Assessment of Oral Complications in Children Receiving Chemotherapy

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The aim of this study was to assess the early oral complications in pediatric patients receiving chemotherapy. An interview and oral examination was conducted on 150 pediatric cancer patients receiving standard dose chemotherapy. Results showed that oral pain and dry mouth were the most frequent patients' complaints. The prevalences of chemotherapy-induced oral mucositis and oral infections were relatively high. The chemotherapeutic antimetabolites were the most frequently associated with oral complications than other types of chemotherapy. The present results indicate that the oral complications among patients receiving chemotherapy are common
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INTRODUCTION

Cancer is a major public health problem. There are more than 10 million patients worldwide diagnosed with cancer.[1] Although cancer is considered rare as a childhood disease, its incidence seems to be increasing by 1% average yearly, and cancer is now the main cause of death by disease in children between the ages of one and 14 years.[2]

In developing countries the childhood cancer is completely different from that in developed countries, the rapid increase in population, poverty, poor hygiene, lack of education and multiple health problems count for its high incidence. More than 85% of pediatric cancer cases occur in developing countries.[3] In Egypt, which shares most of the environmental problems of developing countries[4], it was reported that over 100,000 Egyptian children are suffering from cancer, with a rate of six times higher than it is in the western countries and approximately 4,000 to 5,500 cases are diagnosed annually.[5]

Pediatric cancer patients are usually suffering from serious oral and dental complications during treatment. The severity of these complications is affected by many factors. These factors include age, type of malignancy, condition of the oral cavity before treatment, and the level of oral care during anticancer therapy.[6,7] They also include type of chemotherapeutic agents used for therapy, the total dose of the drug used, the timing and delivery of the chemotherapy, and other treatment modalities such as radiotherapy used in concomitant with chemotherapy.[6,8-10] Stomatotoxicity is also related to the total dose of the drug administered; prolonged or repetitive administration of lower doses of cytotoxic agents have been associated with an increased risk for the development of oral complications.[6,11] In addition, the intervals in which the doses are given, the duration over which the patient receives the dose, the therapeutic regimen, the concomitant medication and previous cytotoxic treatments, and the prolonged myelosuppression of the patient are also important factors affecting the severity of the oral complications.[6,11]

The condition of the oral cavity before commencing treatment is an important consideration in the development of oral complications; patients with existing oral disease, irregular, sharp teeth and irritating appliances are at higher risk for developing oral complications. Pre-treatment oral care and oral care during therapy have been shown to decrease oral complications with no increase in risk of fever or bacteremia.[6,7,10]

The common early complications of chemotherapy include oral mucositis,[11-16] intra oral infections,[6,17-21] xerostomia,[6,22] acute ascending sialadenitis,[6,12] intra oral hemorrhage,[6,23] and mucosal bleeding.[6,22]

The Oral mucositis represents a major non-hematologic complication of cytotoxic chemotherapy. It is considered one of the most debilitating side effects of cancer therapy.[8,16,24,25] The movable nonkeratinized mucosa of the soft palate, cheeks and lips, the ventral surface of the tongue, and the floor of the mouth are most vulnerable to direct stomatotoxicity. Oral lesions usually disappear without scar formation unless mucositis is complicated by serious infection or xerostomia.[11]

One of the most common complications involved in treating patients with cancer especially hematologic cancer is infection. In patients with acute or chronic leukemia, oral infection may be identified in approximately one-third of patients, while in patients receiving chemotherapy for solid tumors only ten per cent of pa-

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tients may develop oral infections.[6,7,10] Oropharyngeal fungal infection is of considerable importance in any condition that results in an immune suppressed state.[19] Although bacteria are usually the primary pathogens in neutropenic patients, most bacterial infections can now be treated successfully with currently available antibacterial drugs. In contrast, fungal infections are increasing in frequency and are now responsible for most fatal infections. A prospective study that conducted in Egypt showed that out of 1917 infectious episodes, the fungal infection rate; as documented both clinically and microbiologically; was 70 cases (3.7%). Out of these 70 cases, there was an infection-related mortality of 28.5% (20 cases).[26]

