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Cytomegalovirus Urinary Excretion in Children with Congenital and Postnatally Acquired Infection

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Abstract

Background: Cytomegalovirus (CMV) infection in children is associated with prolonged viral excretion in urine and saliva. This study characterizes CMV urinary excretion in children with congenital (cCMV) and postnatally acquired CMV infection.

Methods: Children with virologically confirmed cCMV (75 symptomatic and 105 asymptomatic at birth) and 51 children without cCMV were followed through median 11, 18 and 17 years of age, respectively. In children with cCMV, duration of CMV excretion was defined as uninterrupted positive results from initial to last positive culture, and recurrent CMV excretion as ≥ 1 positive following >1 negative result. CMV urinary excretion in children without cCMV was defined as resulting from postnatally acquired CMV infection.

Results: Mean duration of persistent CMV urinary excretion in children with cCMV was 1.9 (maximum 8.7) years for symptomatic and 2.8 (maximum 9.8) years for asymptomatic children ($P=0.011$). Mean duration of CMV excretion was not statistically different for 17 symptomatic children treated with ganciclovir (2.4 years) compared with 58 untreated (1.8 years); $P=0.356$. Recurrent excretion occurred in 19 (25%) symptomatic and 21 (20%) asymptomatic children, at mean age 4.0 and 6.2 years, respectively ($P=0.084$). In 16 (31%) children with postnatally acquired CMV infection, CMV urinary excretion began at mean age 1.8 (range 0.3–7.3) years.

Conclusions: Both symptomatic and asymptomatic cCMV were associated with persistent long-term CMV excretion in urine, which was significantly longer in asymptomatic cCMV and not influenced by ganciclovir treatment in symptomatic cCMV. CMV urinary excretion was common in young children without cCMV, suggesting rapid CMV acquisition in childhood.

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Keywords

Cytomegalovirus; congenital; urinary excretion; culture

Introduction

In the United States, approximately 1 in 200 children are born with congenital cytomegalovirus (cCMV) infection [1, 2]. By 5 years of age, roughly 1 in 3 children are seropositive for cytomegalovirus (CMV) immunoglobulin G, indicating acquisition of CMV infection early in life [3]. Both congenital and postnatally acquired CMV infection in children are associated with prolonged viral excretion in urine and saliva [4]. Limited data suggest that viral excretion is shorter in children born with symptomatic rather than asymptomatic cCMV [5], and in children with vs. without sensorineural hearing loss [6]. Postnatally acquired CMV infection, which is strongly associated with breastfeeding and childcare groups, results in a rapid increase in the pool of infectious children who may pose a risk of infection to pregnant people [7]. Annual seroconversion rates are highest among parents of children shedding CMV (24%) and daycare providers (8.5%) [4].

In children with cCMV, viral excretion peaks at birth and typically decreases steadily over the next 5 years of life [5]. These data come from a few small studies conducted over short periods of follow-up and relatively little is known about the long-term duration and pattern of CMV urinary excretion in children with cCMV [4, 5, 8–10]. One study has evaluated the longer-term urinary and salivary excretion in children with cCMV but did not include a comparison group in the follow-up [11]. In children without cCMV, the frequency of CMV excretion varies by breastfeeding and childcare attendance and is in the range of 10–25%, peaking in the second year of life and lasting for 2 or more years [4, 12–14].

This study describes the long-term pattern and duration of CMV urinary excretion in children with cCMV, born with or without symptomatic infection at birth, and onset of CMV urinary excretion in children born without cCMV.

Methods

The Houston Congenital CMV Longitudinal Study started in 1982 and followed participants through adolescence [15, 16]. A total of 237 children participated in the study: 77 with symptomatic and 109 with asymptomatic cCMV at birth, and 51 children, who were CMV-negative at birth, enrolled as a comparison group without cCMV. Children with cCMV (i.e. a positive urine CMV culture in the first 3 weeks of life) were classified as symptomatic at birth if they had at least one of the following clinical or laboratory features: intrauterine growth restriction, small for gestational age, microcephaly, petechiae, jaundice, splenomegaly, hepatomegaly, seizures, chorioretinitis, pneumonia, thrombocytopenia, hepatitis, or direct hyperbilirubinemia. Seventy-three (95%) children with symptomatic cCMV were identified through referrals from Houston-area hospitals during 1982–2005.

