Positive Pretransplantation Cytomegalovirus Serology Is a Risk Factor for Cardiac Allograft Vasculopathy in Children

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Background—Cytomegalovirus (CMV) infection has been implicated as a cause of posttransplantation coronary artery disease in adults. The purpose of this retrospective observational study was to evaluate the effect of CMV on outcome after heart transplantation in children.

Methods and Results—Risk factors tested were recipient age, sex, and pretransplantation CMV serology; use of anti-CMV prophylaxis; posttransplantation evidence of CMV infection; and donor CMV serology. Transplantations were stratified traditionally according to CMV risk as low risk (recipient negative/donor negative), intermediate risk (recipient positive), and high risk (recipient negative/donor positive). Primary outcome measures were (1) development of coronary artery vasculopathy, (2) mortality (or graft loss) that occurred outside the early postoperative period, and (3) death (or graft loss) due to vasculopathy. Analysis was by proportional hazards modeling. A total of 165 children underwent heart transplantation, with a mean age at transplantation of 7.8 (SD 5.6) years. Thirty-two children had laboratory evidence of CMV infection after transplantation, but only 6 developed CMV disease or syndrome. Traditional CMV risk stratification correlated well with CMV infection but did not predict mortality, coronary artery disease, or coronary death. In contrast, positive recipient CMV was the only independent predictor of all 3 outcome measures: coronary artery disease (hazard ratio 3.6), all-cause mortality (partial hazard ratio 4.1), and coronary death (hazard ratio 4.6).

Conclusions—in children, pretransplantation recipient CMV status is a more powerful predictor for the development of clinically significant vasculopathy and subsequent death than traditional risk stratification. This phenomenon warrants further investigation. (Circulation. 2007;115:1798-1805.)

Key Words: coronary disease ■ pediatrics ■ transplantation ■ viruses

Cardiac allograft vasculopathy is an important cause of morbidity and mortality in heart transplant recipients. In adults, it is detectable on angiography in more than 40% of recipients at 5 years after transplantation. On intravascular ultrasonography, however, rapid progression of coronary intimal thickening is seen in 37% of adult recipients after only 1 year. Furthermore, the progression of such intimal thickening is a powerful predictor of all-cause mortality. In children, angiographic evidence of vasculopathy is present in only 17% of recipients at 5 years, but in contrast to adults (in whom malignant disease is a more common cause of death), vasculopathy is the leading cause of death and retransplantation beyond the first year after transplantation.

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Outside transplantation medicine, a substantial amount of evidence now exists that local and systemic inflammation may play a role in the initiation and progression of atherosclerosis and ischemic heart disease. Cytomegalovirus (CMV) is an intracellular pathogen that has been implicated as a cause of chronic local inflammation within the atherosclerotic plaque. It is postulated that a periodically active latent CMV infection within the coronary arterial walls is responsible for modulating inflammation within the atherosclerotic plaque. Both serological CMV reactivation and CMV infection occur more commonly in the immunosuppressed transplant recipient. Hence, it would be expected that CMV would be even more important in the pathogenesis of cardiac allograft vasculopathy. The first report of an association between CMV infection and vasculopathy in adults was in 1989. This association in adult recipients has been confirmed subsequently. Furthermore, documented CMV infection has been shown to be associated with impaired coronary endothelial function in heart transplant recipients. A number of reasons can be offered why it is important to consider the role of CMV in the development of vasculopathy.
in children separately. First, less donor atherosclerosis (because of younger donors) and fewer recipient risk factors for the development of atherosclerosis exist. This allows for a purer assessment of risk factors for developing vasculopathy, with less confounding by concurrent atherosclerotic disease. Second, vasculopathy is the leading cause of late death (beyond 1 year) in children but not in adults. Third, the majority of children, in contrast to adults, are seronegative for CMV.

