

Randomized Comparison of Ganciclovir Plus Intravenous Immune Globulin (IVIG) with IVIG Alone for Prevention of Primary Cytomegalovirus Disease in Children Receiving Liver Transplants

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A randomized placebo-controlled trial was conducted to determine the benefit of ganciclovir (5 mg/[kg · d]) for 30 days in addition to intravenous immune globulin (IVIG) for 16 weeks for prevention of primary cytomegalovirus (CMV) disease in children receiving liver transplants. Patients were monitored for 6 months after transplantation. The two groups of patients (recipients of 29 ganciclovir plus IVIG and 27 recipients of IVIG alone) were similar in terms of age, sex, and underlying disease. The incidence of CMV disease among the ganciclovir plus IVIG recipients and the IVIG alone recipients was 17% and 26%, respectively, and the time to disease in these recipients was 46 days and 32 days, respectively. There was no difference between groups in terms of survival; episodes of rejection, bacteremia, or fungemia; use of immunosuppressive agents; and incidence of leukopenia or thrombocytopenia. These results suggest that a 4-week course of ganciclovir with IVIG is not more effective than IVIG alone for prevention of primary CMV disease. Since short-term prophylaxis with ganciclovir may delay the onset of CMV disease, further studies with a longer course of ganciclovir prophylaxis are warranted.

In children, as in adults, cytomegalovirus (CMV) has been a major cause of morbidity after solid-organ transplantation [1–5]. Infected patients may develop symptomatic CMV disease with pneumonia, hepatitis, gastrointestinal ulcers, retinitis, or a viral syndrome with persistent fever, neutropenia, and thrombocytopenia. CMV infection has also been associated with an increased risk of both fungal infections [5, 6] and bacterial infections [7, 8] as well as with allograft injury [1]. The major factors contributing to the risk of severe CMV disease are donor/recipient serostatus and the use of monoclonal antibodies to T cells (OKT3) or antilymphocyte products [9]. CMV-seronegative recipients of transplants from CMV-seropositive donors develop primary CMV disease that is associated with high morbidity and mortality [1–5].

Prophylactic strategies for CMV disease have included use of CMV-seronegative blood products, intravenous immune globulin (IVIG), high-dose acyclovir, and ganciclovir. Prospective,

randomized, controlled trials evaluating these strategies have enrolled mostly adult transplant recipients, with only a few transplant recipients at risk for primary infection (CMV-seropositive donor/CMV-seronegative recipient) [10–17]. None of these prophylactic strategies have been demonstrated to be consistently effective in prevention of primary CMV disease. However, a meta-analysis of randomized, controlled trials of immune globulin as prophylaxis for CMV disease in transplant recipients found a significant beneficial effect with a common odds ratio of 0.58 [18]. In this analysis, the common odds ratio for a CMV-seropositive donor/CMV-seronegative recipient was 0.46 (95% CI, 0.24–0.81). Therefore, in many pediatric transplant programs, immune globulin prophylaxis was given to CMV-seronegative recipients of transplants from CMV-seropositive donors.

We hypothesized that a combination strategy consisting of both passive immunization and antiviral chemotherapy would be more effective than passive immunization alone in this group of transplant recipients at risk of primary CMV disease. The objective of this randomized study was to assess the effectiveness of a 4-week course of intravenous ganciclovir, given in combination with a 4-month course of IVIG after transplantation, for prevention of primary CMV disease. The control group was given IVIG alone for 4 months after transplantation.

Methods

From January 1991 to December 1994, children undergoing liver transplantation in six transplantation centers in Canada

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and the United States were enrolled in the study if they met the following criteria: age younger than 18 years, CMV-seronegative recipient, and CMV-seropositive donor. The donor's CMV serostatus was determined by latex agglutination (CMV SCAN, Becton Dickinson Microbiology Systems, Cockeysville, MD). The recipient's CMV serostatus was measured by commercial assays with use of either latex agglutination or ELISA [18]. Informed consent was obtained for each patient.

