Open Forum Infectious Diseases

MAJOR ARTICLE

Risk Factors for CMV Viremia and Treatment-Associated Adverse Events Among Pediatric Hematopoietic Stem Cell Transplant Recipients

Sarah M. Heston,[1] Rebecca R. Young,[1,2] John S. Tanaka,[3] Kirsten Jenkins,[1] Richard Vinesett,[4] Frances M. Saccoccio,[5] Paul L. Martin,[4] Nelson J. Chao,[6] and Matthew S. Kelly[1]

[1]Division of Pediatric Infectious Diseases, Duke University Medical Center, Durham, North Carolina, USA, [2]Duke Clinical Research Institute, Durham, North Carolina, USA, [3]Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA, [4]Division of Pediatric Transplant and Cellular Therapy, Duke University Medical Center, Durham, North Carolina, USA, [5]Division of Pediatric Infectious Diseases, University of Florida Shands Children's Hospital, Gainesville, Florida, USA, and [6]Division of Hematologic Malignancies and Cellular Therapy, Duke University Medical Center, Durham, North Carolina, USA

Background. Cytomegalovirus (CMV) causes substantial morbidity and mortality after hematopoietic stem cell transplantation (HSCT). There are limited data on risk factors for CMV viremia and the safety of antiviral medications used to treat CMV in children.

Methods. We conducted a single-center retrospective study of children who underwent HSCT between 2000 and 2016. We used log-logistic regression to evaluate associations between clinical characteristics and CMV-free survival at 100 days after HSCT. We compared the incidences of laboratory-defined adverse events (AEs) during treatment with ganciclovir and foscarnet.

Results. Among 969 children, the median (interquartile range) age was 6.5 (3.1–11.5) years, and 80% underwent allogeneic HSCT. Two hundred forty-four (25%) children developed CMV viremia. Older age (odds ratio [OR], 0.95; 95% CI, 0.92–0.98), male sex (OR, 0.71; 95% CI, 0.51–0.99), non-Black, non-White race (OR, 0.56; 95% CI, 0.36–0.87), umbilical cord blood donor source (OR, 0.28; 95% CI, 0.08–0.97), and CMV seropositivity (R-/D+: OR, 0.17; 95% CI, 0.07–0.41; R+/D-: OR, 0.14; 95% CI, 0.09–0.21; R+/D+: OR, 0.08; 95% CI, 0.04–0.15) were associated with lower odds of 100-day CMV-free survival. Compared with foscarnet, ganciclovir was associated with lower incidences of thrombocytopenia (incidence rate ratio [IRR], 0.38; 95% CI, 0.15–0.97), electrolyte AEs (IRR, 0.42; 95% CI, 0.24–0.75), endocrine AEs (IRR, 0.52; 95% CI, 0.34–0.79), and renal AEs (IRR, 0.36; 95% CI, 0.19–0.65).

Conclusions. CMV viremia occurred commonly among children after HSCT, and ganciclovir and foscarnet were associated with distinct toxicity profiles among children with CMV infection. These findings should be considered when developing CMV prevention and treatment strategies for children after HSCT.

Keywords. antivirals; cytomegalovirus viremia; ganciclovir; foscarnet; immunocompromised children.

Cytomegalovirus (CMV) infection occurs frequently after hematopoietic stem cell transplantation (HSCT) and is associated with substantial morbidity and mortality. In the first year after HSCT, CMV viremia occurs in up to 50% of adult allogeneic HSCT recipients and progresses to end-organ disease in 20% of these patients [1–3]. CMV disease can manifest as pneumonitis, gastritis, colitis, hepatitis, fever, or leukopenia and is associated with a mortality rate as high as 43% in adults [4, 5]. Prior studies in adult HSCT recipients identified risk factors for CMV disease and viremia, including HSCT recipient and donor CMV seropositivity, underlying diagnosis, patient age, conditioning regimen, HSCT donor source, and receipt of immunosuppressive therapies [1, 4, 6–8]. In contrast, there is a significant gap in our understanding of the risk factors for CMV viremia in pediatric HSCT recipients, as prior studies in this population have been limited by small sample size and varied CMV antiviral prophylaxis or surveillance strategies [9–11]. The identification of risk factors for CMV viremia among pediatric HSCT recipients could facilitate the risk stratification of patients for evaluation of new antiviral medications and other novel preventive and treatment strategies for CMV.

Management of CMV in children after HSCT most frequently involves routine surveillance for CMV viremia and initiation of preemptive antiviral therapy. Such an approach has been shown to both limit progression to CMV end-organ disease and improve overall survival among adult HSCT recipients [12]. Ganciclovir and foscarnet are the current agents of choice for the treatment of CMV viremia [13]. These antivirals

Received 5 November 2021; editorial decision 7 December 2021; accepted 13 December 2021; published online 16 December 2021.

Correspondence: Sarah Heston, MD, Duke Children's Health Center, Box 102346, Durham, NC 27710 (sarah.heston@duke.edu).

Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofab639

have similar efficacy but are each associated with significant toxicities; in particular, ganciclovir has frequently been associated with bone marrow suppression while foscarnet has been associated with renal impairment [14–16]. Ganciclovir and foscarnet have been used extensively in infants and children, despite limited safety data. Age-related differences in drug distribution, metabolism, and elimination could affect the safety profiles of these antivirals in children compared with adults [16–18]. Access to safety data is imperative in choosing an antiviral agent for use in a vulnerable population with complex underlying disorders, high risk for CMV end-organ disease, and frequent exposure to other medications.

In this retrospective study, we sought to identify patient and transplant characteristics associated with the risk of CMV viremia in the first 100 days after HSCT in children. As a secondary objective, we compared the incidence of laboratory-defined adverse events (AEs) among children with CMV viremia treated with ganciclovir or foscarnet.