Traditionally, we have stratified CMV risk as low (recipient negative/donor negative), intermediate (recipient positive), and high (recipient negative/donor positive). This retrospective observational study was designed to interrogate the relationship between CMV, posttransplantation survival, and vasculopathy in children. It was initially postulated that both the development of vasculopathy and graft survival would be predicted by the pretransplantation risk stratification for developing CMV infection.

Methods

Data were collected from the records of all patients undergoing heart transplantation at Great Ormond Street hospital from the start of the program in February 1989 until July 2003. Retransplantations were excluded from the present study. Follow-up data were collected until the end of September 2003. Sources of information were patient case notes, laboratory databases, and copies of records held by UK Transplant. The study was approved and registered by our institution’s research and development department.

Risk factors tested were recipient age, sex, and pretransplantation CMV serology; era of transplantation; use of anti-CMV prophylaxis; use of anti-lymphocyte globulin; number of episodes of acute rejection in the first 6 months after transplantation; laboratory evidence of posttransplantation CMV infection; clinical evidence of posttransplantation CMV infection; and donor CMV serology. Recipient and donor CMV serology were recorded as positive (antibodies present) or negative. The era of the transplantation was defined by how long ago the transplantation took place (in years). This parameter was included in the analysis to allow for possible improvement in outcome over the course of the program. If anti-CMV prophylaxis was given around the time of transplantation before any evidence of CMV infection, this was recorded (for example, ganciclovir, valganciclovir, or anti-CMV hyperimmune globulin). The use of anti-lymphocyte globulin, either as induction or rescue immunosuppression, was also recorded. Acute rejection was defined as any rejection (either biopsy proven or clinically suspected) that resulted in an increase of immunosuppression. It was quantified by the number of episodes of acute rejection episodes that occurred in the first 6 months after transplantation. Laboratory evidence of CMV infection was defined as demonstration of CMV antigen in body fluids (from urine, throat, or bufty coat) by DEAFF (detection of early antigen fluorescent foci), viral culture, or positive blood polymerase chain reaction for CMV. Seroconversion alone was not taken as evidence of CMV infection. Clinical evidence of CMV infection was either CMV disease or CMV syndrome. CMV disease was defined as evidence of CMV infection together with organ-specific disease (e.g., pneumonitis, colitis, or hepatitis). CMV syndrome was defined as evidence of CMV infection along with fever (≥38°C on 2 occasions at least 24 hours apart) and 1 or more of the following: malaise, leucopenia, atypical lymphocytosis, thrombocytopenia, or elevated hepatic enzymes.

Primary outcome measures were (1) vasculopathy, defined as development of cardiac allograft vasculopathy; (2) all-cause mortality, defined as death or retransplantation (excluding early mortality or graft loss within 6 months after transplantation); and (3) vasculopathy-related mortality, defined as death or retransplantation due to coronary artery disease. The presence of vasculopathy was confirmed by angiography, along with autopsy results (if performed and histology reports on explanted grafts (if the patient underwent retransplantation). Coronary angiography is routinely performed on annual review at our center starting 1 year after transplantation. Abnormalities on angiography are confirmed by a second observer and defined as mild if less than 50% in any branch and moderate if 50% or more in 1 primary vessel (or in branches of 2 vessels). Only unequivocal and consistent reports of vasculopathy on autopsy, histology, or 2 angiograms were recorded as confirmation of coronary disease. Cause of death was defined as being due to coronary artery disease if it was confirmed on autopsy or if an autopsy was not performed but coronary artery disease was given as the cause of death due to clinical indications. All-cause mortality conditional on survival to 6 months after transplantation was used as an outcome measure to avoid confounding by risk factors more pertinent to early postoperative mortality.

In the primary analysis, the effect of traditional risk stratification was tested for each of the outcome measures by (1) construction of Kaplan-Meier survival curves, (2) performance of a series of univariate Cox regression analyses, and (3) construction of a series of multivariate Cox regression models, informed by the results of the previous analyses. Risk factors that did not contribute to model fit (ie, no improvement in omnibus model coefficient test score) and did not have any significant correlation with other variables were excluded from these models. Secondary analyses, which examined the independent effects of donor and recipient CMV status, were performed in an identical manner.