Second to fungi, viruses, particularly herpes simplex virus type (HSV) and varicella zoster virus (VZV), represent the most common pathogens aggravating oral mucositis in the course of antineoplastic therapy. In immunocompromised patients, the mucositis associated with viral infection is more painful, severe, and of longer duration than mucositis uncomplicated by viral infection.[11,17,27] Reactivation of latent oral HSV is very common in patients receiving cytotoxic chemotherapy, it may appear at any time during treatment and its incidence ranges between 50 and 90% in patients which are seropositive for HSV in the absence of viral prophylaxis.[17,27-30]

Studies show that odontogenic and gingival infections represent the major source of bacteria complicating mucositis; patients with chronic oral or dental infections receiving high dose chemotherapy have a high risk to develop acute exacerbations from pre-existing sites of disease during periods of neutropenia.[7,18,31]

Spontaneous bleeding and hemorrhage from the gingiva or from the mucositis ulcerations may be observed as an immediate problem or may occur after treatment commences in approximately 10 to 14 days. It is usually occurred as the patient becomes more thrombocytopenic. Severe thrombocytopenia may predispose patients to bleeding from routine mechanical oral hygiene procedures.[6,17]

The main aim of this study was to assess the oral complications of chemotherapy in pediatric cancer patients, and to find the possible factors that affect the severity of these complications.

MATERIAL AND METHODS

One hundred and fifty pediatric patients undergoing chemotherapy were randomly drawn from the Oncology Department, Faculty of Medicine, Alexandria University, and from El-Talaba hospital of Alexandria. The sample was drawn from those children whose ages were ≤ 12 years, and were suffering from any type of malignancy (except oral malignancy) requiring chemotherapeutic treatment, and who did not receive any radiotherapy on their head and neck. All randomly drawn patients were subjected to an interview with their parents and oral examination. Data were collected in a specially designed sheet that included sociodemographic information (age, gender, parents' occupation, and social level identified by the hospitalization level), general health information such as; data concerning the malignancy(type whether solid tumor, or hematologic malignancy, the Overall Stage Grouping (OSG) system which was also referred to as Roman Numeral Staging system was used to identify the malignancy staging[32], onset of malignancy and duration of chemotherapeutic treatment), and data concerning the chemotherapeutic drug (type, dose and number of chemotherapeutic cycles).[32] Current blood data with particular attention to the white blood cells (WBCs) count, the absolute neutrophil count (ANC), the platelet count (PC), and the hemoglobin level (Hb)[32,33], systemic diseases other than the malignancy and any other treatments given to the patients by their physicians were also recorded. Information concerning oral hygiene habits (methods and frequency of teeth cleaning), dietary habits (type and frequency of food intake) as well as patient complaints such as dry mouth, difficulty in swallowing, in mastication, or in speech, and pain were also collected.

Oral examinations were then performed at the previously mentioned pediatric oncology units. Some patients were at the outpatient clinic but most of them were hospitalized. The patients were in bed, and examination was done in the day light using latex gloves, plain mouth mirrors, probes, periodontal probes, tweezers, containers, cottons/gauze to remove any food debris and dry the mucosa, and sometimes wooden tongue depressors.

The patients were examined for:

1. Scoring of the chemotherapy-induced oral mucositis according to WHO classification[10]; Grade 0: No change, Grade 1: Soreness/erythema, Grade 2: Erythema, and Ulcers; patient can eat solids, Grade 3: Ulcers; the patient requires liquid diet only, and Grade 4: Food intake is not possible.
2. Assessment of any fungal, viral, and bacterial infected lesions following criteria described by Carranza.[34]
3. Plaque index of Silness and Löe[35] and Gingival index of Löe and Silness.[36] Six surfaces were selected for assessment of Plaque and Gingival indices according to Wei *et al*[37]
4. The decayed, missing, and filled teeth per subject (dmf) for primary and (DMF) for permanent were recorded according to the WHO criteria.[38]

Statistical analysis: Descriptive statistics were performed using frequency counts and percentages. Logistic regression models were used to identify predictors of dichotomous variables. Statistical significance was set at 5%. Simple and clustered bar charts were used for graphical display of data.

RESULTS

The study subjects consisted of 82 (54.7%) males and 68 (45.3%) females. Their age was ranging from 7 months to 12 years, with a mean age of 6.98±3.56 years. Table 1 shows the sociodemographic information, the oral hygiene and dietary habits of all the patients who participated in the present study.