METHODS

Study Design and Population

We conducted a retrospective cohort study of children 1 to 17 years of age who underwent HSCT through the Duke University Pediatric Transplant and Cellular Therapy Program between January 1, 2000, and December 31, 2016. Data were collected from a secure database maintained by the HSCT program, electronic medical records, and the Duke Enterprise Data Unified Content Explorer (DEDUCE) [19]. We limited eligibility to children 1 year of age or older because of the difficulty in interpreting CMV serological testing from younger infants who may still have maternally derived CMV-specific antibodies. We excluded children with missing CMV serologies from either the donor or the recipient (n = 18), children for whom the donor was a CMV-seropositive infant under 1 year of age (n = 3), and children who were receiving foscarnet or ganciclovir on the day of HSCT (n = 19). The study protocol was approved by the Duke Health Institutional Review Board.

Transplant Practices

All HSCT recipients and donors were evaluated for CMV infection before HSCT. Between 2000 and 2005, umbilical cord blood units were not used if maternal serum was positive for CMV immunoglobulin M (IgM); beginning in 2006, units were not used if CMV polymerase chain reaction (PCR) testing of the cord blood unit was positive. Bone marrow donors and transplant recipients were screened for CMV using serum IgM and immunoglobulin G (IgG).

After HSCT, surveillance for CMV viremia among HSCT recipients was performed weekly until day +100 after HSCT. CMV DNA hybrid capture assays on whole blood were used for surveillance from 2000 until 2006; from 2006 onward, weekly quantitative CMV PCR on plasma became standard practice. Antiviral therapy was initiated for any symptomatic CMV infection. Preemptive therapy was initiated after 2 consecutive weeks of CMV PCR >500 IU/mL or after 1 measurement >1000 IU/mL. Children with serological evidence of previous infection with herpes simplex viruses received acyclovir 250 mg/m^2/dose given intravenously every 12 hours for the first year after allogeneic HSCT and for 3–6 months after autologous HSCT.

At our institution, children are typically hospitalized until they demonstrate stable donor cell engraftment and are otherwise clinically stable. Most laboratory values used to assess for AEs were measured daily while inpatient and at least weekly during outpatient encounters as part of routine clinical care. Hospital discharge and collection of laboratories were ultimately at the discretion of the clinical provider.

Statistical Analyses

We used multivariable log-logistic regression, a parametric survival analysis, to evaluate associations between patient and transplant characteristics and CMV viremia within the first 100 days after HSCT [20]. Children were censored on the day of death, second HSCT, last recorded health care encounter, or when initiating treatment with an antiviral medication with activity against CMV. We used this model to estimate odds ratios (ORs) of 100-day CMV-free survival for each potential risk factor, with a lower OR indicating a higher odds of CMV viremia by 100 days after HSCT. We similarly used multivariable log-logistic regression to evaluate associations between patient and transplant characteristics and all-cause mortality in the 2 years after HSCT. Multivariable models were adjusted for patient and transplant characteristics, including patient age, sex, race, underlying diagnosis, HSCT type and donor source, conditioning regimen, year of HSCT, and CMV serostatus.

We identified treatment-associated AEs through analysis of laboratory results from patients who developed CMV viremia (Table 1). We used Wilcoxon rank-sum tests to compare baseline laboratory values collected on the first day of therapy or, if unavailable, up to 3 days preceding start of therapy among children starting ganciclovir or foscarnet. We compared incidence rates of AEs during treatment with ganciclovir and foscarnet. Due to the frequency of laboratory abnormalities in this patient population, we did not attribute an AE to receipt of an antiviral if the laboratory abnormality was present in the 3 days before starting antiviral treatment. Moreover, to prevent overestimation of the incidence of treatment-associated AEs, a patient could only meet criteria for a specific AE once during each antiviral treatment course; however, a patient could meet criteria for multiple different AEs during the same treatment course. We lagged laboratory results by 1 day to ensure that AEs were assessed after antiviral exposures. Finally, we used longitudinal, multivariable mixed-effect regression models to compare the effects of ganciclovir and foscarnet treatment on

Table 1. Laboratory-Defined Adverse Events

	AE Value
Electrolyte AEs	
Hyponatremia	≤124 mEq/L
Hypernatremia	≥151 mEq/L
Hypokalemia	≤2.5 mEq/L
Hyperkalemia	≥7.0 mEq/L
Bicarbonate: low	≤14 mEq/L
Bicarbonate: high	≥35 mEq/L
Hypocalcemia	≤7.5 mg/dL
Hypercalcemia	≥11.2 mg/dL
Hematological AEs	
Leukopenia	$\leq 2 \times 10^3/\mu L$
Leukocytosis	$\geq 100 \times 10^3/\mu L$
Anemia (hemoglobin)	≤7 g/dL
Polycythemia (hemoglobin)	≥24 g/dL
Thrombocytopenia	$\leq 50 \times 10^3/\mu L$
Thrombocytosis	$\geq 1000 \times 10^3/\mu L$
Prothrombin time	≥18 sec
Activated partial thromboplastin time	≥79 sec
Endocrine AEs	
Hypoglycemia	≤60 mg/dL
Hyperglycemia	≥200 mg/dL
Gastrointestinal	
Aspartate aminotransferase	≥100 U/L
Alanine aminotransferase	≥100 U/L
Alkaline phosphatase	≥500 U/L
Conjugated bilirubin	≥1 mg/dL
Gamma-glutamyl transferase	≥75 U/L
Lipase	≥200 U/L
Renal AEs	
Blood urea nitrogen	≥50 mg/dL
Creatinine	≥1.5 mg/dL

Abbreviation: AE, adverse event.

liver enzymes and renal function tests. Laboratory values were log-transformed to achieve normality, and these models were adjusted for clinical factors as above, for day after HSCT as a fixed effect, and for subject as a random effect. Statistical analyses were performed using the *survival* (version 3.12) and *lme4* (version 1.1-26) packages within R, version 4.0.2.

RESULTS

Patient Characteristics

Patient and transplant characteristics of the 969 children included in this study are shown in Table 2. The median (interquartile range [IQR]) age was 6.5 (3.1–11.5) years, and most children were male (61%) and White (69%). Fewer than half (43%) of transplants were performed for a hematological malignancy, and most were allogeneic transplants with an umbilical cord blood donor (59%). Among the allogeneic transplants, 165 (81%) of the bone marrow transplants and 18 (3%) of the umbilical cord blood transplants were from related donors. Few children (5%) received nonmyeloablative or reduced-intensity conditioning regimens. The most common graft-vs-host disease (GVHD) prophylaxis regimens after allogeneic HSCT were a calcineurin inhibitor with mycophenolate mofetil (41%), a calcineurin inhibitor with steroids (39%), and a calcineurin inhibitor with methotrexate (18%). More than half of recipients (58%) and the vast majority of donors (84%) were CMV-seronegative.