Children with cCMV and none of the clinical or laboratory features previously mentioned were categorized as asymptomatic; 92 (84%) were identified through hospital-based screening during 1982–1992 [17] and 17 (16%) through referrals, typically after a diagnosis of primary CMV infection during pregnancy. Among children without cCMV (i.e. who had a negative urine CMV culture in the first 3 days of life) enrolled in the study as a comparison group, 42 (82%) were selected from the screened cohort (within 298 CMV-negative newborns randomly preselected within 6 days of birth of a CMV-positive newborn, born during 1982–1992), and 9 (18%) were either siblings of children with symptomatic cCMV or born to women diagnosed with CMV infection during pregnancy but CMV-negative (born during 1982–2005) [15]. A prior publication described maternal infections during pregnancy [18]. The study was approved by the Baylor College of Medicine Institutional Review Board and informed consent was obtained from parents prior to enrollment in the study. Long-term outcomes, including hearing loss, vision impairment, and cognitive outcomes in children with asymptomatic and symptomatic cCMV, with and without ganciclovir treatment, have been previously described [6, 15, 16, 18–21].

As part of the longitudinal study, urine specimens were collected for CMV culture at each study follow-up visit (per protocol, annually until 6 years of age, and once during elementary, middle and high school years) for children with and without cCMV [6, 15], and processed shortly after, beginning in August 1982. CMV was cultured using traditional virologic technique of using human foreskin fibroblasts (not shell vial or molecular techniques), incubated for 28 days, examined daily under light microscopy for typical cytopathic effect associated with CMV, based on the presence of focal areas of large, rounded, refractile, CMV infected cells. Presumptively positive cell cultures for CMV were scraped and stained with fluorescein labeled CMV antibody and confirmed with virus specific immunofluorescence assay [22, 23]. This method, standard during the time of the study, was also used for screening newborns for cCMV in the study [24].

A prior analysis including a subset of this cohort (12 children with symptomatic and 58 children with asymptomatic cCMV) examined the relationship between duration of CMV urinary excretion and growth, neurodevelopment, and hearing loss presence and progression by 6 years of age [6]. In this analysis, we included all children who had at least 1 urine CMV culture performed after 29 days of age and through December of 2013; 6 children (2 symptomatic and 4 asymptomatic) without at least 1 follow-up urine culture were excluded. Children with cCMV were followed through median age of 11 and 18 years, respectively, and children without cCMV through 17 years (Table 1). CMV excretion was defined as a positive urine CMV culture. In children with cCMV, duration of CMV excretion was defined as uninterrupted positive results from initial to last positive culture, and recurrent CMV excretion as at least 1 positive following at least 1 negative result. Onset of CMV urinary excretion in children born without cCMV was defined as postnatally acquired CMV infection.

Analysis was conducted using IBM SPSS Statistics Version 21 (IBM Corporation, Armonk, NY). Demographic features were described using frequencies and measures of central tendency and compared between groups using Chi-Square tests and t-tests. Duration of follow-up, number of cultures performed, and duration of CMV urinary excretion

were described using means and ranges and compared using parametric tests (ANOVA for comparisons between 3 groups and t-tests for comparisons between 2 groups). The frequency of CMV excretion (for all children, not only those continuously excreting) by age was presented graphically to visually display the differences between symptomatic, asymptomatic, and non-cCMV groups, as well as between symptomatic with and without ganciclovir treatment. Recurrent CMV excretion was described using frequencies and age at recurrence.

Results

The analysis included 75 children with symptomatic cCMV (17 received ganciclovir), 105 with asymptomatic cCMV and 51 children without cCMV who had serial urine CMV cultures performed. There were demographic differences in the study groups (Table 2). Symptomatic and asymptomatic cCMV groups were each approximately 50% male but the non-cCMV group were more likely to be male than female, albeit the difference was not statistically significant. The mothers of children with symptomatic cCMV were significantly younger than mothers of asymptomatic or non-cCMV children. All groups were predominantly white non-Hispanic but children with symptomatic cCMV were more likely to be white Hispanic than the other groups.

Duration of follow-up, number of cultures, and duration of CMV excretion were different among the three groups (Table 1). Mean duration of persistent CMV urinary excretion was 1.9 years (maximum 8.7 years) for symptomatic and 2.8 years (maximum 9.8 years) for asymptomatic cCMV children ($P=0.011$). Duration of CMV excretion was similar for symptomatic children who were treated vs. not treated with ganciclovir (2.4 vs 1.8 years, $P=0.356$).