For survival analyses, cases were censored if the outcome measure did not occur during the completed follow-up period. Hence, for the final outcome measure, cases were censored at the point of death, if death was not due to vasculopathy. Also, the occurrence of CMV infection was assessed in the multivariate model as a time-dependent covariate.

Interactions between variables were not formally tested. The inclusion of variables for the multivariable analysis was done in a systematic manner. Recipient CMV serology, donor CMV serology, laboratory CMV infection, clinical CMV infection, and use of anti-CMV prophylaxis were important variables without which we would be unable to answer the study question. The univariate analysis showed that sex was a significant predictor and should be included in the multivariate analysis. Age was also a highly important clinical variable and should be included in the analysis. Of the remaining, variables, only era of transplantation had significant independent relationships with the other included variables. Hence, age, sex, recipient CMV serology, era, anti-CMV prophylaxis, laboratory CMV infection, clinical CMV infection, and donor CMV serology were all included in the multivariate analyses. Models were constructed both with and without the remaining variables. The addition of either anti-lymphocyte globulin use or rejection episodes to the model (either together or independently) did not alter model fit; hence, they were excluded from the final analysis. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Population Characteristics

During the study period, 165 children underwent heart transplantation with a mean age at transplantation of 7.8 (SD 5.6) years. The youngest patient was 8 days old and the oldest was 19 years old. A total of 82 grafts were transplanted into boys and 83 into girls. Pretransplantation diagnoses were congenital heart disease (n=50), cardiomyopathies (n=113), and cardiac rhabdomyoma (n=1).

In total, 32 recipients developed laboratory evidence of CMV infection. The median time to infection was 32 days (interquartile range 47 days). Only 6 of these patients developed CMV disease or syndrome (3 CMV syndrome, 2 pneumonitis, and 1 hepatitis).
Only 14 patients received anti-CMV prophylaxis (5 received between 2 and 23 days of intravenous ganciclovir; 1 received 90 days of oral ganciclovir; 5 received CMV hyperimmune globulin on days 1, 2, and 7 after transplantation; 2 received a combination of hyperimmune globulin and intravenous ganciclovir; and 1 received a combination of hyperimmune globulin and intravenous ganciclovir followed by 90 days of oral valganciclovir). Thirty patients developed vasculopathy. Twenty-four of these were diagnosed angiographically according to criteria set out in the Methods section, and 6 were diagnosed on postmortem examination. The median time for graft vasculopathy was 2.96 years (interquartile range 4.74 years). A total of 65 patients either died or required retransplantation. Twenty-three of these deaths or retransplantations were due to vasculopathy. This was the leading cause of death or retransplantations (35.4% of total). No significant differences in age, sex, ethnicity, or pretransplantation diagnoses were seen between study groups, whether these were classified according to traditional CMV risk or separately by recipient or donor CMV status.

Survival Curves
Analysis was performed by stratification according to traditional CMV risk category, and Kaplan-Meier curves were constructed for the 3 outcome measures. Contrary to expectations, recipients who were negative for CMV before transplantation had less coronary disease (P<0.01 by log-rank test), irrespective of their donor serology. Similar results were seen for the other 2 outcome measures.

On secondary analysis of the independent effects of donor and recipient CMV status, the most striking differences between survival curves were seen for recipient CMV-positive versus recipient CMV-negative curves. Importantly, overall graft survival (conditional on 6 months survival) was significantly worse in CMV-positive recipients (by log-rank testing, P<0.05; Figure 1). Recipient CMV-positive patients also had significantly earlier vasculopathy (by log-rank testing, P<0.01; Figure 2) and had significantly greater vasculopathy-associated mortality (by log-rank testing, P<0.05; Figure 3).