Outcomes

Two hundred forty-four (25%) children developed CMV viremia at a median (IQR) of 25 (12–40) days after HSCT. CMV viremia was identified by DNA hybrid capture assay in 120 (49%) children and by PCR in 124 (51%) children. CMV viremia occurred in 226 (29%) children who underwent allogeneic HSCT and 18 (9%) children who underwent autologous HSCT. Of the 539 recipient-seronegative (R-)/donor-seronegative (D-) transplants, there were 53 (10%) primary CMV infections among allogeneic HSCT recipients and 4 (1%) among autologous HSCT recipients. Older age (OR, 0.95; 95% CI, 0.92–0.98), male sex (OR, 0.71; 95% CI, 0.51–0.99), non-Black, non-White race (OR, 0.56; 95% CI, 0.36–0.87), umbilical cord blood donor source (OR, 0.28; 95% CI, 0.08–0.97), and CMV seropositivity in either the donor or recipient (R-/D+: OR, 0.17; 95% CI, 0.07–0.41; R+/D-: OR, 0.14; 95% CI, 0.09–0.21; R+/D+: OR, 0.08; 95% CI, 0.04–0.15) were associated with a lower odds of 100-day CMV-free survival (Table 2). In the 2 years after HSCT, 318 (33%) children died, including 95 (39%) children who developed CMV viremia in the 100 days after HSCT and 233 (32%) who did not develop CMV viremia. CMV viremia was not associated with 2-year all-cause mortality (OR, 1.13; 95% CI, 0.84–1.52).

Treatment-Associated Adverse Events

Of the 244 children who developed CMV viremia, 180 (74%) received antiviral therapy with ganciclovir or foscarnet, including 77 (43%) who received ganciclovir only, 14 (8%) who received foscarnet only, and 89 (49%) who received both ganciclovir and foscarnet. Of the 64 children who did not receive ganciclovir or foscarnet, 4 (6%) received CMV immune globulin, 3 (5%) received valganciclovir, and 1 (2%) received both valganciclovir and CMV immune globulin. The remaining children received no directed treatment for CMV viremia. Children starting foscarnet treatment had lower values of potassium ($P = .04$), white blood cell count (WBC; $P < .0001$), platelet count ($P = .03$), aspartate transaminase (AST; $P = .0005$), alanine transaminase (ALT; $P = .04$), alkaline phosphatase (ALP; $P = .01$), and creatinine ($P = .04$) than children starting ganciclovir (Table 3). In total, there were 6533 patient-days of ganciclovir monotherapy in 169 treatment courses, 2742 patient-days of foscarnet monotherapy in 103 treatment courses, and 517 patient-days of treatment with both ganciclovir and foscarnet in 78 treatment courses. Foscarnet was started earlier after HSCT than ganciclovir (median [IQR], 34 [14–54] days vs 40 [30–55] days; Wilcoxon-rank

Table 2. Patient and Transplant Characteristics of the Study Population

	No CMV Viremia (n = 725)	CMV Viremia (n = 244)			
	No. (%)	No. (%)	OR	95% CI	*P*
Age, median (IQR), y	6.0 (2.8–10.9)	8.5 (4.2–13.3)	0.95	0.92–0.98	.005
Sex					
Female	291 (40)	88 (36)	1.00	Ref	-
Male	434 (60)	156 (64)	0.71	0.51–0.99	.04
Race					
White	524 (72)	143 (59)	1.00	Ref	-
Black	121 (17)	53 (22)	0.79	0.52–1.20	.27
Other races	80 (11)	48 (20)	0.56	0.36–0.87	.01
Underlying diagnosis					
Hematological malignancy	293 (40)	125 (51)	1.00	Ref	-
Genetic or metabolic disorder	139 (19)	38 (16)	0.67	0.41–1.08	.10
Nonmalignant hematological disorder	77 (11)	48 (20)	0.74	0.45–1.21	.23
Immunodeficiency or autoimmune disease	52 (7)	18 (7)	0.78	0.41–1.48	.45
Solid tumor	164 (23)	15 (6)	2.23	0.69–7.24	.18
HSCT type					
Autologous	178 (25)	18 (7)	1.00	Ref	-
Allogeneic, bone marrow source	130 (18)	74 (30)	0.46	0.15–1.47	.19
Allogeneic, umbilical cord blood source	417 (58)	152 (62)	0.28	0.08–0.97	.045
Conditioning regimen					
Myeloablative	688 (95)	229 (94)	1.00	Ref	-
Nonmyeloablative or reduced intensity	37 (5)	15 (6)	0.72	0.36–1.43	.34
CMV serostatus					
R-/D-	482 (66)	57 (23)	1.00	Ref	-
R-/D+	13 (2)	11 (5)	0.17	0.07–0.41	<.0001
R+/D-	143 (20)	128 (52)	0.14	0.09–0.21	<.0001
R+/D+	87 (12)	48 (20)	0.08	0.04–0.15	<.0001

Abbreviations: CMV, cytomegalovirus; D, donor; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; OR, odds ratio; R, recipient.

