Factors associated with time free of oral candidiasis in children living with HIV/AIDS, São Paulo, Brazil

Fatores associados ao tempo livre de candidíase oral em crianças vivendo com HIV/AIDS, São Paulo, Brasil

Factores asociados al tiempo libre y la candidiasis oral en niños que viven con VIH/SIDA, São Paulo, Brasil

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Abstract

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In clinical practice, recurrence of thrush is common in children living with HIV/AIDS. The aim of this study was to determine the factors associated with time spent free of oral candidiasis using survival analysis for recurrent events. A retrospective cohort study was carried out with 287 children treated between 1985 and 2009 at a reference center in the city of São Paulo, Brazil. The Prentice, Williams and Peterson model for recurrent events was used for the investigation of factors associated with the time free of oral candidiasis. The following factors were associated with the time patients were free of oral candidiasis: moderate immunodepression (HR = 2.5; p = 0.005), severe immunodepression (HR = 3.5; p < 0.001), anemia (HR = 3.3; p < 0.001), malnutrition (HR = 2.6; p = 0.004), hospitalization (HR = 2.2; p < 0.001), monotherapy (HR = 0.5; p = 0.006), dual therapy (HR = 0.3; p < 0.001) and triple therapy/highly active antiretroviral therapy (HR = 0.1; p < 0.001). The method analyzed in the present study proved useful for the investigation of recurrent events in patients living with HIV/AIDS.

Oral Candidiasis; HIV; Acquired Immunodeficiency Syndrome; Child; Survival Analysis

Resumo

A recorrência da candidíase oral em crianças vivendo com HIV/AIDS é um acontecimento muito comum na prática clínica. O objetivo foi verificar os fatores associados ao tempo livre de candidíase oral, utilizando técnica de análise de sobrevida para eventos recorrentes. Estudo de coorte retrospectivo com 287 crianças, atendidas entre 1985 e 2009, em um serviço de saúde de São Paulo, Brasil. Foi utilizado o modelo marginal para eventos recorrentes de Prentice, Williams e Peterson para investigação dos fatores associados ao tempo livre de candidíase oral. Imunodepressão moderada (HR = 2,5; p = 0,005) ou grave (HR = 3,5; p < 0,001), anemia (HR = 3,3; p < 0,001), desnutrição (HR = 2,6; p = 0,004) e internação (HR = 2,2; p < 0,001), monoterapia (HR = 0,5; p = 0,006), terapia dupla (HR = 0,3; p < 0,001) e terapia tripla/HAART (HR = 0,1; p < 0,001) foram associados ao tempo livre de candidíase oral. A metodologia apresentada neste artigo pode ser bastante útil em pesquisas na área de HIV/AIDS, quando pretende-se estudar eventos com comportamento de recorrência.

Candidíase Bucal; HIV; Síndrome de Imunodeficiência Adquirida; Criança; Análise de Sobrevida

Introduction

Persistent oral candidiasis (thrush) is the most frequent fungal condition among children living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) [1]. On the systemic level, this population is prone to the development of thrush due to the immunodeficiency caused by the harmful action of HIV on CD4+ T lymphocytes. Locally, an increase in the permeability of the epithelium and change in humoral immunity (IgA) of the oral mucosa stemming from the action of HIV facilitate infection by *Candida* [2]. Other factors commonly found in children living with HIV/AIDS, such as anemia, hospitalization, antiretroviral drugs and broad-spectrum antibiotics, have also been implicated in the pathological mechanism of thrush [3,4].

Persistent oral candidiasis is considered an important condition in the context of HIV/AIDS, as it affects quality of life and is an indicator of the progression of HIV infection [5,6,7,8,9]. Consequently, a large amount of information has been published on the incidence of thrush and associated factors in periods prior to and following the advent of highly active antiretroviral therapy (HAART) using a single episode of thrush per individual as the unit of analysis [10,11,12]. However, the recurrence of this condition is a very common event in clinical practice, as children living with HIV/AIDS often experience numerous episodes throughout their lives. Thus, the question arises as to whether the study of factors associated with the occurrence of thrush should consider only a single episode or multiple episodes throughout patient follow-up.