Univariate and Multivariate Analyses
On primary analysis, traditional risk stratification did not predict development of vasculopathy, all-cause mortality, or vasculopathy-related mortality, either in isolation or after adjustment for confounding variables. Results from the secondary analyses are presented in Tables 1, 2, and 3. On univariate analysis, female sex, laboratory evidence of CMV, and positive recipient CMV status were identified as risk factors for the development of vasculopathy. For all-cause mortality, only positive recipient CMV status was a significant predictor. For death due to vasculopathy, only positive recipient CMV status and female sex were significant predictors. Final multivariate models constructed for all-cause mortality, vasculopathy, and vasculopathy-related mortality were robust model predictors. The validity of the proportional hazards assumption was assessed by plotting covariate-specific residuals against time (Schoenfeld residual plots). The graphs for each of the covariates showed that the proportional hazards assumption was reasonable for all 3 outcome measures (ie, plots did not indicate any systematic trend over time).

By multivariate analysis, positive recipient CMV status (hazard ratio [HR]=3.6), negative donor CMV status (HR=7.9), female sex (HR=2.2), and laboratory evidence of CMV infection (HR=4.7) were all independent predictors of coronary artery disease after adjustment for confounders.
Positive recipient CMV status was the only independent predictor of coronary death (HR = 4.6) and of all-cause mortality (HR = 4.1).

CMV Infection

Over the period of the study, our institution moved from testing serology, detection of early antigen fluorescent foci, and culture (on urine, throat swabs, buffy coat, and other samples) toward using less frequent tests but monitoring quantitative blood polymerase chain reaction. There has been a nonsignificant trend over time toward increased detection of CMV infection (P = 0.14 by independent t test).

Figure 3. Vasculopathy-related mortality. Recipients who were CMV-negative (CMV NEG) at time of transplantation had significantly (P = 0.033) less death or retransplantation due to vasculopathy than CMV-positive (CMV POS) recipients: at 0 years, n = 164 (112 CMV-negative); at 1 year, n = 120 (85 CMV-negative); at 5 years, n = 57 (49 CMV-negative); and at 10 years, n = 21 (17 CMV-negative).

The correlation between laboratory CMV infection and traditional CMV risk category was tested with life tables, with laboratory CMV infection being the time-dependent covariate. Life-table survival analysis was used because assumptions for this analysis were met (whereas assumptions for other analyses, such as Kaplan-Meier or Cox regression analyses, were not). As expected, the occurrence of laboratory CMV infection correlated most strongly with the traditional CMV risk-stratification category. High-risk patients had proportionally the greatest number of laboratory-confirmed infections, followed by intermediate- and then low-risk patients (P < 0.0001 by comparison of life-table survival experience with Wilcoxon statistic).

Of further interest was that CMV-positive recipients did have more and earlier laboratory evidence of CMV infection than CMV-negative recipients (P = 0.012 by comparison of life-table survival experience with Wilcoxon statistic). This association remained true if we excluded all patients who received prophylaxis.

CMV Prophylaxis

Practice varied as to which risk category of patient received prophylaxis, what type of prophylaxis was used, and for how long it was given. Fourteen patients received prophylaxis in total (10 in the high-risk group, 2 in the intermediate-risk group, and 2 in the low-risk group). Five of these 14 patients went on to develop CMV infection.

The number of patients who received prophylaxis was too small to make useful survival analyses, but it is of note that no patient who received CMV prophylaxis either died or needed retransplantation because of vasculopathy. Because no event occurred, a probability value cannot be given (Figure 4).

Preemptive Treatment of CMV Infection

Of the 32 laboratory-confirmed infections, 11 were treated preemptively (ie, before onset of clinical infection). Preemptive therapy varied in length (10 to 90 days) and mode (intravenous ganciclovir or oral ganciclovir, valganciclovir, or valacyclovir). Numbers were too small to reliably analyze

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis (n = 142)</th>
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<tr>
<td></td>
<td>HR</td>
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<tr>
<td>Age</td>
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<td>Female sex</td>
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<tr>
<td>Rejection</td>
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<td>154</td>
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</table>

n Indicates number of patients with complete data set included in analysis; ALG, anti-lymphocyte globulin; and ellipses, no data available.