Table 3. Median Laboratory Values at the Start of Therapy by Antiviral

	Median (IQR) Value		
	Ganciclovir (n = 169)	Foscarnet (n = 103)	*P*
Electrolyte			
Sodium, mEq/L	138 (136–139)	139 (136–141)	.24
Potassium, mEq/L	4.1 (3.7–4.5)	4.0 (3.6–4.2)	.04
Bicarbonate, mEq/L	24 (22–26)	24 (22–25.3)	.10
Calcium, mg/dL	9.1 (8.7–9.5)	9.0 (8.6–9.4)	.18
Hematological			
WBC, 10^3/uL	7.9 (4.7–12.25)	1.6 (0.3–7.25)	<.0001
Hemoglobin, g/dL	9.8 (8.8–10.7)	9.6 (8.9–10.5)	.71
Platelet count, 10^3/µL	49 (31.5–80.5)	38 (24.8–59)	.03
Prothrombin time, sec	12.7 (11.8–13.4)	12.5 (12–13.5)	.89
Activated PTT, sec	29.4 (26.4–35.6)	30.4 (27.1–35.1)	.75
Endocrine			
Glucose, mg/dL	114 (91–143)	118 (99–145.2)	.13
Gastrointestinal			
AST, U/L	45 (33–66)	36 (25–58)	.0005
ALT, U/L	58 (36–92)	44 (26–89)	.04
ALP, U/L	131 (95–183)	110 (89–147)	.01
Renal			
BUN, mg/dL	23 (16–39)	25 (16–45)	.44
Creatinine, mg/dL	0.6 (0.4–0.8)	0.5 (0.3–0.7)	.04

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; IQR, interquartile range; PTT, partial thromboplastin time; WBC, white blood cell count.

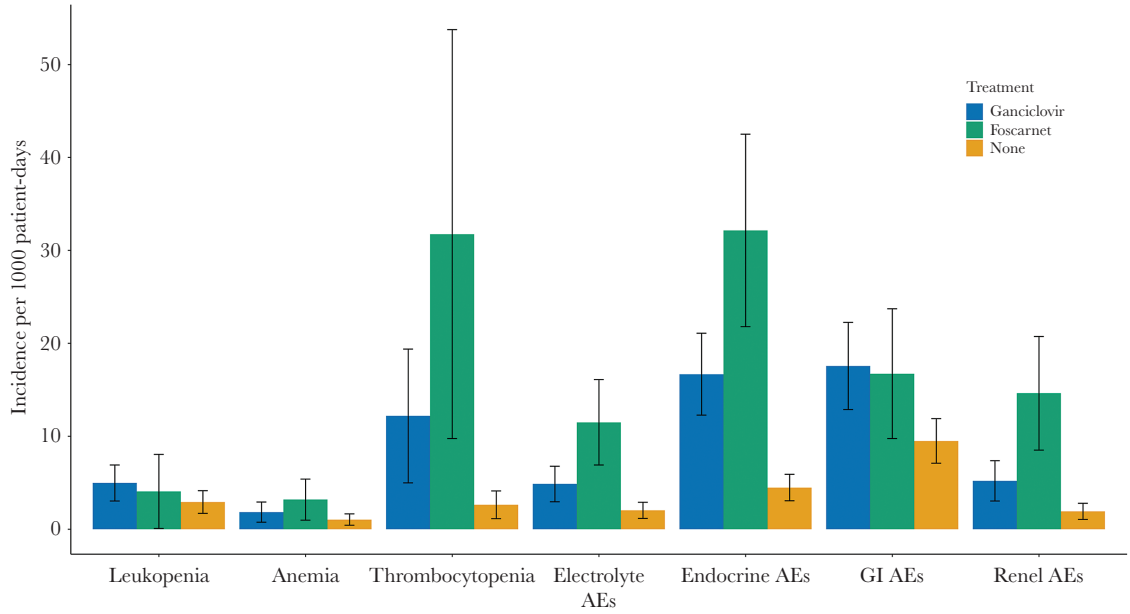

Figure 1. Incidence of adverse events among children with CMV viremia by antiviral treatment. For the selected AEs, the incidence rates per 1000 patient-days are shown by antiviral treatment during episodes of CMV viremia. Electrolyte AEs include hyponatremia, hypernatremia, hypokalemia, hyperkalemia, low bicarbonate, high bicarbonate, hypocalcemia, and hypercalcemia; endocrine AEs include hypoglycemia and hyperglycemia; GI AEs include aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, elevated conjugated bilirubin, elevated gamma-glutamyl transferase, and elevated lipase; and renal AEs include elevated blood urea nitrogen and elevated creatinine. Error bars represent 95% CIs. Abbreviations: AEs, adverse events; CMV, cytomegalovirus; GI, gastrointestinal.

sum test, $P = .01$). Ganciclovir treatment courses were also of longer duration than foscarnet treatment courses (median [IQR], 39.5 [17–64] vs 22 [11–40.5] days; Wilcoxon rank-sum test, $P < .0001$).

We then compared AEs that occurred during ganciclovir treatment, foscarnet treatment, or with no antiviral treatment (Figure 1; Supplementary Table 1). Compared with treatment with foscarnet, ganciclovir treatment was associated with lower incidence rates of thrombocytopenia (incidence rate ratio [IRR], 0.38; 95% CI, 0.15–0.97), electrolyte AEs (IRR, 0.42; 95% CI, 0.24–0.75), endocrine AEs (IRR, 0.52; 95% CI, 0.34–0.79), and renal AEs (IRR, 0.36; 95% CI, 0.19–0.65). No differences in the incidence rates of leukopenia, anemia, and gastrointestinal AEs were observed during treatment with ganciclovir and foscarnet. A significant proportion of the 523 AEs attributed to ganciclovir or foscarnet occurred in the first several weeks of antiviral therapy. Of the 316 AEs attributed to ganciclovir, 79 (25%) occurred during the first 7 days of therapy and 67 (21%) were in the second week of ganciclovir therapy. Of the 207 AEs attributed to foscarnet, 73 (35%) occurring during the first 7 days of therapy and 59 (29%) were in the second week of foscarnet therapy (Supplementary Table 1). Compared with no antiviral therapy, ganciclovir was associated with a 4% (95% CI, 2%–6%) increase in blood urea nitrogen (BUN) per patient-day of therapy, while foscarnet was associated with a 32% (95% CI, 29%–35%) increase in BUN and a 14% (95% CI, 12%–16%) increase in serum creatinine per patient-day of therapy (Table 4, Figure 2). Finally, ganciclovir was associated with a 9% (95%

Table 4. Association Between Receipt of Antiviral Medications and Changes in Laboratory Values

	β	95% CI
AST		
Antiviral		
None	Reference	
Ganciclovir	1.09	1.05–1.12
Foscarnet	1.01	0.97–1.05
Alt		
Antiviral		
None	Reference	
Ganciclovir	1.07	1.03–1.11
Foscarnet	0.94	0.90–0.99
Alp		
Antiviral		
None	Reference	
Ganciclovir	1.03	1.01–1.05
Foscarnet	0.95	0.93–0.98
Bun		
Antiviral		
None	Reference	
Ganciclovir	1.04	1.02–1.06
Foscarnet	1.32	1.29–1.35
Creatinine		
Antiviral		
None	Reference	
Ganciclovir	1.00	0.98–1.01
Foscarnet	1.14	1.12–1.16

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen.