Few studies have employed survival analysis techniques developed for recurrent events, such as marginal models, in the investigation of this condition [13,14,15,16,17]. Thus, the aim of the present study was to determine factors associated with the time spent free of oral candidiasis in children living with HIV/AIDS using survival analysis for recurrent events.

Methods

A retrospective cohort study was carried out with children treated at a reference center for the treatment of AIDS in the city of São Paulo, Brazil. Data from medical charts were collected by a team of healthcare professionals using a previously tested, standardized chart.

The physicians at the reference center were trained to diagnose persistent oral candidiasis through: (i) a microscopic examination of a sample of the oral mucosa with characteristic findings; or (ii) a macroscopic examination of removable white plaques on erythematous tissue, following the recommendations of the Brazilian Ministry of Health [18].

The study population was made up of patients with a laboratory confirmation of HIV infection contracted through vertical transmission and less than 13 years of age at the time of admission to the health center. Patients in follow up for less than 90 days were excluded from the study. Children admitted to the health center between January 1, 1985 and October 1, 2009 were included and followed up until December 31, 2009 (end of the study). Different criteria for the definition of HIV infection and clinical conditions were used during the long follow-up period of the cohort, according to year of diagnosis [18,19,20,21].

The initial population was made up of 452 children, 325 of whom met the inclusion criteria. However, 38 were excluded for having a follow-up period of less than 90 days. Thus, the final sample was made up of 287 children.

A descriptive analysis (absolute and relative frequency distribution) of the cohort was first performed. The Kaplan-Meier product limit estimator [22] was then used to estimate the cumulative probability curves for the time between admission to the study and the emergence of oral candidiasis in relation to the independent variables (time of HIV diagnosis, gender, age, immune system impairment, viral load, anemia, malnutrition, hospitalization and antiretroviral regimen). The log-rank test was used for the comparison of the curves [23,24]. The (-ln(-ln(S(t)))) method in function of the follow-up time logarithm was used to determine the parallelism of the curves.

The Prentice, Williams and Peterson (PWP) marginal model for recurrent events was used to investigate factors associated with the time free of oral candidiasis. This model considers events in time and assumes that the basal risk of a new event is different from but dependent on the previous event [24,25]. The hazard ratio (HR) was estimated for each independent variable. The Wald test was used to test the hypothesis that HR = 1 [25]. The null hypothesis was rejected when the p-value was ≤ 0.05.

For the use of the PWP model, an event was considered to be the occurrence of an episode of oral candidiasis and it was defined that up to three episodes per individual could be counted. Censure occurred in four situations: (i) patients in follow up at the end of the study; (ii) those transferred to another health center; (iii) those who abandoned follow up; and (iv) those who died.

The 287 children were distributed among three risk strata. A particular number of obser-

vations were entered in the database for each child based on the number of episodes of oral candidiasis: 198 children who did not develop oral candidiasis made up stratum 1 (each contributed one observation to the database); 44 exhibited one episode of oral candidiasis and made up strata 1 and 2 (each contributed two observations to the database); 26 exhibited two episodes of oral candidiasis and made up strata 1, 2 and 3 (each contributed three observations to the database); and 19 exhibited three episodes of oral candidiasis and made up strata 1, 2 and 3 (each contributed three observations to the database). Thus, the cohort was formed by 421 observations among 287 children (Figure 1).

Time was the dependent variable and was defined based on the order of occurrence of events:

• 1st time interval (stratum 1): period (in years) between the beginning of follow up at the reference center and the date of the first episode of oral candidiasis or censure;

• 2nd time interval (stratum 2): period (in years) between the date of the first episode and the date of the second episode of oral candidiasis or censure;

• 3rd time interval (stratum 3): period (in years) between the date of the second episode and the date of the third episode of oral candidiasis or censure.