*Significant difference.
the effect of preemptive therapy on the development of vasculopathy.

**Missing Data**
Twenty-two cases were excluded from multivariate analyses because of missing data on risk factors. The cases that were excluded were not significantly different from the included cases in terms of the outcomes measured (by Cox regression analysis, \( P = 0.15 \) for all-cause mortality, \( P = 0.30 \) for vasculopathy, and \( P = 0.89 \) for vasculopathy-related mortality). Therefore, the conclusions reached by the multivariate analyses are unlikely to be prejudiced by the exclusion of these cases.

**Discussion**
This is the first study to confirm a relationship between CMV and vasculopathy in children. Our expectation was that children who were CMV-negative before transplantation and received CMV-positive grafts would have the highest incidence of vasculopathy. Contrary to these expectations, our data showed that children who were CMV-positive before transplantation were at higher risk of vasculopathy and had higher late mortality rates, even after adjustment for anti-CMV therapy.

This is the first large study to investigate the link between pretransplantation CMV status and vasculopathy in children, although a number of much smaller studies have reported inconsistent results.\(^{27-30}\) A recent large, multi-institutional study from the Pediatric Transplant Database conducted over a 9-year period did not show a difference in the incidence of vasculopathy in patients who acquired CMV infection.\(^3\) In that study, which is the largest published pediatric vasculopathy series, the only significant risk factors identified were older donor and recipient age; however, that study did not assess CMV status before transplantation or anti-CMV prophylaxis and therefore cannot be related to the present findings. There have been a number of adult studies that have previously examined the relationship between CMV and

**TABLE 2. Multivariate Analysis of Predictors for All-Cause Mortality or Graft Loss (Beyond 6 Months After Transplantation)**

<table>
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<td>Prophylaxis used</td>
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<tr>
<td>CMV disease/syndrome</td>
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<td>Rejection</td>
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*Significant difference.

**Abbreviations as in Table 1.

TABLE 3. Multivariate Analysis of Predictors for Vasculopathy-Related Mortality**

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<td>Prophylaxis used</td>
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<td>CMV disease/syndrome</td>
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<tr>
<td>ALG used</td>
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<tr>
<td>Rejection</td>
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<td>154</td>
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</table>

*Significant difference.

*Abbreviations as in Table 1.
vasculopathy. The first showed that patients who develop CMV infection after transplantation (as evidenced by histology, culture, or serological rise in antibody titers) had more severe vasculopathy than patients who had no evidence of active infection after transplantation. Subsequent studies therefore concentrated on the role of CMV infection after transplantation and have confirmed a positive association between active infection and vasculopathy.

These results have led to the current consensus with regard to CMV risk stratification, with CMV-negative recipients of CMV-positive grafts classified as high risk. We are able to cite 2 previous studies that support our challenge to this consensus. The first, an autopsy study reported in 1993, included patients who died within the first year of transplantation and demonstrated endothelial inflammation and vasculopathy in recipients who were positive for CMV preoperatively regardless of the occurrence of infection. The second, a clinical study of 217 patients reported in 1995, confirmed that preoperative positive CMV status predisposed patients to graft vasculopathy. Some support also exists for the present data from a pediatric intravascular ultrasound study that showed a higher maximal intimal thickness (although no increase in intimal index occurred) in a subgroup of older children who were CMV-positive.

The present results imply that the risk from CMV-induced vasculopathy in children in the posttransplantation period comes more from reactivation in CMV-positive recipients than from de novo infection in CMV-negative recipients. We suggest that the reason many studies have not demonstrated this relationship is in part because they have not specifically asked this question. In addition, the investigation of pediatric vasculopathy allows a purer assessment of CMV risk, because conventional risk factors, such as diabetes mellitus, smoking, hypertension, and elderly donors, are uncommon. Also, again in contrast to adults, the pediatric transplantation population will be expected to have a higher proportion of CMV-positive donors and recipients, as we discovered in the present study population.