Recurrent CMV urinary excretion occurred later in asymptomatic than symptomatic cCMV but with similar frequency (Table 3). Recurrent CMV urinary excretion occurred in 19 (25%) of 75 symptomatic (mean age 4.0 years), and 21 (20%) of 105 asymptomatic (mean age 6.2 years) cCMV ($P=0.084$). Postnatally acquired CMV infection was detected in 16 (31%) of 51 children without cCMV, and CMV urinary excretion started at mean age 1.8 years (range 0.3 to 7.3 years).

The frequency of CMV urinary excretion varied by age; in the first year of life, it was the highest for children with cCMV the lowest for those without cCMV (Figure 1). For all groups, the frequency of excretion declined through age 8 years and remained low thereafter. The frequency of excretion appeared to be higher for asymptomatic than symptomatic cCMV children before 2 years of age and between the ages of 4 to 8 years. The frequency of CMV urinary excretion in symptomatic children varied with ganciclovir treatment (Figure 2). Under the age of 1 year, the frequency of excretion was higher in the treated than untreated group, whereas after the age of 1 year, the frequency was higher in the untreated group. In both groups, frequency of CMV excretion after 1 year of age decreased until age 5 years and remained consistently low thereafter.

Discussion

Prior studies have described long-term hearing, vision, and cognitive outcomes of children in our cohort, including CMV urinary excretion for a subset of children with cCMV this cohort [6, 15, 16, 18–21]. In this study, we assessed the long-term pattern and duration of CMV urinary excretion in children with cCMV and onset of CMV urinary excretion in children born without cCMV. We found that both symptomatic and asymptomatic cCMV were associated with persistent long-term CMV urinary excretion, which was significantly longer in asymptomatic than symptomatic children and, among the latter group, was not influenced by ganciclovir treatment. Additionally, CMV urinary excretion was common in young children without cCMV, suggesting rapid CMV acquisition in childhood.

Previous studies have also found longer duration of excretion in asymptomatic than symptomatic children with cCMV [5]. Before the age of 5 years, the proportion of CMV-positive urine cultures has been found to be similar between children with asymptomatic and symptomatic cCMV but, between the ages of 5 and 8 years of age, children with asymptomatic cCMV have been found to have a higher proportion of CMV-positive urine cultures than children with symptomatic cCMV [5]. Consistent with these findings, our study also demonstrated that the proportion of CMV-positive urine cultures was again similar among asymptomatic and symptomatic children with cCMV, and low, after the age of 8 years.

Most asymptomatic children were identified through hospital-based newborn screening during 1982–1992, while most symptomatic children were identified through referrals and born up to 2005. Therefore, asymptomatic children were studied for longer than the symptomatic ones, raising the question as to whether a longer duration of follow-up contributed to the differential findings in duration of CMV urinary excretion. However, the mean duration of follow-up in the symptomatic group was longer than the age at which CMV urinary excretion declined. Specifically, children with a negative culture at any time would no longer meet criteria for continuous CMV excretion with future urine cultures, and the maximum duration of excretion in the asymptomatic group was less than the duration of follow-up for the symptomatic. Thus, it is unlikely that the differential follow-up periods influenced the group differences in the duration of excretion. It is more likely that the differential follow-up influenced the difference in recurrent excretion. It is possible that the true mean age of recurrence is older than 4 years for the symptomatic group.

Our study provides longitudinal data on long-term CMV urinary excretion among children with and without cCMV. CMV urinary excretion was detected by urine culture, which implies infectious virus as opposed to detection by PCR. An earlier study including a subset of the Houston cohort found that children who stopped excreting CMV before 4 years had a higher frequency of hearing loss and progressive hearing loss by 6 years of age than those excreting CMV for longer, but no association was found between long-term growth or cognitive outcome and duration of CMV urinary excretion [6]. Though the children in this study were born during 1982–2005, these data are still relevant and future analysis could include the full cohort. Most asymptomatic children were identified through hospital-based screening using urine samples which may be informative for current or proposed

introduction of cCMV newborn screening in a few US states and Canadian provinces [25, 26]. Although these programs are using CMV PCR testing in dried blood spots [27], the predictive value of neonatal blood viral load for long-term sequelae, especially in cohorts of children with cCMV identified through universal newborn screening, remains poorly understood and could be further investigated by state-based screening, follow-up, and surveillance programs. Furthermore, assessing the correlation of blood, saliva and urine viral loads with symptomatic disease at birth or long-term sequelae in children with cCMV identified through newborn screening may be helpful to inform clinical guidance.

