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Oral Considerations in Pediatric Patients with Acute Lymphoblastic Leukemia

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Trabalho realizado à Universidade Fernando Pessoa como parte dos requisitos para a obtenção do grau de Mestre em Medicina Dentária, sob orientação da Prof. Doutora Teresa Sequeira e co-orientação da Prof. Doutora Augusta Silveira.

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Abstract

Introduction: Acute lymphocytic leukemia is one of the most common type of cancer in children and it is characterized by excessive and disordered immature leukocytes in the bone marrow.

Objectives: Identify oral and general common signs and symptoms of Acute lymphocytic leukemia in pediatric patients and when receiving chemotherapy, hematopoietic cell transplantation, and/or radiation therapy.

Methods: A systematic literature search in PubMed, Scielo and B-on data base was made, giving preference to articles from the last 10 years and with free access, using the following keywords: children, acute lymphoblastic leukemia, treatment, early effects, long-term effects, oral health.

Development: There are many oral manifestations in this patients either from the disease it self or from the treatment. Some of the most common are: bone alterations, trismus, gingival bleeding, echymoses, mucosal pallor, mucositis, xerostomia and oportunistic infections.

Discussion and Conclusion: The dental clinicians may contribute to a higher survival rate and improved oral related quality of life in ALL patients since they might enable an early diagnose, they are able to support antineoplastic treatment success and monitoring / treatment of long term changes. Dentists shall, therefore, be a critical element of the multidisciplinary team in hematology-oncology context.

Keywords: children, acute lymphoblastic leukemia, treatment, early effects, long-term effects, oral health.

Resumo

Introdução: A leucemia linfocítica aguda é um dos tipos de cancro mais comuns em crianças e é caracterizada pela produção excessiva e desordenada de leucócitos imaturos na medula óssea.

Objetivo: Identificar sinais, sintomas gerais e orais da leucemia linfocítica aguda em crianças, sujeitas a tratamento (quimioterapia, transplante de células hematopóieticas e ou radioterapia). Identificar o potencial contributo do médico dentista quer na sobrevida quer na qualidade de vida relacionada com a saúde oral destes pacientes.

Metodologia: Foi realizada uma pesquisa bibliográfica nas base de dados PubMed, Scielo e B-on, considerados preferencialmente os artigos publicados nos últimos 10 anos e os artigos de acesso livre; foram utilizadas as palavras-chave: children, acute lymphoblastic leukemia, treatment, early effects, long-term effects, and oral health.

Desenvolvimento: São muitas as manifestações orais presentes nestes pacientes, quer resultantes da doença quer do tratamento. Algumas das mais comuns são: alterações ósseas, trismus, sangramento gengival, equimoses, palidez das mucosas, mucosite, xerostomia, e infecções oportunistas.

Discussão e Conclusão: O médico dentista pode contribuir para uma maior taxa de sobrevivência e melhoria da qualidade de vida relacionada com a saúde oral dos pacientes com ALL uma vez que possibilita um diagnóstico precoce, apoia o sucesso do tratamento antineoplásico e o acompanhamento/tratamento das alterações que podem surgir a longo prazo. O médico dentista pode ser assim um elemento crítico da equipa multidisciplinar no contexto da hematologia-oncologia.

Palavras-chave: crianças, leucemia linfocítica aguda, tratamento, efeitos a curto prazo, efeitos a longo prazo, saúde oral.

Index

I. Introduction

Leukemia constitutes approximately 30% of all childhood cancers (Padmini and Bai, 2014; Cho, Cheng & Cheng, 2000; Francisconi *et al*, 2016). Acute lymphoblastic leukemia (ALL) is the most common type of malignancy encountered in children and accounts for about 75% of childhood leukemia's (Javed *et al.,* 2012). ALL is a malignant disorder resulting from the clonal proliferation of lymphoid precursors with arrested maturation giving rise to B-cell or T-cell leukemias or sometimes to mixed lineage leukemia (Padmini and Bai, 2014).

The cause of leukemia is unknown although certain leucogenic factors are postulated, including ionizing radiation, genetic and immunological factors, viruses and exposure to benzene derivatives and ethyl carbonates (Xavier and Hegde, 2010).

