on standard of care treatment for infection.

iii) Enteric viruses such as norovirus, astrovirus and sapovirus: In addition to supportive therapy, there are limited data that nitazoxanide, a thiazolide anti-infective agent, may be of benefit (albeit very modest) in patients with persistent infections (10). There are also limited data on the use of enteral immunoglobulins in this setting (11); these are expensive and need authorization for us.

iv) Cryptosporidium: In immunocompromised patients cryptosporidiosis can result in profuse diarrhea lasting weeks to months, which can lead to severe, even life-threatening dehydration, malnutrition, and wasting. Nitazoxanide is FDA approved for treatment of cryptosporidiosis in immunocompetent people. However, it is less effective in transplant patients. In transplant recipients, there is emerging data on antiparasitic combinations for cryptosporidiosis, including combinations of nitazoxanide, azithromycin, and in one case rifaximin (12).

V. RESPONSIBILITY

Pediatric nephrologist (primary/on call nephrologist)

VI. REFERENCES

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VIII. REVIEWED DATE and REVIEW CYCLE

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