Table 2 presents the data concerning type and stage of the malignancy, the duration of treatment, dose and number of cycles of the chemotherapy. The most common encountered solid tumor was the neuroblastoma (29.7%), followed by Wilm's tumor (20.3%), then the oesteosarcoma (15.6%), and the Ewing sarcoma (9.4%), however, the other types of solid tumors(brain tumor (6.3%) , rhabdomyosarcoma (6.3%), medulloblastoma (3.1%),) were not frequent. Other types namely; nasopharyngeal carcinoma, rhinoblastoma, Ovarian carcinoma, Testis tumor, Fibrosarcoma, Round cell tumor were also found; each of them was represnted in one pediatric patient (1.6%). Eighty-six (57.3%) patients received chemotherapy for hematologic malignancies; 50 patients (58.1%) had acute leukemias, 35 patients (40.7%) had lymphomas, and only one patient (1.2%) had Langerhan's

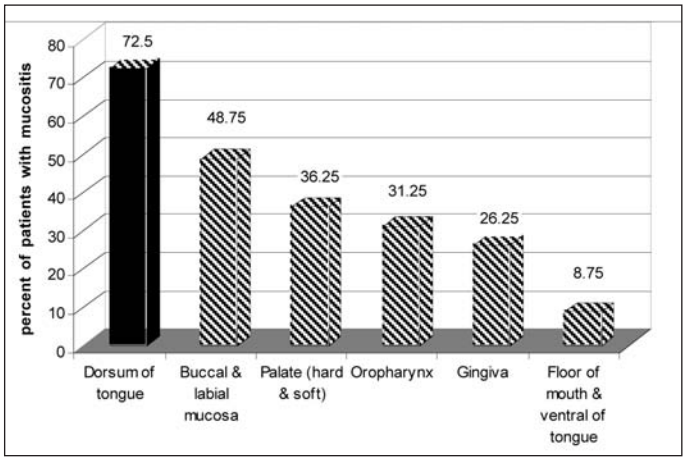

Figure 1: Distribution of the patients according to their complaints

Table 1: Distribution of the studied sample (n=150) according to sociodemographic characteristics, oral hygiene and dietary habits

Variables	Subcategories	n	%
Gender	Male	82	54.70
	Female	68	45.30
Social status	Poor	129	86.00
	Moderate	19	12.70
	High	2	1.30
Father's job	Manual	125	83.3
	Skilled/semi skilled	21	14.0
	Professional	2	1.30
	Dead	2	1.30
Practice oral hygiene	No	120	80
	Yes	30	20
Method used for oral hygiene	Brushing	22	73.3
	Gargle	8	26.7
	Flossing	--	0
	Others	--	0
Frequency of oral hygiene procedures	Three times per day	7	23.3
	Twice per day	2	6.7
	Once per day	13	43.3
	Rarely	8	26.7
Type of food intake	Normal	64	42.7
	Soft	35	23.3
	Liquids	36	24
	Parenteral	15	10
Frequency of food intake	As usual	51	34
	Less than usual	26	17.3
	Rarely	58	38.7
	Parenteral	15	10

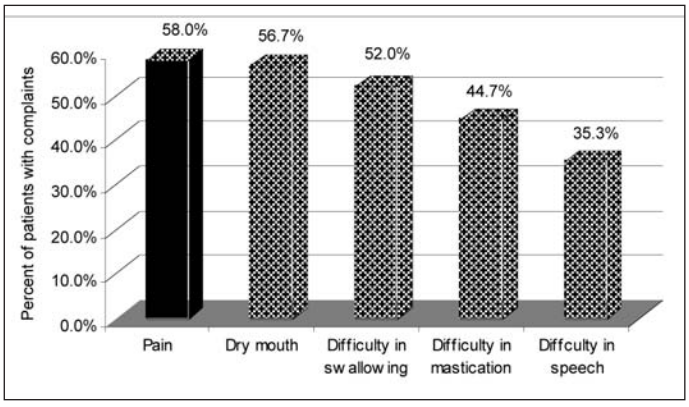

Figure 2: Distribution of the patients with mucositis according to site of the lesions