Among children born without cCMV, nearly one-third acquired CMV infection, with CMV urinary excretion starting at mean age 1.8 years, suggesting rapid acquisition of CMV infection early in childhood. Another cohort study found that 31% of children <4 years of age were CMV IgG seropositive and half of them were excreting virus in urine or saliva when assessed by PCR [28]; children excreting CMV at the study enrollment were still excreting 11 to 12 weeks after at high, stable viral loads, especially in saliva [29]. The high prevalence of CMV excretion in children's saliva and urine represents an exposure risk to adults, including pregnant people, especially given the median interpregnancy interval (timing between a live birth and the next pregnancy) of 27 to 29 months in the United States [30]. One study documented a higher risk of cCMV infection with a shorter (<24 months) interval between births [31].

Our study has some limitations. First, we used urine CMV culture to define CMV excretion. In a review of 12 studies including urine and saliva cultures in children, CMV was more prevalent in urine than saliva cultures (mean difference 11.5%) [4]. CMV culture is neither 100% sensitive nor specific for the identification of CMV infection. However, CMV culture at the time of this study was the standard for CMV identification and the diagnostic accuracy should be similar between study groups. Second, our sample size was small and we did not assess CMV seroconversion. Third, CMV samples were not subtyped in this study, thus it is not possible to determine if repeated cultures in a single patient were the same or different viruses. For this reason, it is possible that the duration of excretion and frequency of recurrence is overestimated. However, this overestimation is not likely to have differed between study groups and therefore, should not influence the comparative findings. Though urine specimens were collected at each study follow-up visit, we did not evaluate potential triggers of CMV recurrence such as a recent episode of acute illness; none of the children, however, were deemed immunocompromised. Finally, because antiviral treatment was not the standard of care at the time, our cohort included treated and untreated symptomatic children. As previously described, symptomatic children were treated with ganciclovir for a median of 40 (range: 11–63) days and tended to have more severe disease than the untreated symptomatic children [32]. Thus, heterogeneity and the low number of children in the study subgroups precludes further conclusions.

From a public health perspective, cCMV-associated disabilities are the most relevant consequence of CMV infection and CMV has been a priority target for vaccine development for decades [33]. Data on CMV urinary excretion in children with cCMV and postnatally acquired CMV infection coupled with population-based seroprevalence estimates may be

useful to inform infectious disease modeling to assess optimal ages for vaccination, which will in turn inform vaccination policy.

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Data statement

Requests should be submitted to Principal Investigator Gail Demmler-Harrison (gdemmler@bcm.edu).

Abbreviations:

