

Microbiologic Testing in Post–Solid Organ Transplant Diarrhea

Christopher R. Polage^{1,2}

Departments of ¹Pathology and Laboratory Medicine, and ²Internal Medicine, Division of Infectious Diseases, University of California, Davis Medical Center, Sacramento

(See the Major Article by Echenique et al on pages 729–37.)

Keywords. solid organ transplant; diarrhea; *C. difficile*; norovirus; testing.

Up to 27% of recipients of solid organ transplant (SOT) experience diarrhea posttransplant, with some episodes being severe enough to require hospitalization [1–3]. Immunosuppressive medications are a common cause, but reduction of immunosuppression carries the risk of allograft rejection, making it necessary to rule out other causes, such as infection, before modifying the immunosuppressive regimen [3–7].

In this issue of *Clinical Infectious Diseases*, Echenique and colleagues report the frequency of infectious causes and diagnostic yield of microbiologic tests in a large retrospective cohort of hospitalized SOT patients with community- and hospital-onset diarrhea [8]. An implied goal of the study was to determine if a targeted approach to testing for

infectious causes of diarrhea could be considered as an alternative to the more comprehensive testing strategies recommended at their facility and elsewhere [7, 8]. With this question in mind, it is striking that most diarrheal episodes in their study had no specific etiology identified, infectious or otherwise, and >90% resolved in the hospital before discharge. A potential infectious cause was identified in 30% of community-onset and 19% of hospital-onset diarrheal episodes overall. Most infections were limited to just 3 agents—*Clostridium difficile*, norovirus, or cytomegalovirus—which comprised >90% of the infectious cases identified. Other infectious causes of diarrhea, such as *Campylobacter*, *Salmonella*, rotavirus, adenovirus, astrovirus, *Cryptosporidium*, and *Giardia*, were rarely identified. In light of these findings, the authors suggest that initial testing for infectious causes of diarrhea in SOT recipients could potentially be limited to a few tests (eg, blood quantitative cytomegalovirus polymerase chain reaction [PCR], *C. difficile* PCR, norovirus reverse transcription PCR, bacterial stool culture) in most patients. Then, if symptoms persist, additional testing could be performed to diagnose or rule out less common infectious causes before modifying immunosuppressive regimens. An analogous tiered approach to testing has been used for decades in immunocompetent patients with diarrhea.

However, there are several important points that should be considered before generalizing the results of this study to other centers. First, the frequencies of several potentially significant pathogens in immunocompromised hosts, such as *Campylobacter* and *Cryptosporidium*, were lower in this study than previous studies based in Europe (Table 1). Conversely, the rate of *C. difficile* among community-onset diarrheal episodes was higher than other studies and comparable to the rate of *C. difficile* in hospital-onset diarrheal episodes. This may be a manifestation of the changing epidemiology of *C. difficile* with more transmission and infection in the community or simply due to community onset of symptoms after hospitalization [11, 12]. Alternatively, it is possible that some of the *C. difficile* identified in community-onset diarrheal episodes were recurrent infections or lingering colonization with another cause of symptoms, as many patients had a history of prior *C. difficile* infection. In any case, the differences in the rates of individual diarrheal pathogens in this study vs previous studies suggests that the etiologies of infectious diarrhea in SOT recipients likely differ between transplant centers. Hence, the authors note in their discussion that the results of this study should not be generalized without verification of the local epidemiology and validation.

Received 17 October 2014; accepted 22 October 2014; electronically published 3 November 2014.

Correspondence: Christopher R. Polage, MD, Department of Pathology and Laboratory Medicine, University of California Davis Medical Center, 4400 V St, Sacramento, CA 95817 (christopher.polage@ucdmc.ucdavis.edu).

Clinical Infectious Diseases® 2015;60(5):738–40

© The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work properly cited. For commercial re-use, please contact journals.permissions@oup.com.

DOI: 10.1093/cid/ciu884

Table 1. Frequency of Infectious Causes in Patients With Posttransplant Diarrhea, by Study

Study	Echenique, 2014 (This Issue) [8]		Maes et al, 2006 [7]	Roos-Weil et al, 2011 [9]	Coste et al, 2013 [10]	
Test Methods	Molecular and Classical		Classical	Molecular and Classical	Multiplex Molecular Panels	
Country	United States		Belgium	France	France	
Population	CO Diarrhea	HO Diarrhea	Diarrhea	CO Diarrhea	CO Diarrhea	No Diarrhea
Transplant type	Mixed	Mixed	Renal	Renal	Renal	Renal
Positive (total)	30%	19%	28%	42%	56%–72%	20%–47%
Bacteria						
<i>Clostridium difficile</i>	13%	12%	2%	10%	2%	0%–3%
<i>Campylobacter, Salmonella</i>	1%	0%	12%	4%	30%	3%–7%
Viruses						
CMV	6%	3%	7%	0%–2%	0%–2%	NT
Norovirus	9%	4%	NT	17%	26%	10%–13%
Other GI viruses	0%	0%	1%	1%	6%	0%
Parasites						
<i>Cryptosporidium, Giardia</i>	<1%	0%	2%	4%	4%	0%
Other	0%–<1%	0%	2%	3%	0%	0%–3%

Abbreviations: CMV, cytomegalovirus; CO, community-onset; GI, gastrointestinal; HO, hospital-onset; NT, not tested.