The forward stepwise method was employed in the multivariate modeling. For such, variables with a p-value < 0.20 in the univariate analysis of the PWP model were selected. The variables that maintained statistical significance ($p \leq 0.05$) (immune system impairment, anemia, malnutrition, hospitalization and antiretroviral regimen) and those that statistically adjusted the parameters of the other variables (time of HIV diagnosis) remained in the final model. Proportionality of risk over time was determined using Schoenfeld's residual analysis, which employs a chi-square statistic with one degree of freedom based on the proportion of observed and expected survival [22]. All analyses were performed using the Stata program, version 11 (Stata Corp., College Station, USA).

This study received approval from the Human Research Ethics Committee of the School of Public Health, São Paulo University, Brazil (USP) under process number CEP/FSP n. 2033.

Figure 1

Formation of cohort for analysis of factors associated with oral candidiasis in children infected by HIV; reference center in São Paulo, Brazil, 1985-2009.
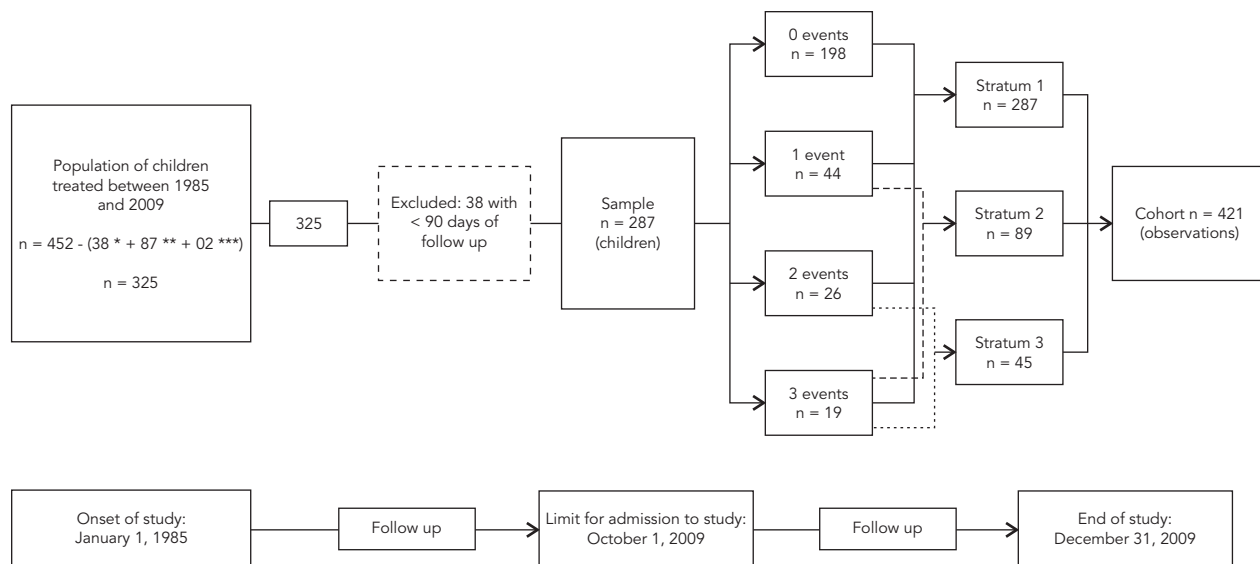
* Children without laboratory exams confirming HIV infection;

** Children who did not acquire HIV infection through vertical transmission;

*** Children aged ≥ 13 years upon admission to healthcare center.

Results

A total of 421 observations relating to 287 children with HIV infection between 1985 and 2009 were analyzed. Mean follow-up time was 6.8 ± 5.0 years (range: 0.3 to 17.8 years). Table 1 displays the distribution of observations according to the demographic, clinical and treatment characteristics of the children. The majority (67.5%) received a laboratory diagnosis of HIV prior to the advent of HAART; 51.3% were female and nearly half (47.5%) were aged between one and five at onset of follow up. More than 70% exhibited immune system impairment and nearly 100% had a detectable plasma viral load during the follow-up period for oral candidiasis. Up to three months before the appearance of oral candidiasis, 8.1% of exhibited anemia, 6.2% were diagnosed with malnutrition and 31.3% had at least one hospitalization. Regarding antiretroviral treatment, HAART (43.4%) was the most recent regimen both prior to the appearance of oral candidiasis as well as among those patients with no diagnosis of this condition.