CMV	cytomegalovirus
cCMV	congenital cytomegalovirus

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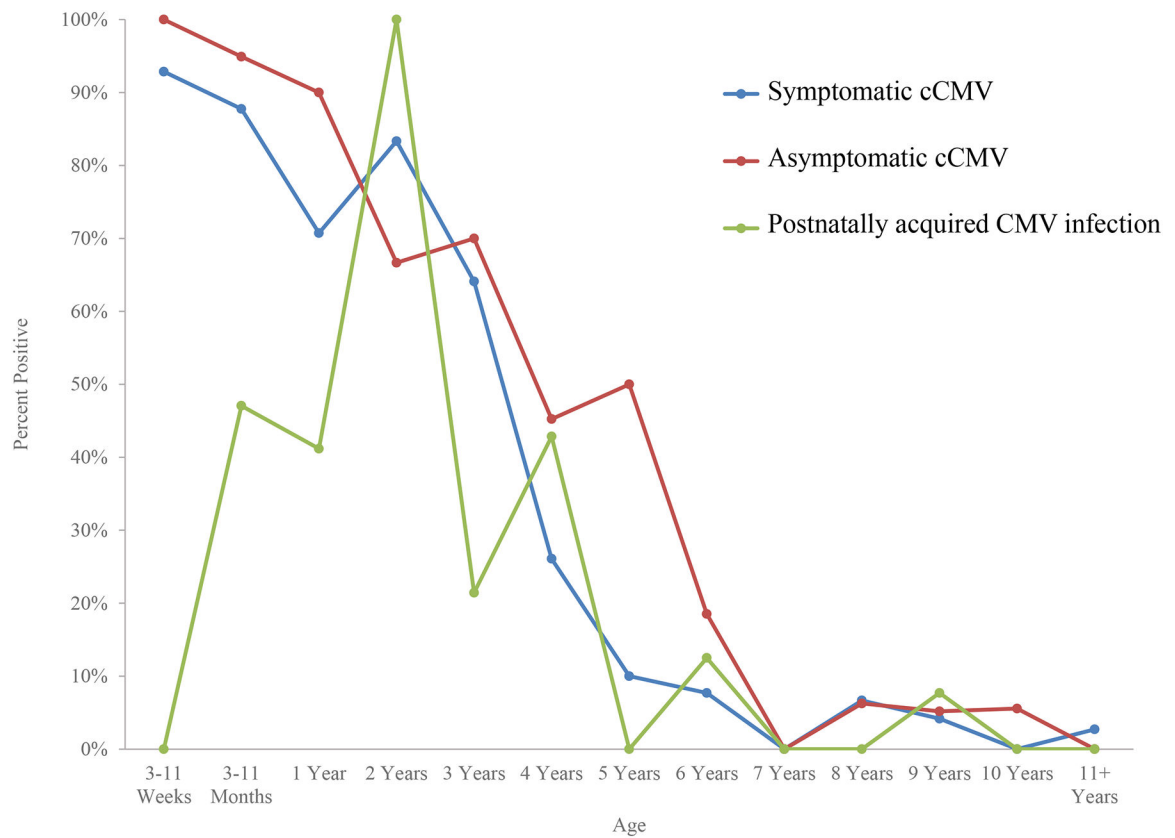


Figure 1.
Percentage of CMV-positive urines by age of test stratified by children with symptomatic or asymptomatic cCMV and children with postnatally acquired CMV infection.