Study Drugs

Patients were assigned consecutively at each center to receive either ganciclovir or placebo (saline) intravenously for 30 days after transplantation. Randomization was stratified by center by means of block randomization with blocks of variable size. Assignment was double blind. Ganciclovir (5 mg/[kg · d]) was given once daily. The dose of ganciclovir was modified for renal function according to guidelines from the manufacturer (Syntex, Palo Alto, CA). Ganciclovir administration was interrupted if the absolute neutrophil count (ANC) fell to $<500/\text{mm}^3$ and was reinstituted when the ANC rose to $\geq 750/\text{mm}^3$. Ganciclovir administration also was interrupted if the platelet count fell to $<25,000/\text{mm}^3$ and was reinstituted when the platelet count rose to $\geq 50,000/\text{mm}^3$.

All patients, both those receiving ganciclovir and those receiving placebo, were given infusions with IVIG (Gammagard, Hyland Division, Baxter Healthcare Corporation, Glendale, CA) in the following schedule after transplantation: 1 g/kg within 72 hours and then 500 mg/kg weekly for weeks 1 to 8 and biweekly for weeks 10 to 16.

If a patient developed CMV disease, the primary physician could discontinue administration of the study drug and start treatment with ganciclovir.

CMV Infection

CMV infection was defined as isolation of CMV from a specimen obtained from any site or as histological evidence of CMV in a tissue specimen, as indicated by the presence of cytomegalic cells with nuclear inclusions or CMV DNA by *in situ* hybridization [19]. The shell vial technique with use of monoclonal antibody was used for detection of CMV in the buffy coat of the blood and in other specimens. Seroconversion was not used to diagnose infection because of administration of IVIG.

CMV Disease

CMV hepatitis was defined as clinical evidence of hepatitis and biopsy-proven tissue invasion by CMV. CMV gastrointestinal disease was defined as biopsy-proven tissue invasion by CMV along with gastrointestinal symptoms not explainable by other causes. CMV pneumonia was diagnosed if there were symptoms and signs of pneumonia and interstitial pulmonary

infiltrates on the chest roentgenogram and if CMV was recovered from a bronchoalveolar lavage fluid or lung biopsy specimen (as defined above). CMV viral syndrome was defined as persistent fever with neutropenia or thrombocytopenia in a patient with CMV infection (as defined above) and no other attributable cause.

Laboratory Procedures

Patients were followed up for 6 months after transplantation. Throat, urine, and buffy coat specimens for viral cultures were obtained at entry into the study, weekly from weeks 1 to 8, biweekly from weeks 10 to 16, and at week 24. Whenever appropriate, viral cultures of lesions, bronchoalveolar lavage fluid, biopsy tissue, and autopsy tissue specimens were performed. Bronchoalveolar lavage fluid and tissue specimens were also examined histologically. Complete blood counts and assays for serum creatinine levels, electrolyte levels, and liver function were done before and during the study to assess for treatment-related side effects. Liver biopsy specimens were graded histologically for rejection.

Transplant Procedures

In this multicenter study, patients were treated according to standard practice at their transplantation centers. Acyclovir was not used as prophylaxis for CMV disease or herpes simplex. Acyclovir was used as treatment of symptoms or signs consistent with herpes simplex or varicella. The use of blood products screened as CMV-seronegative was standard practice in all transplantation centers.

Study Approval

The protocol was approved by the human subjects review committee at each participating center. In addition, since at the time of starting the study ganciclovir was not licensed for use in either the United States or Canada and IVIG was not licensed for use in Canada, the protocol was reviewed and approved by the U.S. Food and Drug Administration and the Health Protection Branch of Canada.

Safety Committee

The safety committee was independent of the study investigators and consisted of members with differing areas of expertise, including infectious diseases, transplant medicine, and biostatistics. This committee reviewed the events of the study on an ongoing basis. The committee knew the group to which a subject had been assigned but were not aware of which intervention had been assigned to each group.

Table 1. Characteristics of children undergoing liver transplantation who were receiving either ganciclovir plus IVIG or IVIG alone as prophylaxis for CMV disease.