Figure 2 shows the cumulated probability of time free of oral candidiasis according to the independent variables. Significant differences among the curves were found for the following variables: period of HIV diagnosis ($p < 0.001$), immune system impairment ($p < 0.001$), anemia ($p < 0.001$), malnutrition ($p < 0.001$), hospitalization ($p < 0.001$) and antiretroviral regimen ($p < 0.001$). The survival time free of oral candidiasis was greater among the children with a diagnosis of infection following the advent of HAART and those without anemia, malnutrition or hospitalization. In contrast, the survival time was reduced with the exacerbation of immune system impairment as well as with the reduction in the number of drugs in the antiretroviral regimen.

Table 2 displays the results of the analysis using the PWP model. In the univariate analysis, the following variables were associated with the time free of oral candidiasis: laboratory diagnosis of HIV prior to the advent of HAART (HR = 2.5; $p < 0.001$), severe immunodepression (HR = 2.3; $p = 0.001$), anemia (HR = 5.7; $p < 0.001$), malnutrition (HR = 6.3; $p < 0.001$) and hospitalization (HR = 3.2; $p < 0.001$). Dual therapy (HR = 0.3; $p < 0.001$) and triple therapy/HAART (HR = 0.1; $p < 0.001$) were protection factors against the manifestation of oral candidiasis.

Year of HIV diagnosis, immune system impairment, anemia, malnutrition, hospitalization and antiretroviral regimen were selected for multivariate modeling and 352 observations made up the final model. The following variables were independently associated with time free of oral candidiasis: moderate immunodepression (HR = 2.5; $p = 0.005$), severe immunodepression (HR = 3.5; $p < 0.001$), anemia (HR = 3.3; $p < 0.001$), malnutrition (HR = 2.6; $p = 0.004$) and hospitalization (HR = 2.2; $p < 0.001$). Monotherapy (HR = 0.5; $p = 0.006$), dual therapy (HR = 0.3; $p < 0.001$) and triple therapy/HAART (HR = 0.1; $p < 0.001$) were independent protection factors. Time of the laboratory diagnosis of HIV infection remained in the final model for adjustments, but was nonsignificant. The risk proportionality of the model was determined and this presupposition was fulfilled ($\chi^2 = 9.84$; $p = 0.363$).

Discussion

Candidiasis has considerable clinical significance in the prognosis of HIV infection and as an indicator of the non-effectiveness of antiretroviral treatment [26,27]. While some authors state that the use of statistical methods that do not consider the recurrence of episodes of thrush could lead to errors in the estimate of risks [14,28,29,30], there is debate regarding whether the analysis of a single episode may correspond equally to the joint analysis of multiple episodes in some situations [31].

In the present study, the investigation of factors associated with the time patients are free of oral candidiasis revealed the following independent predictors of the disease: moderate to severe immunodepression, anemia, malnutrition and hospitalization. Moreover, the use of antiretroviral therapy (monotherapy, dual therapy or triple therapy/HAART) proved to be an independent protection factor.

Survival free of disease was closely linked to the degree of immunodepression, as risk increased with the exacerbation of immune system impairment. This association has been described in previous cohorts of children throughout the world [32,33,34]. However, researchers state that defenses against *Candida* may be compromised by HIV even before the drop in the levels of CD4+ T lymphocytes [35,36], which may explain the appearance of thrush in individuals with HIV whose defense cell counts are within the range of normality.