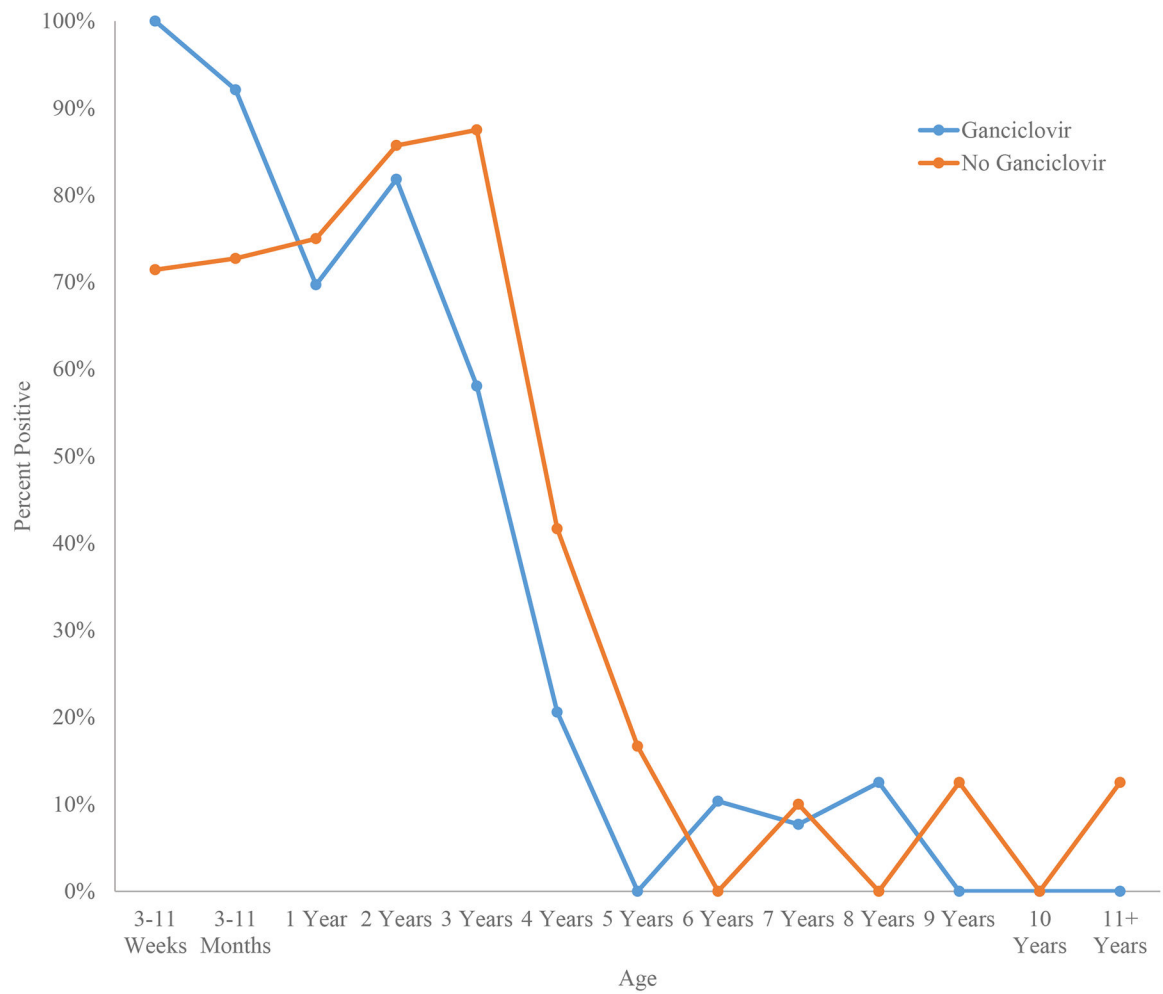


Figure 2.
Percentage of CMV-positive urines by age of test for children with symptomatic cCMV stratified by ganciclovir treatment.

Table 1.

Mean duration of CMV urinary excretion in all groups of children with and without cCMV and with or without ganciclovir treatment.

Category	N	Mean Duration of Excretion (range)	Mean Duration of Follow-up (range)	Mean Number of Cultures (range)
Symptomatic cCMV	75	1.9 yrs (Up to 8.7)	11.2 yrs (0.4 to 27.4)	7.9 (2 to 15)
Ganciclovir	17	2.4 yrs (Up to 7.7)	11.0 yrs (0.4 to 20.1)	9.8 (2 to 14)
No Ganciclovir	58	1.8 yrs (Up to 8.7)	11.2 yrs (0.4 to 27.4)	7.3 (2 to 15)
Asymptomatic cCMV	105	2.8 yrs (Up to 9.8)	18.1yrs (0.4 to 27.8)	8.0 (2 to 13)
No cCMV	51	Not Applicable	17.2 yrs (0.2 to 28.2)	5.1 (2 to 12)

P=0.011 for comparison of mean duration of CMV urinary excretion between children with symptomatic and asymptomatic cCMV and 0.356 between treated and untreated children with symptomatic cCMV.

For 16 (31%) children with postnatally acquired CMV infection, CMV urinary excretion started at mean age 1.8 years (range 0.3 to 7.3 years).

Table 2.

Demographic characteristics of children with symptomatic cCMV, asymptomatic cCMV, and without cCMV followed for CMV urinary excretion.

Characteristic	Symptomatic cCMV N=75	Asymptomatic cCMV N=105	No cCMV N=51	P-Value
Subject Gender				0.086
Male	37 (49%)	56 (53%)	35 (69%)	
Female	38 (51%)	49 (47%)	16 (31%)	
Maternal Age (Mean)	24 Years	28 Years	29 Years	<0.0001
Mother's Race/Ethnicity				0.001
White Non-Hispanic	43 (59%)	82 (78%)	44 (86%)	
Black Non-Hispanic	11 (15%)	14 (13%)	5 (10%)	
White Hispanic	19 (26%)	9 (9%)	2 (4%)	

Table 3.

Percentage of recurrent CMV urinary excretion in all groups of children with and without cCMV and with or without antiviral treatment.

	N	Recurrent Excretion	Mean Age at Recurrence
Asymptomatic cCMV	105	21 (20%)	6.2 yrs (0.9 to 17.2 yrs)
Symptomatic cCMV	75	19 (25%)	4.0 yrs (0.5 to 14.5 yrs)
Ganciclovir	17	6 (35%)	6.4 yrs (0.5 to 14.5 yrs)
No Ganciclovir	58	13 (22%)	2.9 yrs (0.9 to 7.6 yrs)

P=0.084 for comparison of mean age at recurrence of CMV urinary excretion between children with symptomatic and asymptomatic cCMV.