Characteristic	Ganciclovir plus IVIG recipients (n = 29)	IVIG alone recipients (n = 27)	P value
Mean age (range) in mo	65 (3–197)	75 (7–191)	.59
No. of males/no. of females	14/15	16/11	.45
No. with indicated underlying disease			.49
Biliary atresia (hypoplasia)	14	16	
Hepatitis	5	3	
α_1 -Antitrypsin deficiency	2	4	
Hepatoblastoma or carcinoma	1	2	
Wilson's disease	2	0	
Tyrosinemia	2	0	
Congenital cirrhosis or fibrosis	1	2	
Cholestatic disease	1	0	
Sclerosing cholangitis	1	0	
No. who underwent repeated transplantation during study	2	5	.18
No. with indicated no. of rejection episodes			.60
0	10	6	
1	8	9	
>1	10	11	
No. who received indicated treatment for rejection			
None	10	6	.36
Steroids	20	21	.36
OKT3	8	7	.90
FK-506	2	5	.15

NOTE. CMV = cytomegalovirus; IVIG = intravenous immune globulin; OKT3 = monoclonal antibodies to T cells; FK-506 = tacrolimus (Fujisawa, Deerfield, IL).

Statistical Analysis

Fisher's exact test was used to compare differences in proportions, and Student's *t*-test was used to compare means. The comparison of times to events was performed by the Kaplan-Meier method and was analyzed by the logrank test [20]. A sample size of 42 per group would have given an 80% power for the primary outcome of incidence of CMV disease to detect a 50% reduction in the baseline event rate of 60% at a .05 level of significance.

Results

Enrollment was stopped early because by January 1995, the treating physicians wanted to give antiviral drugs as prophylaxis or preemptive therapy for CMV disease in this population. Sixty-two patients were enrolled from six centers (median, eight patients per center; range, four to 21 patients per center). Six were excluded within 72 hours of enrollment because of the following reasons: two were seropositive recipients, one had a seronegative donor, two were older than 18 years of age, and one was withdrawn at the request of the transplant surgeon. Of the remaining 56 study patients, 29 received ganciclovir plus IVIG, and 27 received IVIG alone. The two groups of

patients were similar in terms of age, sex, underlying disease, immunosuppressive agents, and rejection episodes (table 1).

The incidence of CMV disease and infection in the two study groups is shown in figure 1. By 6 months after transplantation, CMV disease had developed in five (17%) of the 29 ganciclovir

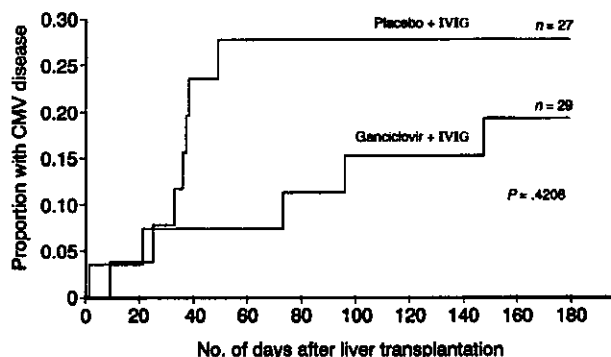


Figure 1. The cumulative probability (Kaplan-Meier curves) of cytomegalovirus (CMV) disease during the first 180 days after liver transplantation in children receiving ganciclovir plus intravenous immune globulin (IVIG) ($n = 29$) or placebo plus IVIG ($n = 27$) as prophylaxis for CMV disease.

Table 2. CMV disease after liver transplantation in children who were receiving either ganciclovir plus IVIG or IVIG alone as prophylaxis for CMV disease.

Variable	Ganciclovir plus IVIG (n = 29)	IVIG alone (n = 27)
No. (%) with CMV disease	5 (17)	7 (26)
Mean time (d) to CMV disease	46	32
No. with indicated site or manifestation of CMV disease		
Liver	3	6
Lung	1	1*
Gastrointestinal tract	0	1*
Viral syndrome	1	1

NOTE. CMV = cytomegalovirus; IVIG = intravenous immune globulin.

* Disease was diagnosed after CMV hepatitis was diagnosed.

plus IVIG recipients and seven (26%) of the 27 IVIG alone recipients (logrank χ^2 test; $P = .4208$) (table 2). All IVIG recipients with CMV disease had onset of the disease before 8 weeks after transplantation, whereas only two of five ganciclovir plus IVIG recipients with CMV disease had onset in the first 8 weeks after transplant. The mean time to onset of CMV disease was 46 days for the ganciclovir plus IVIG group and 32 days for the IVIG alone group ($P = .36$).