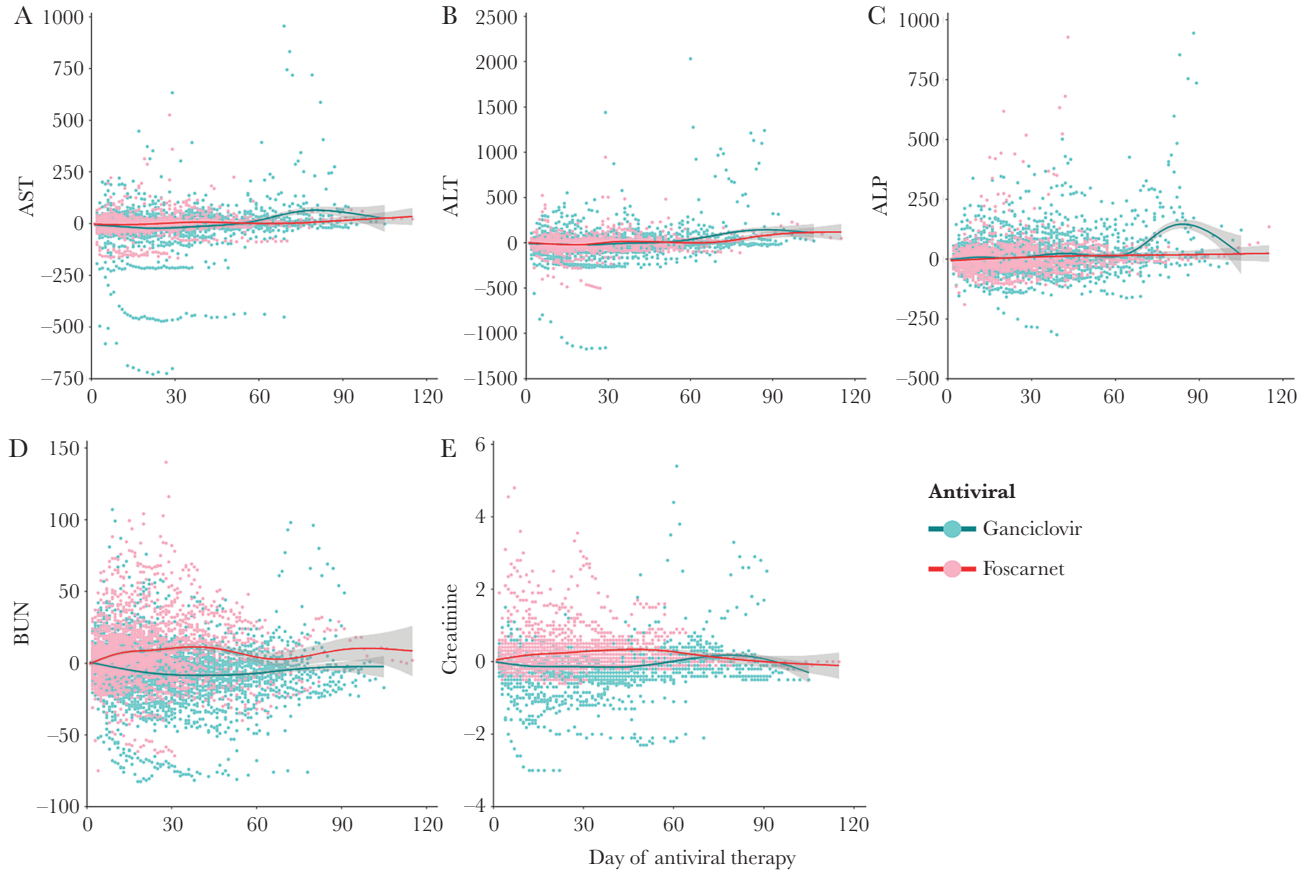

Figure 2. Trends in laboratory values by day of antiviral therapy with ganciclovir and foscarnet. The changes in selected serum laboratory measures are shown over time by day of therapy with ganciclovir or foscarnet. Points represent the change from the baseline laboratory value at the start of therapy. Fitted lines were estimated by the restricted maximum likelihood, with error shading representing 95% CIs. A, Serum aspartate aminotransferase. B, Serum alanine aminotransferase. C, Serum alkaline phosphatase. D, Blood urea nitrogen. E, Serum creatinine. Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen.

CI, 5%–12%) increase in AST, a 7% increase in ALT (95% CI, 3%–11%), and a 3% increase in ALP (95% CI, 1%–5%) per patient-day of therapy compared with no antiviral therapy, and foscarnet was associated with a 6% decrease in ALT (95% CI, 1%–10%) and a 5% decrease in ALP (95% CI, 7%–2%).

DISCUSSION

We described the incidence of and risk factors for CMV viremia after HSCT in the largest pediatric cohort studied to date. Without antiviral prophylaxis, CMV viremia occurred in approximately one-quarter of children in the 100 days after HSCT. We found that older age, male sex, non-Black, non-White race, umbilical cord blood transplant, and CMV seropositivity in either the recipient or donor were associated with an increased risk of CMV viremia. Finally, we identified distinct toxicity profiles associated with receipt of ganciclovir and foscarnet in this patient population that could be used to inform treatment decisions for children with CMV viremia after HSCT.

