Adenovirus (ADV) has been identified as an important cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT) [1–8]. Polymerase chain reaction (PCR)–based assays now allow rapid quantification of ADV load in the blood. However, unlike cytomegalovirus (CMV), for which preemptive therapy is well established, the monitoring and treatment of ADV viremia or infection remain controversial, particularly given the limited treatment options.

To establish recommendations for monitoring of ADV following HSCT, several questions would need to be answered: (1) What is the incidence of ADV viremia in HSCT recipients? (2) Is there a correlation between viral load and organ involvement as well as survival? (3) Are there risk factors (either patient or transplant characteristics) that can predict viremia and outcomes? (4) Can these risk factors be mitigated? (5) Are there effective treatments and has early treatment been shown to affect outcome?

The reported incidence of ADV viremia and associated morbidity and mortality vary widely in the literature. For example, consistently high rates of ADV infection have been reported in pediatric populations, with an incidence of up to 84% in children <5 years of age in one series [5, 6]. In contrast, in a large retrospective review that included almost 2900 transplant recipients, the incidence was 3%, with an associated 26% mortality [3]. Adenovirus infection in this study was detected via culture or immunohistochemistry, possibly underestimating the true incidence, as more sensitive PCR was not used.

Similarly, many of the older reports either did not include PCR monitoring or were case-finding studies. More recent studies have included PCR monitoring. One study prospectively tested for ADV in a cohort of 76 allogeneic HSCT patients by testing stool, urine, and pharyngeal specimens every other week for 6 months after transplant, and performing blood PCR only in patients with a positive tissue sample. The reported incidence was 19.7% with a 3% mortality rate [4]. Several other small studies have reported an incidence of about 5% when routine screening with blood PCR was performed [9, 10]. A recent large retrospective review reported a similar 5% incidence in 539 patients tested for ADV by PCR [8]. Mortality was high in this group, and 7 of the 27 patients succumbed to ADV disease. Both T-cell depletion and high viral loads were identified as risk factors for fatal ADV.

T-cell depletion has been identified as a risk factor for ADV infection in a number of studies [4, 9, 11–13]. In particular, the use of in vivo T-cell depletion with alemtuzumab has been associated with an increased risk of ADV infection [4, 12, 13]. Additional risk factors for ADV viremia are young age, acute graft-versus-host disease, and the use of cord blood as a stem cell source [4, 11, 12, 14, 15].

As reported in this issue of Clinical Infectious Diseases, Sive and colleagues instituted weekly blood quantitative PCR monitoring for ADV in 116 patients receiving reduced-intensity conditioning with alemtuzumab. In addition to weekly blood PCR until day 100, symptomatic patients had evaluation of stool
or nasopharyngeal samples. Instituting this surveillance program integrated well with their routine weekly screening of CMV and Epstein-Barr virus. The incidence of adenovirus viremia in this cohort was 12% with 1 death (incidence of 0.9% in the entire cohort, 7% of those with viremia). Patients with low ADV titers never developed clinically relevant disease and patients with elevated titers were treated preemptively with modulation of immunosuppression first, and cidofovir if this failed. Another interesting finding was the fact that ADV was detected much earlier after HSCT than in previously reported studies, which could potentially allow for earlier modulation of immunosuppression. Finally, an underlying diagnosis of lymphoid malignancy and CMV seropositive status were identified as additional risk factors. Although the current study does not definitively establish the optimal screening strategy for ADV, this approach has the potential to detect infections early, allowing for institution of early therapy and possibly preventing more serious outcomes.

Cidofovir is a nucleoside analogue with in vitro activity against ADV. It has been used to treat invasive ADV disease, but its efficacy has not been evaluated in randomized clinical trials [7, 15–19]. Preemptive treatment for ADV viremia has also not been validated in clinical trials. In addition, preemptive use of cidofovir is limited by its toxicity profile, particularly when used in conjunction with other nephrotoxic agents. CMX001 is an orally bioavailable lipid conjugate of cidofovir that has activity against ADV [20]. It is currently in clinical trials for preemptive treatment of ADV viremia in HSCT.

Future studies will need to examine the screening approach described by Sive et al in other transplant regimens that do not incorporate alemtuzumab. With the advent of novel agents to treat ADV and a growing number of targeted cellular therapies [21, 22], early identification will become all the more relevant.

**Note**

**Potential conflicts of interest.** All authors: No reported conflicts.

Both authors have 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.

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