By 6 months after transplantation, CMV infection had been detected in 16 (55%) of the 29 ganciclovir plus IVIG recipients and 11 (41%) of the 27 IVIG alone recipients (logrank χ^2 test; $P = .4877$). Viremia occurred in five ganciclovir plus IVIG recipients (17%) and five IVIG alone recipients (19%). Twelve patients in the ganciclovir plus IVIG group and 10 in the IVIG alone group were treated for confirmed or suspected CMV disease. Confirmed CMV disease was as defined under Methods. CMV disease was suspected during episodes of CMV viremia when there was clinical evidence of CMV disease before a tissue sample or bronchoalveolar lavage fluid specimen had been obtained. For treatment of CMV disease, the dosage of ganciclovir was increased to 10 mg/(kg · d) in two divided doses for 2–3 weeks. The timing of starting open-label ganciclovir administration was similar for the two groups: day 43 for the ganciclovir plus IVIG group and day 44 for the IVIG alone group.

The survival rate was similar among both groups: 79% (23 of 29) among the ganciclovir plus IVIG group and 85% (23 of 27) among the IVIG group. The causes of death in the ganciclovir plus IVIG group were CMV disease (1 patient), liver failure (1 patient), lymphoproliferative disease (1 patient), multiorgan failure (2 patients), and sepsis (1 patient). The causes of death in the IVIG alone group were lymphoproliferative disease (1 patient) and multiorgan failure (3 patients). There were no deaths due to CMV disease in the IVIG alone group. The one death classified as CMV-associated was due to respiratory arrest on day 148 in a patient who had been

treated for CMV pneumonia on day 53. An autopsy was not performed. Another patient in the ganciclovir plus IVIG group developed CMV retinitis 7 months after transplantation, followed by Kaposi's sarcoma; this patient died at 10 months. CMV pneumonia was diagnosed at autopsy.

There was no difference between the groups in terms of days of fever or episodes of bacteria or fungemia during the 6 months after transplantation. The mean number of days of fever (\pm SE) over the 6 months after transplantation was 12.7 ± 12.7 days for the ganciclovir plus IVIG group and 16.7 ± 18.0 days for the IVIG alone group ($P = .35$). The mean number of episodes of bacteremia and fungemia (\pm SE) was 1.07 ± 1.36 and 0.43 ± 1.01 episodes, respectively, for the ganciclovir plus IVIG group and 1.63 ± 1.74 episodes, and 0.52 ± 1.05 episodes, respectively, for the IVIG alone group ($P = .18$ and $P = .76$, respectively).

The groups did not differ in terms of the number of episodes of rejection or the immunosuppressive agents used (table 1). The mean WBC counts were similar for both groups throughout the study period, including the 30 days of ganciclovir administration (figure 2). The number of episodes of neutropenia (ANC, $<1,000/\text{mm}^3$) was similar in the two groups, as was the number of episodes of thrombocytopenia (platelet count, $<100,000/\text{mm}^3$). One patient in the ganciclovir plus IVIG group and seven in the IVIG alone group had episodes of neutropenia. There were 27 and 25 episodes of severe thrombocytopenia (platelet count, $<20,000/\text{mm}^3$) in the ganciclovir plus IVIG and IVIG alone groups, respectively.

Seven patients in the ganciclovir plus IVIG group and four in the IVIG alone group were treated with acyclovir. The durations of acyclovir use in these two groups were 24 and 39 days, respectively. The mean day of starting acyclovir therapy was day 39 for the ganciclovir plus IVIG group and day 17 for the IVIG alone group. None of these differences was statistically significant. The outcomes of CMV disease and infection and

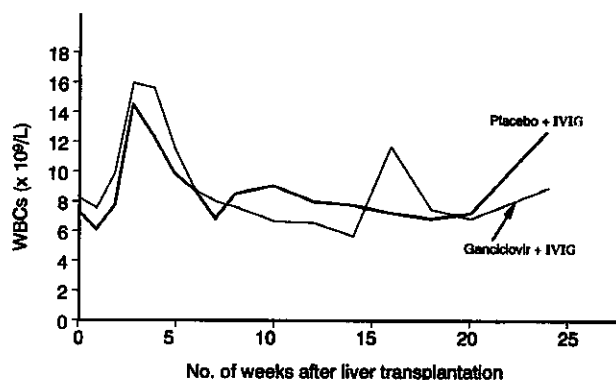


Figure 2. The mean WBC count ($\times 10^9/\text{L}$) during the first 180 days after liver transplantation for children receiving ganciclovir plus intravenous immune globulin (IVIG) ($n = 29$) or placebo plus IVIG ($n = 27$) as prophylaxis for cytomegalovirus disease.