In the present study, anemia was a predictor of oral candidiasis, as the time free of this disease was greater in children without anemia. Different clinical presentations of oral candidiasis, especially the mucocutaneous and angular forms, have previously been associated with anemia [37]. Besides iron deficiency, which is the main cause of childhood anemia, other nutritional disorders have been implicated in the occurrence of oral

Table 1

Distribution of observations * according to demographic, clinical, laboratory and treatment characteristics; reference center in São Paulo, Brazil, 1985-2009.

Variable	n	%
Period of HIV diagnosis		
Pre-HAART (1985-1997)	284	67.5
Post-HAART (1998-2009)	137	32.5
Total	421	100.0
Gender		
Female	216	51.3
Male	205	48.7
Total	421	100.0
Age at onset of follow up (years)		
< 1	144	34.2
1-5	200	47.5
≥ 6	77	18.3
Total	421	100.0
Immune system impairment **		
Absence	88	24.0
Moderate	125	34.2
Severe	153	41.8
Total	366	100.0
Plasma viral load ** [n = 248]		
Undetectable	1	0.4
Detectable	247	99.6
Total	248	100.0
Anemia ***		
No	387	91.9
Yes	34	8.1
Malnutrition ***		
No	395	93.8
Yes	26	6.2
Hospitalization ***		
No	279	68.7
Yes	127	31.3
Total	406	100.0
Antiretroviral regimen #		
No treatment	89	21.2
Monotherapy	66	15.8
Dual therapy	82	19.6
Triple therapy/HAART	182	43.4
Total	419	100.0

HAART: highly active antiretroviral therapy.

* Relating to 287 children;

** Up to three months before or three months after appearance of oral candidiasis in cases of occurrence of disease or at end of study for cases in which disease did not occur;

*** Up to three months before appearance of oral candidiasis in cases of occurrence of disease or throughout study for cases in which disease did not occur;

Most recent regimen before appearance of oral candidiasis in cases of occurrence of disease or last regimen received throughout study for cases in which disease did not occur.
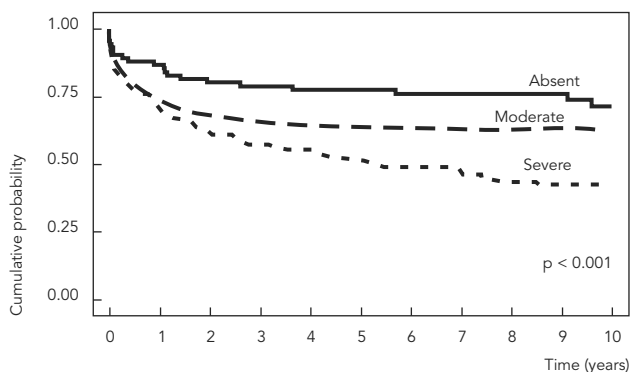
Figure 2