Table 2: Patients distributed according to the type and stage of the malignancy

%	n	Subcategories	Variables
42.67	64	Solid tumors	**Type of malignancy**
57.33	86	Hematologic malignancies	
25.33	38	I	**Stage of malignancy**
5.33	8	II	
6.00	9	III	
12.67	19	IV	
50.00	75	Microtubule inhibitors	**Drugs**
46.00	69	Alkylating agent	
46.00	69	Cytotoxic antibiotics	
36.67	55	Antimetabolites	
32.67	49	Chromatin function inhibitor	
23.33	35	Heavy metals	
18.67	28	Steroids	
2.00	3	Mixenteron	
91.33	137	Full dose	**Dose**
3.33	5	Reduced to half	
5.33	8	Reduced to quarter	
67.33	101	1-10	**Number of cycles**
11.33	17	11-23	
21.33	32	Too many to count	
0.17 - 72		Range	**Duration of treatment (in months):**
8.57±11.93		mean ± SD	

histiocytosis.

Figure 1 presents the patients' oral complaints. The most frequent oral complaint that prevented the patients from eating and drinking normally was oral pain which was common in 87 patients (58%).

Gingival and plaque indices were recorded in 139 patients of the 150 patients, as the remaining 11 patients (7.3%) were not reported as they were too young to have teeth. The mean plaque index was 1.8 ± 0.65, while, the mean gingival index was 1.5 ± 0.64. Out of the 50 leukemic patients only 4 patients (8%) had leukemic gingival hyperplasia. Concerning dental caries, out of the 150 patients, 10 patients (6.7%) were very young and had unerupted teeth, 46 patients (30.7%) had primary dentition with a mean dmf of 3.48 ± 4.76, 89 patients (59.3%) had mixed dentition with a mean dmf of 2.74 ± 3.84 and mean DMF of 0.39 ± 0.85, and 5 patients (3.3%) had only permanent dentition, none of them had caries.

Table 3 shows distribution of the patients with chemotherapy-induced oral complications. By examining the oral cavity of

Table 3: Distribution of the patients with clinical oral complications

Type	Subcategories	n	%
Oral mucositis	Grade 1	27	33.8
	Grade 2	16	20.0
	Grade 3	30	37.5
	Grade 4	7	8.8
	Total	80	53.3
Oral infections		73	48.7
Spontaneous oral bleeding		13	8.7

Table 4: Logistic regression model for factors predicting the presence of oral mucositis

Predictors	Wald-χ^2	P-value	OR	95% CI
Using antimetabolites	13.842	<0.001*	4.18	1.97-8.93
Duration of treatment	0.797	0.372	0.987	0.96-1.02
Not performing oral hygiene	4.048	0.044*	2.46	1.02-5.91

* Statistically significant at $p \leq 0.05$

Table 5: Variables predicting oral infections in three (for viral, bacterial, and fungal) different logistic regression models

Model	Predictors	Wald χ^2	P value	OR	CI
Model (a) (viral)	Plaque index	4.43	0.04*	3.75	1.10-12.84
	Gingival index	0.825	0.36	0.55	0.15-1.99
	Prescribed topical antifungal	3.08	0.08	3.13	0.88-11.11
	Prescribed systemic antibiotic	8.23	0.004*	7.69	1.92-33.33
	Prescribed systemic antiviral	0	1.00	0	0
	Alkylating therapy	2.135	0.14	2.70	0.71-10.00
	Antimetabolites therapy	6.38	0.01*	6.25	1.52-25.00
Model (b) (bacterial)	Plaque index	2.69	1.01	2.46	0.84-7.24
	Number of decayed teeth	9.45	0.002*	1.24	1.08-1.42
Model (c) (fungal)	Plaque index	1.69	0.19	1.60	0.79-3.26
	Gingival index	2.49	0.12	0.54	0.25-1.17
	Having mucositis	6.28	0.012*	0.37	0.17-0.81
	Mixenteron drugs therapy	0	0.999	0	0

* Statistically significant.

Table 6: Variables predicting spontaneous oral bleeding in a logistic regression model

Predictors	Wald χ^2	P value	OR	CI
Platelet count	6.56	0.01*	0.989	0.96-0.997
Microtubule inhibitor therapy	0.097	0.76	0.83	0.25-2.76

* Statistically significant.

all the patients (n=150) clinically, it was found that 80 patients (53.3%) were suffering from chemotherapy-induced oral mucositis. Their distribution according to site has been illustrated in figure 2.