Table 3. Summary of data on outcome for CMV-seronegative recipients of liver transplants from CMV-seropositive donors.

[Reference]	No. of patients		Prophylaxis (duration)	Age group	No. (%) with	
	Total	CMV-seropositive donor/ CMV-seronegative recipient			CMV infection	CMV disease
[PR]	27	27	IVIG (16 w)	Pediatric	11 (41)	7 (26)
[PR]	29	29	Gcv (30 d) plus IVIG (16 w)	Pediatric	16 (55)	5 (17)
[11]	126	11	Acy (1–100 d)	Adult	6 (55)	1 (9)
[11]	124	10	Gcv (1–100 d)	Adult	2 (20)	1 (10)
[10]	72	19	None	Adult	17 (90)	10 (53)
[10]	69	19	CMVIG (16 w)	Adult	11 (58)	10 (53)
[5]	71	11	Acy (12 w)	Adult	NA	7 (64)
[5]	68	7	Gcv (2 w) then Acy (10 w)	Adult	NA	3 (43)
[6]	45	2	Acy (24 w)	Adult	2 (100)	2 (100)
[6]	49	2	Gcv if CMV shedding	Adult	1 (50)	0
[7]	19	3	Gcv (2 w)	Pediatric	0	0
[7]	10	1	Gcv (2 w) then Acy (50 w)	Pediatric	1 (100)	1 (100)

NOTE. Acy = acyclovir; CMV = cytomegalovirus; CMVIG = cytomegalovirus immune globulin; Gcv = ganciclovir; IVIG = intravenous immune globulin; NA = not available; PR = present report.

the survival among these 11 patients treated with acyclovir were not different from those for the whole study group.

Discussion

Prophylactic strategies for CMV disease have included use of CMV-seronegative blood products, IVIG, high-dose acyclovir, and ganciclovir. Prospective, randomized, controlled trials evaluating these strategies have enrolled mostly adult transplant recipients, with only a few transplant recipients at risk for primary infection (CMV-seropositive donor/CMV-seronegative recipient) [10–17]. None of these prophylactic strategies have been demonstrated to be consistently effective in the prevention of primary CMV disease. The results from these trials for CMV-seronegative recipients of transplants from CMV-seropositive donors are shown in table 3. One of the lowest rates of primary CMV disease (10%) was reported with use of a long course of ganciclovir prophylaxis. However, these results are based on a small number of CMV-seronegative recipients of transplants from CMV-seropositive donors.

To our knowledge, our study is the largest randomized trial of prophylaxis for CMV disease in CMV-seronegative recipients of liver transplants from CMV-seropositive donors ever reported. Since transplant recipients were recruited from six centers in North America, the results are likely to be generalizable to other North American transplant programs. One of the problems with this study is its length. During the study period (1991–1994), many changes occurred that improved the outcome for liver transplant recipients. On the basis of data before 1990, the expected incidence of CMV disease among CMV-seronegative recipients of liver transplants from CMV-seropositive donors was 60%, but in our study, the incidence was 26% among the IVIG alone (control) group. Possible explanations

for this improvement in outcome for the control group are as follows: improvement in transplantation procedures not related to CMV disease, such as organ harvesting, surgical techniques, and treatment of bacterial and fungal infections; increased awareness of CMV disease, leading to earlier diagnosis and treatment; improved diagnostic tests for CMV disease, leading to earlier diagnosis; and the prophylactic effect of IVIG on CMV disease. It is probable that all of these explanations contributed to the decrease in the incidence of CMV disease.