Cumulative probability of time free of oral candidiasis in children infected by HIV; reference center in São Paulo, Brazil, 1985-2009.
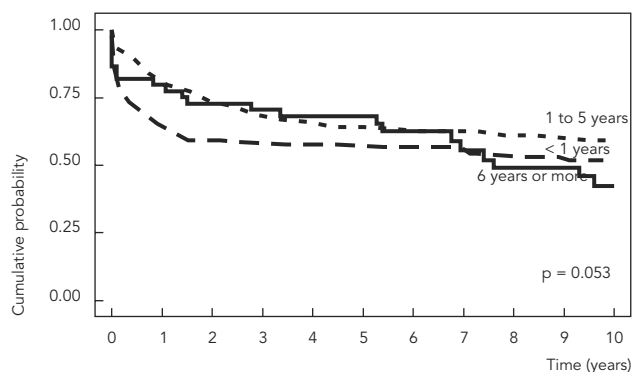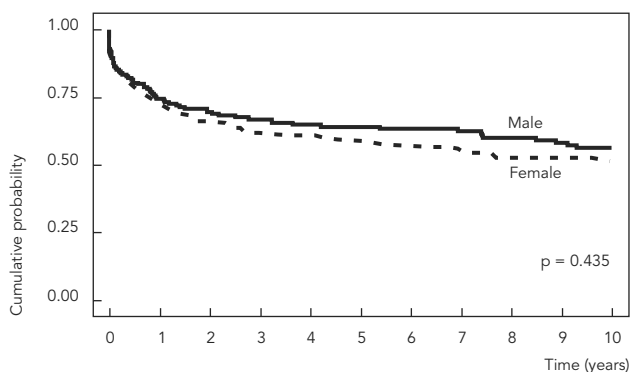
2a) Period of HIV diagnosis
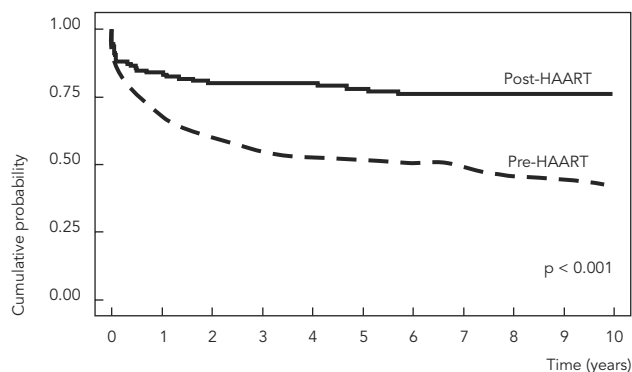
2b) Immune system impairment

2c) Age

2d) Gender

(continues)

candidiasis among children living with HIV/AIDS. In the present study, the time patients were free of oral candidiasis was significantly shorter among malnourished children. Previous studies have also found malnutrition to be a systemic risk factor for the development of oral candidiasis [38,39].

Hospitalization was investigated as a proxy variable of serious diseases to which children infected with HIV are subject. Hospitalization is a frequent, critical process among such children due to the exacerbation of the clinical situation or the social status of the child [40,41]. In the present study, a significant association was found with hospitalization (regardless of the determinant cause), as survival time free of oral

candidiasis was greater in children who had not been hospitalized.

The present study also demonstrated the beneficial effect of antiretroviral drugs, especially HAART, in the prevention of oral candidiasis. This finding has been previously reported for Brazilian children [42,43]. Moreover, the time patients were free of oral candidiasis increased with the addition of new drugs to the antiretroviral regimen. These results are in agreement with findings reported in previous studies, which defend the hypothesis that antiretroviral drugs not only reestablish systemic immunological competence, but also improve the immune response of the oral mucosa against the fungus [44,45]. This may explain situations in which the resolution of
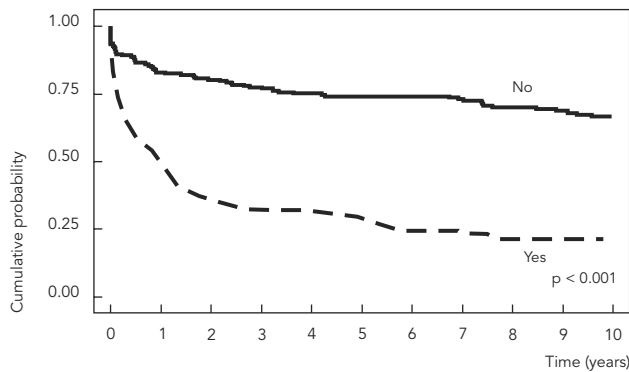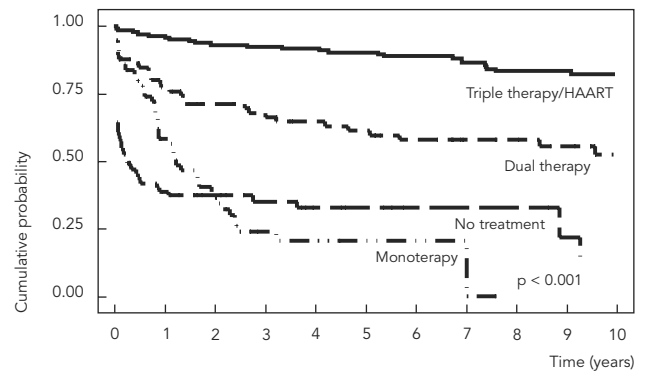
Figure 2 (continued)