However, although rates of CMV infection are similar in both adults and children (the frequency of CMV infection in recipients in the present study was 19%, and this was comparable to a rate of ~13% from a large study of adults), a much lower incidence of invasive CMV infection existed in the present study population (18% of infections compared with the 56% reported in the adult study). The low incidence of invasive CMV disease in the present pediatric population may explain why we were able to identify positive pretransplantation CMV serology as a significant risk factor for vasculopathy in this population. Furthermore, the low incidence of invasive CMV infection in the present study population would suggest that we cannot dismiss the importance of active CMV infection in the development of vasculopathy in children given the present data.

Another important point of note is that CMV-positive recipients were more likely to develop CMV infection and did so significantly earlier than the CMV-negative recipients; however, we did not identify an association between CMV infection and subsequent vasculopathy. The present results may therefore indicate that the coronary vascular endothelium is particularly vulnerable to the inflammation caused by CMV during the immediate posttransplantation period. Alternatively, vasculopathy may result from low-grade CMV infection or reactivation that is not detectable by the methods used in the present study. Either hypothesis would indicate a role for initial prophylaxis in this group of patients. In the small number of children given prophylaxis in the present study, the use of prophylaxis showed a trend toward preventing graft loss due to vasculopathy. Although the small numbers preclude any robust conclusions, these findings do correlate with work in animals that showed that prophylactic ganciclovir entirely abolished the accelerating effect of CMV infection on vasculopathy. It further correlates with clinical findings that, in the era of prophylaxis, the influence of recipient-donor CMV matching on vasculopathy is abolished. Still more support is given by evidence suggesting that prophylactic ganciclovir administration reduces the risk of developing vasculopathy.

Some methodological flaws exist in the present study. Laboratory methods of detecting CMV infection varied, with a nonsignificant trend toward improved detection of CMV infection over time. This potential bias should be corrected in the multivariate analysis by adjustment for the era of transplantation. Second, strategies on type and length of anti-CMV prophylaxis, as well as which patient groups received prophylaxis, varied between attending clinicians. Similarly, strategies on preemptive treatment of laboratory-proven infection were inconsistent, and the numbers of patients receiving preemptive therapy were too small to perform subanalyses.

Another shortcoming of the present study is that angiography may not be the most sensitive means of detecting or quantifying posttransplantation coronary artery disease. Intravascular ultrasound is superior, although rarely performed in small children. We relied on the contemporaneous reporting system in the case notes to diagnose coronary angiographic abnormalities. Furthermore, the number of patients with
vasculopathy was small, and this limits our ability to detect or account for risk factors. For these reasons, we first constructed models with vasculopathy as the outcome measure and then repeated the analyses with graft survival as the outcome measure. The results were almost identical.

In conclusion, this is the first demonstration of a link between positive pretransplantation CMV serology and subsequent coronary artery disease in pediatric heart transplant recipients. These findings suggest that a wider investigation of prophylaxis in this patient group is justified.

Disclosures
Dr Fenton has received a research grant from the British Heart Foundation for investigation into pathogenesis of coronary artery disease. The remaining authors report no conflicts.

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Clinial Perspective

In the present study, the authors describe the first confirmation of an association between cytomegalovirus (CMV) and vasculopathy in children. The demonstration of this association in children is important because studies in children allow for a purer assessment of vasculopathy than studies in adults because less confounding exists from risk factors for donor and recipient atherosclerosis. Moreover, the study actually describes an association between evidence of pretransplantation (ie, latent) CMV infection and subsequent development of vasculopathy. Previous adult studies have also shown this association. However, more recent studies in this field have not specifically examined this question, with researchers focusing instead on the influence of overt posttransplantation CMV infection on the development of vasculopathy. These data suggest that a wider investigation of the use of CMV prophylaxis is warranted in both adults and children who are CMV seropositive at transplantation and are currently classified as being only at intermediate risk.
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