A more concerning explanation for the low frequency of traditional infectious causes of community-onset diarrhea in this study is underdiagnosis due to lack of testing. Most diarrheal episodes in this study included an abbreviated microbiologic workup in spite of a more complete institutional test protocol. Bacterial stool culture was performed in only 58% of community-onset diarrheal episodes, and testing for *Cryptosporidium* and *Giardia* was performed in only 27% of episodes, making it possible that infectious cases were missed due to lack of testing. Less than 1% of episodes had testing for gastrointestinal viruses other than norovirus. This is not the authors' fault, as the study was a retrospective summary of real-world practice and not a prospective study designed to comprehensively define the infectious etiologies of diarrhea in SOT recipients. The testing strategies observed in this study may also have been reasonable and cost-effective medical practice because most diarrheal episodes appear to have had a relatively short duration. However, it is important to be aware of the limited workup for

intestinal pathogens when interpreting the results of this study.

The final point that should be made is that diagnostic test methods for gastrointestinal pathogens are rapidly and dramatically changing. Highly sensitive, multipathogen nucleic acid amplification test panels are poised to become the routine diagnostic test for gastrointestinal pathogens within the next few years. Two molecular test panels, each detecting multiple diarrheal pathogens, are already approved for in vitro diagnostic testing by the US Food and Drug Administration. Several other multiplex gastrointestinal pathogen panels are in various stages of clinical trials and regulatory review. Similar to what happened with the introduction of multiplex viral respiratory panels, it is likely that these multiplex gastrointestinal pathogen panels will replace traditional, less sensitive tests such as bacterial stool culture and viral and protozoal immunoassays in the near future. Moreover, whether it is cost effective or not, these multiplex molecular panels may obviate the need or choice to target testing to selected pathogens. Investigators

in France recently demonstrated the dramatic potential of these panels to increase the detection of gastrointestinal pathogens in SOT recipients, leading them and others to question the dogma that most posttransplant diarrhea is noninfectious [10]. In this pilot study, the investigators retested stool from 54 episodes of severe diarrhea in recipients of SOT with several multiplex gastrointestinal pathogen panels and compared results with classical test methods (ie, culture, microscopic examinations, immunoassays, some molecular tests) [10]. Strikingly, the proportion of samples with 1 or more potential pathogens detected increased from 23% with classical tests to 72% after performance of the multiplex gastrointestinal pathogen panels. Similar results have been observed in nontransplant populations [13, 14]. However, it is worth noting that asymptomatic transplant patients can also have pathogens detected by these multiplex panels, making it essential to limit testing to symptomatic patients and correlate test results clinically [10]. A partial summary of results from this study using multiplex gastrointestinal pathogen panels are

included in Table 1 (sixth and seventh columns)

for comparison with the Echenique et al study [8] and previous studies published elsewhere [7, 9–10].

In summary, Echenique and colleagues provide valuable real-world data showing that the majority of diarrheal episodes in SOT recipients have no etiology identified, with infectious causes being limited to a few pathogens under existing test methods. Looking forward, clinical implementation of multiplex gastrointestinal pathogen test panels is likely to increase the proportion of diarrheal patients with a potential pathogen identified, changing the question from which test(s) to order, to when to test and when to treat.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Boudjema K, Camus C, Saliba F, et al. Reduced-dose tacrolimus with mycophenolate mofetil vs. standard-dose tacrolimus in liver transplantation: a randomized study. *Am J Transplant* **2011**; 11:965–76.
2. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* **2007**; 357:2562–75.
3. Aulagnon F, Scemla A, DeWolf S, et al. Diarrhea after kidney transplantation: a new look at a frequent symptom. *Transplantation* **2014**; 98:806–16.
4. Bunnapradist S, Lentine KL, Burroughs TE, et al. Mycophenolate mofetil dose reductions and discontinuations after gastrointestinal complications are associated with renal transplant graft failure. *Transplantation* **2006**; 82:102–7.
5. Bunnapradist S, Neri L, Wong W, et al. Incidence and risk factors for diarrhea following kidney transplantation and association with graft loss and mortality. *Am J Kidney Dis* **2008**; 51:478–86.
6. Knoll GA, MacDonald I, Khan A, et al. Mycophenolate mofetil dose reduction and the risk of acute rejection after renal transplantation. *J Am Soc Nephrol* **2003**; 14:2381–6.
7. 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.
8. Echenique IA, Penugonda S, Stosor V, Ison MG, Angarone MP. Diagnostic yields in solid organ transplant recipients admitted with diarrhea. *Clin Infect Dis* **2015**; 60:729–37.
9. Roos-Weil D, Ambert-Balay K, Lanterrier F, et al. Impact of norovirus/sapovirus-related diarrhea in renal transplant recipients hospitalized for diarrhea. *Transplantation* **2011**; 92:61–9.
10. Coste JF, Vuiblet V, Moustapha B, et al. Microbiological diagnosis of severe diarrhea in kidney transplant recipients by use of multiplex PCR assays. *J Clin Microbiol* **2013**; 51:1841–9.
11. McDonald LC, Lessa F, Sievert D, et al. Vital signs: preventing *Clostridium difficile* infections. *MMWR Morb Mortal Wkly Rep* **2012**; 61:157–62.
12. Chitnis AS, Holzbauer SM, Belflower RM, et al. Epidemiology of community-associated *Clostridium difficile* infection, 2009 through 2011. *JAMA Int Med* **2013**; 173:1359–67.
13. McAuliffe GN, Anderson TP, Stevens M, et al. Systematic application of multiplex PCR enhances the detection of bacteria, parasites, and viruses in stool samples. *J Infect* **2013**; 67:122–9.
14. Liu J, Kabir F, Manneh J, et al. Development and assessment of molecular diagnostic tests for 15 enteropathogens causing childhood diarrhoea: a multicentre study. *Lancet Infect Dis* **2014**; 14:716–24.