2e) Anemia
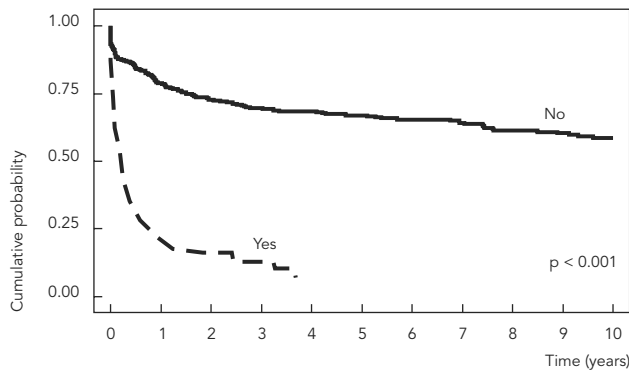
2f) Malnutrition
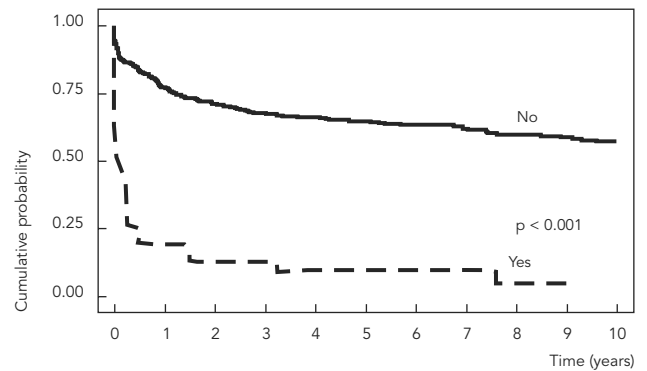
2g) Hospitalization

2h) Antirretroviral regimen

HAART: highly active antiretroviral therapy.

oral candidiasis precedes the reestablishment of normal CD4+ T lymphocyte counts [46].

No associations were found between survival time free of oral candidiasis and the gender or age of children living with HIV/AIDS. These results are in agreement with findings reported in a cohort of American children [33].

Due to the nearly 100% prevalence rate of a detectable viral load, it was not possible to determine the association between this variable and the risk of developing oral candidiasis. However, high viral loads have been associated with compromised oral health in the pediatric population living with HIV/AIDS [36,47,48]. Moreover, while no analysis was performed of associations between the prior use of antibiotics and/or corticoids and the appearance of oral candidiasis in the present study, these groups of medications have been

described as risk factors for this condition due to the fact that they alter the local flora and create a favorable environment for the fungus [37].

The present study has limitations that should be considered. Due to the cohort design, the reference for the comparisons was the availability of different treatment regimens in different times of the year and with different degrees of adherence. However, this strategy is employed and defended by a number of authors [49,50]. Different criteria for the definition of cases were used during the long follow-up period of the cohort, with an increasingly earlier diagnosis and onset of treatment/prophylaxis over the years. Moreover, the source document for the data collection was the child's medical chart, which was not always filled out satisfactorily for the purposes of the present study. To minimize possible bias, care was taken

Table 2

Univariate and multivariate analyses of factors associated with time free of oral candidiasis in children infected by HIV; reference center in São Paulo, Brazil, 1985-2009.