Out of the 150 patients, 73 patients (48.7%) had clinically apparent oral infection; 45 patients (30%) of the cases had clinically obvious fungal infection, while 12 patients (8%) had localized suppuration (dental/others) as an indication for bacterial infection, 2 patients had mixed fungal and bacterial infection, and 18 patients (12%) had clinically obvious viral infection, out of them, only 2 (1. 3%) patients had chicken pox, and the other 16 patients (10.7%) had HSV infection table 3.

Bivariate analysis between the different oral complications and the different studied variables were done in order to determine the possible factors that affect the prevalence and severity of these oral complications. Those variables with significant relationships were reintroduced into a logistic regression model for multivariate analysis. Concerning oral mucositis, Table 4 showed that taking antimetabolites was the most statistically significant variable in both the bivariate and multivariate analysis ($p< 0.001$), and it increased the risk of oral mucositis 4.18 times. This was followed by not performing oral hygiene which increased the risk of oral mucositis 2.46 times.

Table 5 presents three different logistic regression models. In model (a), it was found that receiving the systemic antibiotics increased the risk of viral infection 7.69 times, followed by receiving the antimetabolites which increased the risk of viral infection 6.25 times. Model (b) showed that increased number of decayed teeth is the main factor affecting the presence of bacterial infection. However, none of the related variables could be considered as a factor predicting the presence of fungal infection although having oral mucositis had a strong indirect relationship with the presence of fungal infection (model c).

The logistic regression model in table 6 showed that the decreased platelets count is the main factor affecting the risk of spontaneous oral bleeding in pediatric cancer patients receiving chemotherapy (OR=0.99, CI=0.96-0.99).

DISCUSSION

In contrast to the past, many patients with malignancies are treated as outpatients. Therefore, their oral care will no longer be the exclusive responsibility of the hospital dentist. Rather it is the family pediatric dentist who will probably be consulted for information regarding the oral complications of chemotherapy.[24] Oral pain was the most common complain of the present study population (58%). A previous study conducted by McCarthy *et al* [39] reported that 55% of cancer patients receiving vincristine had oral pain that might be related to the neurotoxicity of this drug. Their results were in consistent with the present study. However, lower percentages (8-16%) were obtained by other investigations[24,40]. On the other hand, higher percentages were reported by McGuire *et al*[41] and Cella *et al*[42] who found that up to 67% and 77% (respectively) of cancer patients receiving high-doses chemotherapy were suffering from oral pain. These higher percentages may be due to high-dose chemotherapy, as compared to standard-dose chemotherapy received by patients in the present study.

The dry mouth which is also considered one of the most serious complications of chemotherapy was the main complain in 85 patients (56.7%) of our total sample. Comparable results were obtained by Dens *et al*[43]; about 66% of cancer patients receiving high-dose chemotherapy had dry mouth. In contrast to the present study, higher percentages of dry mouth (97% and 88%) were obtained from terminally ill cancer patients by Sweeney *et al*[44] and Oneschuk *et al*[40] respectively. However, lower percentages of xerostomia; 12%(24) and 35% 45 were found among cancer patients in other studies. This wide variation may be explained by the multifactorial nature of xerostomia. Chemotherapy is not the only factor affecting the rate of salivation in cancer patients, oral infections for example also leads to xerostomia in cancer patients.[40]

In the present study, 80 patients (53.3%) of the sample had oral mucositis. The frequency of oral mucositis in cancer patients receiving standard dose chemotherapy was studied by many investigators, and a wide variation of results was obtained. Two previous studies reported closer results, and found that 52% and 55% (respectively) of the cancer patients had oral mucositis.[46,47] In contrast, lower percentages (8.33-40%) were reported by several other studies.[24,48-51] However, Wahlin *et al*[52] found a higher percentage of oral mucositis (69%) in pediatric cancer patients. This high prevalence of oral mucositis was affected by many fac-

tors. Poor oral hygiene that was recorded in 120 patients (80%) of the sample was strongly associated with increased incidence of oral mucositis. This result is in agreement with previous studies.[49,53-55] The antimetabolites group; which was one of the most frequently used (received by 37.6% of patients) drugs; was also strongly related to the incidence of oral mucositis in the present study. This direct relationship was detected also by several investigators.[47,55-57] Most of them agreed that the higher incidence of oral mucositis occurred when the antimetabolites were given to the cancer patients.