Current estimates of the incidence of CMV viremia in children after HSCT vary widely, from 13% among a Belgian cohort of 65 pediatric allogeneic HSCT recipients to 46% among a Greek cohort of 110 pediatric allogeneic and autologous HSCT recipients [9–11, 21–23]. This wide range is likely an effect of small sample sizes, differing transplantation practices, and geographical differences in CMV seroprevalence [24]. The incidence of CMV viremia in our cohort was within the range reported by prior pediatric studies and slightly lower than incidence estimates of 36%–39% among adult HSCT recipients [5, 7]. The lower incidence in our cohort is likely due to the large proportion of CMV-seronegative umbilical cord blood donors and HSCT recipients who had not yet experienced primary CMV infection, as well as a shorter period of follow-up for our cohort compared with adult studies. While the majority of episodes of CMV viremia in our cohort were likely due to reactivation or donor-derived infection, we did identify a higher cumulative incidence of primary CMV infection in D-/R- transplants (10%) than has been reported in previous pediatric studies (2%–5%) [10, 21, 23]. Notably, patients in our study were not hospitalized for the duration of the study period, suggesting that some of these primary CMV infections may have occurred outside of the hospital environment, and we

additionally cannot exclude false-negative serological testing, CMV transmission via blood transfusion products, or nosocomial infections. Although prior studies suggest that CMV reactivation and viremia are associated with increased mortality in adult allogeneic HSCT recipients, we found that all-cause mortality at 2 years after HSCT was similar in children who experienced CMV viremia and those who did not [25, 26]. While this finding may result from the relatively small number of cases of CMV viremia in our cohort, the lack of an association between CMV viremia and mortality suggests that preemptive therapy is a successful strategy for preventing excess mortality related to CMV in children.

CMV seropositivity is an established risk factor for CMV viremia after HSCT. In large retrospective adult studies, R+/D- transplants have been associated with the highest risk for CMV reactivation, followed by R+/D+ transplants [8, 26]. A similar risk hierarchy of donor and recipient seropositivity has not been determined for children; however, CMV seropositivity in the recipient or donor has consistently been a risk factor for CMV infections in pediatric studies [9–11, 21–23]. Our findings confirm the importance of CMV seropositivity in pediatric HSCT recipients while suggesting that R+/D+ serostatus transplants may have a particularly high risk of CMV viremia. Other pediatric studies have reported a high risk of CMV infections among R+/D+ transplants compared with transplants with other serostatus combinations [9, 27], suggesting that donor CMV seropositivity may be less protective against CMV viremia in children than in adults [28]. Taken together, our findings of CMV viremia in children after HSCT can inform optimal CMV serostatus recipient–donor pairings and CMV prophylaxis strategies.

While risk factors for CMV viremia can inform screening and preventive strategies, prior studies evaluating pediatric HSCT patients largely failed to identify associations between patient or transplant characteristics and CMV viremia beyond CMV serostatus [10, 22, 29]. A small cohort study of pediatric HSCT recipients reported more CMV infections among children with older age, leukemia, allogeneic HSCT, exposure to antithymocyte globulin, and acute GVHD; however, in multivariable analyses, these factors were not independently associated with CMV viremia [23]. We identified several risk factors for CMV viremia in our cohort, including patient age, sex, race, and donor cell source. The association between an umbilical cord blood donor and CMV viremia is likely due to the prolonged period of immunosuppression and delayed recovery of CMV-specific T-cell immunity among recipients of these transplants compared with recipients of allogeneic transplants from a bone marrow donor source or autologous HSCT recipients [30]. The effects of patient age may in part be explained by differences in CMV-specific T-cell immunity between young children and adults and the relative importance of donor or recipient T-cell function in controlling CMV viremia after HSCT [6, 31]. Finally, the increased risk of CMV viremia observed with male sex and non-Black minority race could be related to donor selection. In particular, higher degrees of HLA mismatch may necessitate increased use of immunosuppressive medications in these children, which could in turn increase the risk for CMV reactivation [4, 32]. While verifying the mechanisms underlying these risk factors is beyond the scope of the current work, our study identifies several unique factors that may influence CMV risk after HSCT and that warrant further study.

Ganciclovir and foscarnet are the mainstays of CMV therapy after HSCT; however, there is a notable lack of safety data for these antivirals for use in children. Through this retrospective study, we sought to provide real-world experience regarding the safety of these antivirals in children. We observed higher incidences of thrombocytopenia, electrolyte and glucose disturbances, and renal impairment in children treated with foscarnet compared with those treated with ganciclovir. While most of these AEs are consistent with data from adult studies, the frequency of thrombocytopenia events was greater than previously reported in adults [33]. Notably, foscarnet was generally initiated earlier after HSCT than ganciclovir and at a time when graft function likely remained relatively poor. Consistent with a prior report, we did not observe a difference in the rate of leukopenia between ganciclovir and foscarnet, suggesting that leukopenia may be an underrecognized toxicity associated with foscarnet use in children [15]. Finally, there were more renal AEs and larger increases in serum BUN and creatinine over time associated with foscarnet exposure, confirming the substantial nephrotoxicity of foscarnet in children. Importantly, there is recent evidence to suggest that there is a non-dose-dependent association between foscarnet exposure and glomerular filtration rates at 6 and 12 months after HSCT [34]. This potential long-term effect of foscarnet is particularly concerning for children, as renal function progressively declines with age, and an accelerated decline in glomerular filtration rate could lead to early progression to end-stage renal disease [35].

While foscarnet was associated with thrombocytopenia and renal AEs, ganciclovir was associated with gastrointestinal-related toxicity, including elevations of serum AST, ALT, and ALP levels. Similar findings were reported among neonates in a phase II trial of ganciclovir for the treatment of congenital CMV, in which >30% of neonates experienced clinically significant elevations in AST, ALT, and conjugated bilirubin [36]. Interestingly, other studies of ganciclovir use in infants have shown improvement in these laboratory measures with the effective treatment of CMV-associated hepatitis [37, 38]. Evidence of hepatotoxicity in adults receiving ganciclovir is limited to case reports, in which other hepatotoxic medication exposures and concomitant infection may have contributed to laboratory abnormalities [39–41]. Given the lack of evidence of hepatotoxicity associated with receipt of ganciclovir in adult HSCT recipients, our findings suggest that ganciclovir-associated elevations

in liver enzymes may be an underappreciated AE of ganciclovir use in pediatric populations and highlight the need for additional safety data for both currently available and new antivirals in pediatric patients.