Variable	Oral candidiasis		HR	p-value	Adjusted HR	p-value
	n	%				
Period of HIV diagnosis						
Pre-HAART (1985-1997)	125	44.0	1.0	< 0.001	1.0	0.093
Post-HAART (1998-2009)	28	20.4	2.5		1.6	
Gender						
Female	80	37.0	1.0	0.974	-	-
Male	73	35.6	1.0		-	
Age at onset of follow up (years)						
≥ 6	28	36.4	1.0		-	-
1-5	65	32.5	0.8	0.353	-	
< 1	60	41.7	1.3	0.280	-	
Immune system impairment *						
Absent	22	25.0	1.0		1.0	
Moderate	40	32.0	1.5	0.121	2.5	0.005
Severe	68	44.4	2.3	0.001	3.5	< 0.001
Anemia **						
No	126	32.6	1.0	< 0.001	1.0	< 0.001
Yes	27	79.4	5.7		3.3	
Malnutrition **						
No	135	34.2	1.0	< 0.001	1.0	0.004
Yes	18	69.2	6.3		2.6	
Hospitalization **						
No	76	27.2	1.0	< 0.001	1.0	< 0.001
Yes	72	56.7	3.2		2.2	
Antiretroviral regimen ***						
No treatment	50	56.2	1.0		1.0	
Monotherapy	40	60.6	0.9	0.670	0.5	0.006
Dual therapy	28	34.1	0.3	< 0.001	0.3	< 0.001
Triple therapy/HAART	35	19.2	0.1	< 0.001	0.1	< 0.001

HAART: highly active antiretroviral therapy; HR: hazard ratio.

* Up to three months before or three months after appearance of oral candidiasis in cases of occurrence of disease or at end of study for cases in which disease did not occur;

** Up to three months before appearance of oral candidiasis in cases of occurrence of disease or throughout study for cases in which disease did not occur;

*** Most recent regimen before appearance of oral candidiasis in cases of occurrence of disease or last regimen received throughout study for cases in which disease did not occur.

to ensure the standardization of the data collection from the charts and a review of all questionnaires. Additionally, the inclusion criteria (acquisition of HIV infection through vertical transmission and age zero to 13 years) minimized difficulties in the comparison of the children analyzed with regard to clinical-epidemiological data and strengthened the homogeneity of the sample.

It should be stressed that the choice of the PWP marginal model is considered adequate for modeling recurrent events and the variables of interest are known and available for the analysis of factors associated with the time patients are free of oral candidiasis [30,51]. Despite the sophistication of current statistical packages, which enable the complete execution of this type of modeling in a matter of minutes, the organization and analysis of the databank were performed with caution, since the statistical theory behind this type of model is complex.

In conclusion, the present study identified immunodepression, anemia, malnutrition, hospitalization and antiretroviral therapy as factors associated with the time patients are free of oral candidiasis in a population of children living with HIV/AIDS in the city of Sao Paulo, Brazil. Moreover, the method presented in this article can be useful for the investigation of recurrent events in studies addressing HIV/AIDS.

Resumen

La repetición de candidiasis oral en los niños que viven con VIH/SIDA es muy común en la práctica clínica. El objetivo fue verificar los factores asociados al tiempo libre y la candidiasis oral, usando la técnica de análisis de supervivencia para eventos recurrentes. Se realizó un estudio de cohorte retrospectiva con 287 niños que visitaron entre 1985 y 2009 un servicio de salud de São Paulo, Brasil. Se usó el modelo marginal para eventos recurrentes de Prentice, Williams y Peterson, con el fin de investigar los factores asociados. Moderada inmunodepresión (HR = 2,5; p = 0,005) o grave (HR = 3,5; p < 0,001), anemia (HR = 3,3; p < 0,001), desnutrición (HR = 2,6; p = 0,004) y hospitalización (HR = 2,2; p < 0,001), monoterapia (HR = 0,5; p = 0, 006), terapia dual (HR = 0,3; p < 0,001) y triple terapia/TARGA (HR = 0,1; p < 0,001) se asociaron al tiempo libre y la candidiasis oral. La metodología presentada en este artículo puede ser útil para la investigación en el área de VIH/SIDA, cuando se pretenda estudiar el comportamiento de la repetición del evento.

Candidiasis Bucal; HIV; Síndrome de Inmunodeficiencia; Niño; Análisis de Supervivencia

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