The direct association between the increased oral mucositis incidence and the decreased granulocytic count previously reported in several studies,[13,52,53] was not detected in the present study. In contrast, it was observed that the granulocytic count in the oral mucositis patients was slightly higher than that of the non oral mucositis patients. An explanation for this variation may be that the oral mucositis in the present study sample was probably associated with some degree of systemic infection that had increased the granulocytic count.

Although the prevalence of oral mucositis was higher in patients with hematologic malignancies, there was no significant relation observed between the prevalence of oral mucositis and the type of tumor, in contrast to what was found by Sonis *et al*[54] who found that the oral mucositis was higher in patients with hematological malignancies, and Childers *et al*[50] who found that the oral mucositis was higher in patients with solid tumors.

The fungal infection was the most common type of infection found in the present study. About 30% of the sample had clinically apparent fungal infection. Closer results were obtained by Wahlin *et al*,[52] Barrett *et al*,[28] and Epstein *et al*[58], they all reported that 31% of the cancer patients had fungal infection. In contrast, lower percentages of 10.7%[50], and 11%[24] were also reported. However, higher percentages were obtained by both Bergmann *et al*[59] who reported that 75% of cancer patients had fungal infection and Al-Abeid *et al*[60] who reported that the fungal colonization was identified in 72.6% of the cancer patients. This variability between the different studies may be attributed to the difference in the type of drugs taken which may have different immunosuppressive action, since the immunosuppressive action of antineoplastic drugs and steroids may predispose the onset of fungal infection by altering the inflammatory response.[8]

The fungal infection was not associated with the increased incidence of oral mucositis in the present study; in contrast the increased incidence of oral mucositis was negatively related to the risk of fungal infection. This finding is supported by Epstein *et al*[58,61], who found that there was no relation between the oral mucositis and the fungal infection. In addition, another inverse relation was found between the fungal infection and both the gingival and plaque indices, this relation which indicates that the risk of fungal infection is not affected by the bad oral hygiene is supported by Bergmann *et al*[59] who found that daily plaque removal did not decrease the prevalence of oral candidiasis in leukemic patients.

There was a direct association between the incidence of viral infection and the systemic antibiotics given to the patients by their physicians, which sounds logic; the abuse of antimicrobial medications is known to increase the risk of opportunistic infections.[62] Other relations were observed between the increased plaque and gingival indices and the viral infection, which might be due to the increased oral soreness and pain associated with the viral lesions leading to oral hygiene negligence and accumulation of food debris in addition to the marginal gingivitis produced by the herpetic infections. Another relation observed was between taking antimetabolites for cancer treatment and the incidence of viral infection, this relation also sounds logic; the antimetabolites are known to be the most chemotherapeutic agents producing marked bone marrow suppression and affect the whole mucosal lining which increases the risk of infection.[32]

The bacterial infection was clinically detected by the localized accumulation of pus, twelve patients (8%) of the sample had abscesses, and most of these abscesses were dental in origin. Previous studies reported almost similar results concerning the frequencies of abscesses in cancer patients receiving chemotherapy.[24,28,63] The caries and the plaque indices were the main factors affecting the incidence of bacterial infection in the present study. In addition the increased number of chemotherapeutic cycles received by the patients was associated with more bacterial infection; which might be due to the prolonged debilitation experienced by the patients.

CONCLUSION

1. Oral complications among patients receiving chemotherapy are common especially oral mucositis, oral infections, and spontaneous oral bleeding. Such complications often affect the quality of life for these patients, and in the cases of severe oral mucositis and infections, they may be a direct threat to survival.

2. The prevalence of oral infections and the spontaneous oral bleeding lied in the same known level worldwide, while that of the oral mucositis and the poor oral hygiene are considered relatively high.

3. The bad oral hygiene and the high caries incidence in the pediatric cancer patients played an important role in the development of serious oral complications.

4. The chemotherapeutic antimetabolites and the systemic antibiotics are associated with more oral complications than other types of drugs.

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