Our study has several notable limitations. First, we focused on CMV viremia and did not distinguish between CMV infection and CMV end-organ disease. Given that the vast majority of pediatric transplant centers use a preemptive approach for CMV management after HSCT, our focus on CMV viremia is likely to be broadly generalizable to current practice. Second, 2 diagnostic assays were used during different periods of the study. While the level of CMV DNA tends to be higher in whole-blood samples, the PCR assay used in the later years of this study was likely more sensitive in detecting CMV viremia, especially at lower viral loads [42]. This may have led to more CMV viremia diagnoses in later years, though year of transplant was not an independent risk factor for CMV viremia at 100 days. Our analyses also did not account for GVHD diagnosis and treatment or other immunosuppressive therapies. Additionally, we did not have data on neutrophil and lymphocyte counts, and we thus used total WBC as a surrogate for neutropenia and lymphopenia. We also chose to focus statistical modeling on gastrointestinal and renal laboratory values because we anticipated that other laboratory parameters would be impacted by transfusions or other supportive care measures in this population. Finally, inherent to the retrospective study design, patients were not randomized to specific antiviral therapy, and the observed AEs may not be directly related to antiviral exposure.

In conclusion, we found that CMV viremia was common among pediatric HSCT recipients and that children who are older, male, from a non-Black racial minority group, who receive an umbilical cord blood transplant, and who are CMV-seropositive or have a CMV-seropositive donor are at the highest risk of CMV viremia. With our current institutional practices, including preemptive therapy for CMV viremia, children who develop CMV viremia during the first 100 days after HSCT are not at higher risk of all-cause mortality at 2 years after HSCT. We also report that ganciclovir and foscarnet are associated with specific toxicities in children, including hepatotoxicity associated with ganciclovir and leukopenia associated with foscarnet, highlighting the need to consider patient characteristics and baseline organ function in selecting antiviral therapy for CMV infection. Finally, our findings highlight the need for children to be included in clinical trials of antivirals for CMV prophylaxis or treatment to facilitate the development of strategies to reduce the burden of CMV infection in pediatric HSCT recipients.

Acknowledgments

Financial support. This work was supported by the National Institute of Child Health and Human Development of the National Institutes of Health (T32HD094671 to S.M.H.), the National Human Genome Research Institute of the National Institutes of Health (5T32HG008955-04 to S.M.H.), and a National Institutes of Health Career Development Award (K23-AI135090 to M.S.K.).

Potential conflicts of interest. The authors have no conflicts of interest to disclose. All 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.

Author contributions. S.M.H., R.R.Y., J.S.T., and M.S.K. designed the study. S.M.H., J.S.T., K.J., R.V., and F.M.S. collected and interpreted data. S.M.H. and R.R.Y. performed data analysis. S.M.H., F.M.S., P.L.M., N.J.C., and M.S.K. interpreted data. S.M.H. prepared the initial draft of the manuscript. All authors critically reviewed and contributed to subsequent versions before approving the final manuscript for submission.

Patient consent. The study protocol was approved by the Duke University Institutional Review Board. This study did not include factors that necessitated patient consent.

References

1. Solano C, Vázquez L, Giménez E, et al. Cytomegalovirus DNAemia and risk of mortality in allogeneic hematopoietic stem cell transplantation: analysis from the Spanish Hematopoietic Transplantation and Cell Therapy Group. Am J Transplant **2021**; 21:258–71.
2. Ljungman P, de la Camara R, Robin C, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis **2019**; 19:e260–72.
3. Jang JE, Hyun SY, Kim YD, et al. Risk factors for progression from cytomegalovirus viremia to cytomegalovirus disease after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **2012**; 18:881–6.
4. Boeckh M, Nichols WG, Papanicolaou G, Rubin R, Wingard JR, Zaia J. Cytomegalovirus in hematopoietic stem cell transplant recipients: current status, known challenges, and future strategies. Biol Blood Marrow Transplant **2003**; 9:543–58.
5. Osarogiagbon RU, Defor TE, Weisdojf MA, Erice A, Weisdorf DJ. CMV antigenemia following bone marrow transplantation: risk factors and outcomes. Biol Blood Marrow Transplant **2000**; 6:280–8.
6. Camargo JF, Komanduri KV. Emerging concepts in cytomegalovirus infection following hematopoietic stem cell transplantation. Hematol Oncol Stem Cell Ther **2017**; 10:233–8.
7. George B, Pati N, Gilroy N, et al. Pre-transplant cytomegalovirus (CMV) serostatus remains the most important determinant of CMV reactivation after allogeneic hematopoietic stem cell transplantation in the era of surveillance and preemptive therapy. Transpl Infect Dis **2010**; 12:322–9.
8. Schmidt-Hieber M, Tridello G, Ljungman P, et al. The prognostic impact of the cytomegalovirus serostatus in patients with chronic hematological malignancies after allogeneic hematopoietic stem cell transplantation: a report from the Infectious Diseases Working Party of EBMT. Ann Hematol **2019**; 98:1755–63.
9. Düver F, Weißbrich B, Eyrich M, Wölfl M, Schlegel PG, Wiegering V. Viral reactivations following hematopoietic stem cell transplantation in pediatric patients - a single center 11-year analysis. PLoS One **2020**; 15:e02284511–17.
10. Bordon V, Bravo S, Van Renterghem L, et al. Surveillance of cytomegalovirus (CMV) DNAemia in pediatric allogeneic stem cell transplantation: incidence and outcome of CMV infection and disease. Transpl Infect Dis **2008**; 10:19–23.
11. Tsoumakas K, Giamaiou K, Goussetis E, et al. Epidemiology of viral infections among children undergoing hematopoietic stem cell transplant: a prospective single-center study. Transpl Infect Dis **2019**; 21:e13095.
12. Goodrich JM, Mori M, Gleaves CA, et al. Early treatment with ganciclovir to prevent cytomegalovirus disease after allogeneic bone marrow transplantation. N Engl J Med **1991**; 325:1601–7.
13. Zhou W, Longmate J, Lacey SF, et al. Impact of donor CMV status on viral infection and reconstitution of multifunction CMV-specific T cells in CMV-positive transplant recipients. Blood **2009**; 113:6465–76.
14. Reusser P, Einsele H, Lee J, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood **2002**; 99:1159–64.
15. Moretti S, Zikos P, Van Lint MT, et al. Foscarnet vs ganciclovir for cytomegalovirus (CMV) antigenemia after allogeneic hemopoietic stem cell transplantation (HSCT): a randomised study. Bone Marrow Transplant **1998**; 22:175–80.
16. Wattles BA, Kim AJ, Cheerva AC, Lucas KG, Elder JJ. Cytomegalovirus treatment in pediatric hematopoietic stem cell transplant patients. J Pediatr Hematol Oncol **2017**; 39:241–8.