Although this study is the largest (56 patients) reported randomized trial of prophylaxis for CMV disease in CMV-seronegative recipients of liver transplants from CMV-seropositive donors, there was no statistically significant difference between the ganciclovir plus IVIG group and the IVIG alone group. A sample size of 350 patients per group would have been required to confirm a difference of CMV disease of 9% with an α error of 0.05 and a β error of 0.20. There was a trend toward later onset of CMV disease in the ganciclovir plus IVIG group, thus suggesting that a longer duration of ganciclovir prophylaxis might be more effective. This trend toward longer ganciclovir prophylaxis being more effective is supported by the results of two studies of ganciclovir prophylaxis, one for 100 days and the other for 7 days, respectively [11, 14]. In the randomized, controlled trial in which ganciclovir was given for 7 days [14], CMV disease occurred in 55% of CMV-seronegative recipients of transplants from CMV-seropositive donors who were in the ganciclovir group. However, in the randomized, controlled trial in which ganciclovir was given for 100 days [11], CMV disease occurred in 10% of CMV-seronegative recipients of transplants from CMV-seropositive donors who were in the ganciclovir group.

To assess the effectiveness of this prophylactic strategy compared with that of others, the outcomes for CMV-seronegative

recipients of liver transplants from CMV-seropositive donors who were from included in other prospective, randomized trials were reviewed (table 3). A meta-analysis was not performed. However, the data from these studies were pooled to show the results of the prophylactic strategies of acyclovir alone, ganciclovir alone (or with sequential acyclovir), IVIG alone, and the combination of ganciclovir and IVIG. The incidence of CMV disease was as follows: patients who received acyclovir alone ($n = 24$), 42%; those who received ganciclovir alone or ganciclovir followed by acyclovir ($n = 23$), 22%; those who received CMV immune globulin (CMVIG) or IVIG alone ($n = 46$), 37%; and those who received the combination of ganciclovir and IVIG ($n = 29$), 17%. These results suggest that prophylaxis with acyclovir alone or IVIG alone is less effective than that with ganciclovir or ganciclovir in combination with IVIG.

Our study was not designed to assess the benefit of IVIG, since IVIG was given to both groups of patients. The role of CMVIG or IVIG in prophylaxis for CMV disease in organ transplant recipients remains controversial. IVIG was used in this trial on the basis of the combined results of the trials conducted between 1980 and 1991, which indicated some benefit when IVIG was used as prophylaxis for CMV disease [18]. However, in a more recent randomized trial comparing CMVIG with placebo as prophylaxis for CMV disease [10], the rate of CMV disease was reduced overall, but not among CMV-seronegative recipients of liver transplants from CMV-seropositive donors. Therefore, although there is a rationale for using the combination of ganciclovir and IVIG as prophylaxis for transplant recipients at risk for primary infection, the evidence that the combination is more effective than ganciclovir alone as prophylaxis for CMV disease in this selected group is weak. In view of the cost of CMVIG or IVIG, more evidence is needed to justify their roles in prophylaxis for CMV disease now that more effective antiviral agents are available.

In bone marrow transplant recipients, the toxic effect of ganciclovir has been a major issue. In studies involving this patient population, bone marrow suppression occurred in up to 50% of transplant recipients [21, 22]. The incidence of leukopenia, thrombocytopenia, and renal failure in adult liver transplant recipients was similar among ganciclovir and control groups [11], as in our study. The results of these studies indicate that with appropriate monitoring, the frequency of toxic effects from ganciclovir in liver transplant recipients, including children, is low.

The evidence is accumulating that ganciclovir as prophylaxis for CMV disease in liver transplant recipients is effective and safe and that a longer course of 3–4 months is more effective than a shorter course of 4 weeks. However, one of the major disadvantages to such a strategy is the cost and inconvenience of maintaining intravenous access for 3–4 months. Oral ganciclovir is now available. In a study presented but not yet reported [23], oral ganciclovir was given for 14 weeks to adult liver transplant recipients. There were 25 and 21 CMV-sero-

negative recipients of transplants from CMV-seropositive donors who were in the control and ganciclovir groups, respectively. The incidence of CMV disease in these groups was 44% and 3%, respectively. The use of oral ganciclovir as prophylaxis for CMV disease is therefore a very attractive option.

Further studies are needed to determine the optimal strategy for prophylaxis for CMV disease, especially in this high-risk group (CMV-seropositive donor/CMV-seronegative recipient). These studies should focus on the effectiveness of longer courses of ganciclovir, perhaps with initial intravenous administration followed by oral administration. The role of IVIG in prophylaxis for CMV disease also must be reevaluated in this setting, since more-effective antiviral agents are now available.

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