Infection with cytomegalovirus (CMV) is an important cause of morbidity and mortality following solid organ transplantation (SOT) [1–3]. CMV causes a range of infections in SOT recipients, from asymptomatic viremia, to CMV syndrome, which is characterized by fever, malaise, and cytopenias, to tissue-invasive disease [3]. The patients at highest risk for CMV infection are CMV-negative recipients who receive an organ from a CMV-positive donor (D+/R−) [2, 3]. It is common practice to use either universal antiviral prophylaxis or preemptive monitoring with the goal of reducing the frequency and severity of CMV in transplant recipients [4]. Nonetheless, CMV replication still occurs in 16%–37% of patients, and 10%–20% of patients will have significant complications from infection [5].

Gastrointestinal (GI) CMV disease is currently the most common manifestation of tissue-invasive CMV [3, 6]. GI CMV disease can affect any part of the GI tract, including the esophagus, stomach, and small and large intestines. The incidence of GI CMV disease appears to be increasing [3, 6]. The reason for this increase in diagnosis is unclear but may be the result of changes in immunosuppressive regimens or a consequence of broader use of antiviral prophylaxis. GI CMV disease generally requires an esophagogastroduodenoscopy or colonoscopy coupled with biopsies for histology or, less frequently, culture to make a definitive diagnosis [3, 4]. A range of visual changes may be noted on endoscopy, including ulcers, hyperemia, and hemorrhage; visible changes in the mucosa are uncommon. Generally, biopsies are routinely stained for CMV with immunohistochemical stains to confirm the presence of replicating virus in the tissue.

A major clinical challenge is determining who should undergo endoscopy to screen for invasive CMV disease. Diarrhea is a common symptom among transplant patients [7, 8]. While there are a number of infectious and noninfectious causes of diarrhea, immunosuppressive medications are the most common cause of diarrhea in SOT recipients. As such, the general approach to evaluate diarrhea in SOT recipients is to screen for common infectious causes with stool culture, Clostridium difficile toxin assays, giardia and cryptosporidium enzyme immunoassays, and norovirus polymerase chain reaction (PCR) of the stool and CMV testing of the serum. If the tests are negative and diarrhea persists, immunosuppression is frequently reduced. If reduction of immunosuppression fails to improve the diarrhea, the patient will often undergo colonoscopy to identify the cause of infection and rule out CMV colitis. Unfortunately, serum CMV can be negative in patients with CMV colitis, and many patients with detectable CMV viremia do not have pathological evidence of CMV colitis [3, 4]. Since colonoscopy with biopsy is an invasive procedure that requires a prep that patients dislike, optimizing the population of patients for whom it is indicated remains an important clinical objective.

In this issue of Clinical Infectious Diseases, Durand and colleagues retrospectively reviewed their kidney and liver transplant population to identify patients with GI symptoms who underwent endoscopy with biopsy looking for CMV and those patients who had plasma CMV quantitative (q)PCR performed within 15 days of the biopsy. Eighty-one symptomatic patients (49, kidney; 25, liver; 4, kidney/liver; 2, kidney/pancreas; 1, kidney/
heart) were included; 20 patients (24.7%) had invasive CMV GI disease documented. Proven disease typically occurred after prophylaxis would have been discontinued (median 206.5 days) but most often within the first year post transplant. qPCR had an 85% sensitivity and 95% specificity to diagnose CMV GI disease; sensitivity was highest in the D+/R− patients (100%) and lowest in the D+/R+ patients (72.7%). Sensitivity was higher for liver transplant recipients (100%) than for kidney transplant recipients (72.7%). The mean plasma CMV viral load was 38,334 copies/mL in patients with proven CMV GI disease; however, 3 (15%) patients with biopsy-proven CMV GI disease had undetectable plasma CMV viral loads.

This was a large cohort study of patients with CMV GI disease that documented that plasma CMV qPCR has generally very good sensitivity for predicting who will have CMV GI disease among symptomatic patients. Nonetheless, 3 (15%) patients with CMV GI disease had an undetectable CMV qPCR and 3 (4.9%) symptomatic patients with positive CMV qPCR had no biopsy evidence of CMV GI disease. CMV qPCR, therefore, is a useful indicator of risk of CMV GI disease but is neither sufficiently sensitive nor specific. In their analysis, the authors did not adjust for propensity to perform endoscopy. As such, it is possible that patients with milder symptoms were not diagnosed with CMV GI disease and that the true sensitivity of qPCR may be under- or overestimated. Further, the full evaluation protocol for patients with GI symptoms was not outlined. Therefore, it is unclear when endoscopy occurred during the evaluation and if there were specific triggers that were more likely to result in endoscopy.

Overall, one can safely conclude that there is a high likelihood of CMV GI disease in symptomatic patients with detectable qPCR, particularly among D+/R− recipients and liver transplant recipients. Yet, clinical judgment must still be used to determine who should undergo endoscopy as qPCR in symptomatic patient will miss some cases of CMV GI disease.

Although this study adds significantly to our understanding of the relative utility of CMV qPCR in screening for CMV GI disease, there are several questions that remain unanswered. In patients with a high probability of invasive CMV GI disease (ie, symptomatic D+/R− liver transplant recipients with detectable qPCR), is the endoscopy necessary or can the patient be treated presumptively for CMV GI disease, typically with intravenous ganciclovir initially? If endoscopy is avoided, how many patients without CMV GI disease will be treated with more challenging therapies, namely, intravenous ganciclovir? Second, is there a need for repeat endoscopy in patients who have improved clinically and become undetectable for CMV by qPCR in the plasma in order to determine if CMV therapy can be discontinued or transitioned to secondary prophylaxis? Third, can the CMV qPCR value provide insight when determining the extent of disease and need for intravenous ganciclovir versus oral valganciclovir? Last, are there other markers that can supplement plasma CMV qPCR to improve the predictive value of the patient having invasive CMV GI disease? Such markers may include markers of inflammation or CMV ongoing replication in the stool.

Future studies are clearly needed to optimize the diagnosis and management of GI CMV disease.

**Note**

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