17. Marshall BC, Koch WC. Antivirals for cytomegalovirus infection in neonates and infants: focus on pharmacokinetics, formulations, dosing, and adverse events. Pediatr Drugs **2009**; 11:309–21.
18. Glotzbecker B, Duncan C, Alyea E, Campbell B, Soiffer R. Important drug interactions in hematopoietic stem cell transplantation: what every physician should know. Biol Blood Marrow Transplant **2012**; 18:989–1006.
19. Horvath MM, Winfield S, Evans S, Slopek S, Shang H, Ferranti J. The DEDUCE Guided Query tool: providing simplified access to clinical data for research and quality improvement. J Biomed Inform **2011**; 44:266–76.
20. Kleinbaum DG, Klein M. Survival Analysis: A Self-Learning Text. 3rd ed. Springer; **2012**.
21. Jaing TH, Chang TY, Chen SH, et al. Factors associated with cytomegalovirus infection in children undergoing allogeneic hematopoietic stem-cell transplantation. Medicine (Baltim) **2019**; 98:e14172.
22. Patel SR, Ridwan RU, Ortín M. Cytomegalovirus reactivation in pediatric hemopoietic progenitors transplant: a retrospective study on the risk factors and the efficacy of treatment. J Pediatr Hematol Oncol **2005**; 27:411–5.
23. Wu J, Ma H, Lu C, et al. Science direct risk factors and outcomes of cytomegalovirus viremia in pediatric hematopoietic stem cell transplantation patients. J Microbiol Immunol Infect **2017**; 50:307–13.
24. Zuhair M, Smit GSA, Wallis G, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: a systematic review and meta-analysis. Rev Med Virol **2019**; 29:e2034.
25. Green ML, Leisenring W, Xie H, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol **2016**; 3:e119–27.
26. Teira P, Battiwalla M, Ramanathan M, et al. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. Blood **2016**; 127:2427–38.
27. Hayes M, Newman AM, Boge CLK, et al. Incidence of CMV infection and disease and adverse events associated with antiviral therapy in a retrospective cohort of allogeneic hematopoietic cell transplant recipients at an academic children's hospital. J Pediatric Infect Dis Soc **2021**; 10:910–8.
28. Ljungman P, Brand R, Hoek J, et al. Donor cytomegalovirus status influences the outcome of allogeneic stem cell transplant: a study by the European Group for Blood and Marrow Transplantation. Clin Infect Dis **2014**; 59:473–81.
29. Hussein AA, Al-Antary ET, Najjar R, Al-Hamdan DS, Al-Zaben A, Frangoul H. Incidence and risk factors for cytomegalovirus (CMV) reactivation following autologous hematopoietic stem cell transplantation in children. Pediatr Blood Cancer **2015**; 62:1099–101.
30. Bejanyan N, Vlasova-St Louis I, Mohei H, et al. Cytomegalovirus-specific immunity recovers more slowly after cord blood transplantation compared with matched sibling donor allogeneic transplantation. Transplant Cell Ther **2021**; 27:187.e1–4.
31. Tu W, Chen S, Sharp M, et al. Persistent and selective deficiency of CD4 + T cell immunity to cytomegalovirus in immunocompetent young children. J Immunol **2004**; 172:3260–7.
32. Seu P, Winston DJ, Holt CD, Kaldas F, Busuttil RW. Long-term ganciclovir prophylaxis for successful prevention of primary cytomegalovirus (CMV) disease in CMV-seronegative liver transplant recipients with CMV-seropositive donors. Transplantation **1997**; 64:1614–7.
33. Foscarnet. Package insert. Clinigen Healthcare Ltd.; **2014**.
34. Foster GG, Grant MJ, Thomas SM, et al. Biology of blood and marrow transplantation treatment with foscarnet after allogeneic hematopoietic cell transplant (Allo-HCT) is associated with long-term loss of renal function. Biol Blood Marrow Transplant **2020**; 26:1597–606.
35. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA **2014**; 311:2518–31.
36. Whitley RJ, Cloud G, Gruber W, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis **1997**; 175:1080–6.
37. Kimberlin DW, Lin CY, Sánchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr **2003**; 143:16–25.
38. Doan TTM, Phung TTB, Pham HV, Pham SH, Nguyen LT. Effect of ganciclovir for the treatment of severe cytomegalovirus-associated pneumonia in children without a specific immunocompromised state. BMC Infect Dis **2013**; 13:424.
39. Shea BF, Hoffman S, Sesin GP, Hammer SM. Ganciclovir hepatotoxicity. Pharmacotherapy **1987**; 7:223–6.
40. Heinemann M-H. Long-term intravitreal ganciclovir therapy for cytomegalovirus retinopathy. Arch Ophthalmol **1989**; 107:1767–72.
41. Figge HL, Bailie GR, Briceland LL, Kowalsky SF. Possible ganciclovir-induced hepatotoxicity in patients with AIDS. Clin Pharm **1992**; 11:432–4.
42. Hanson KE, Reller LB, Kurtzberg J, Horwitz M, Long G, Alexander BD. Comparison of the Digene Hybrid Capture System Cytomegalovirus (CMV) DNA (version 2.0), Roche CMV UL54 analyte-specific reagent, and QIAGEN RealArt CMV LightCycler PCR reagent tests using AcroMetrix OptiQuant CMV DNA quantification panels and specimens from allogeneic-stem-cell transplant recipients. J Clin Microbiol **2007**; 45:1972–3.