Oral complications can compromise the protocols of chemotherapy, often leading to decrease of the administered dose, change in treatment protocol, or even discontinuation of antineoplastic therapy, directly affecting patient survival (Zimmermann *et al.*, 2015).

Chemotherapy and/or radiotherapy for the treatment of cancer or in preparation for hematopoietic cell transplantation (HCT) may cause many acute and long-term side effects in the oral cavity. Furthermore, because of the immunosuppression that patients experience, any existing or potential sources of oral/dental infections and/or soft tissue trauma can compromise the medical treatment, leading to morbidity, mortality, and higher hospitalization costs (American Academy of Pediatric Dentistry, 2013).

Objectives

Identify oral and general common signs and symptoms of Acute lymphocytic leukemia in pediatric patients and when receiving chemotherapy, hematopoietic cell transplantation, and/or radiation therapy.

I.1. Materials and methods

A systematic literature search in PubMed, Scielo and B-on data base was made, giving preference to articles from the last 10 years and with free access, using the following keywords: children, acute lymphoblastic leukemia, treatment, early effects, long-term effects, and oral health.

Manuscript analysis was substantiated on Meta-Analysis Reporting Standards (Module A1 and Module A2*,* APA style).

II. Development

II.1. Signs and symptoms of Acute Lymphoblastic Leukemia

Signs of leukemia often manifest in the mouth, and patients usually search for dental care thinking that diseases is of local origin. It is worth to note that dentists are responsible for initiating the diagnosis in 33% of patients with acute myelomonocytic leukemia (Stafford *et al.,* 1980). These manifestations should be recognizable, leading to a fully investigation with additional tests or referring the patient to a specialized professional in order to reach an early diagnosis (Francisconi *et al.*, 2016).

II.1.1. Common signs and symptoms

Early symptoms, including nonspecific ones, such as fatigue, dyspnea, fever, pallor, weight loss or bleeding, may be associated with pancytopenia (anemia, neutropenia or thrombocytopenia). Blasts may also infiltrate organs or lymph nodes, resulting in hepatosplenomegaly, lymphadenopathy or bone pain. Symptoms of testicular or central nervous system (CNS) involvement are rarely noted at diagnosis (Francisconi *et al.,* 2016).

II.1.2. Oral manifestations

Oral complications occur frequently and may point out the initial evidence of the disease or of its relapse. Oral lesions arise in both acute and chronic forms of all types of leukemia. However, they are far more frequent in acute stages (Francisconi *et al.*, 2016). These oral manifestations either may be the result of direct infiltration of leukemic cells (primary) or secondary to underlying thrombocytopenia, neutropenia, or impaired granulocyte function (Francisconi *et al.*, 2016).

Gingival bleeding, hyperplasia, opportunistic infections and bone alterations are common oral manifestations of leukemia**.** Leukemic infiltration can cause gingival swelling which is a constant finding of the disease. The gingival hyperplasia is usually generalized and differs in severity (Lowal *et al.,* 2015).

Some authors describe gingival swelling as frequent manifestation of ALL (Pai *et al*., 2012; Silva *et al.*, 2012; Lim and Kim., 2014).

Katz and Peretz (2002) reported trismus as the first presentation of ALL in a 6-year-old boy, when intraoral examination and panoramic radiograph demonstrated no signs of infection and/or other pathology. The trismus could be explained as an intensive infiltration of leukemic cells into the deep portion of the muscles of mastication (Katz and Peretz, 2002, Francisconi *et al.,* 2016).

ALL may also involve the lymphoid-bearing tissue of the orofacial region including the tonsils. Lymphadenopathy of the head and neck region is a consistent sign (Declerck and Vinckier, 1988). (Francisconi *et al.,* 2016)

Intraorally, mucosal pallor, or echymoses also may be noted (Declerck and Vinckier, 1998) and petechia as well (Francisconi *et al.*, 2016).

Another possible manifestations can be sore throat, laryngeal pain, and oral ulceration (Padmini and Bai, 2014; da Fonseca, 2004).

Several studies have reported an increased incidence of mucosal anomalies characterized by extensive ulcers, and oral mucosal infections (mucositis, candidiasis, herpes simplex) in ALL patients (Anirudhan *et al.,* 2008).

Pericoronitis may also correspond to an initial manifestation of ALL (Aronovich and Connolly, 2008).

II. 2. Treatment of Acute Lymphoblastic Leukemia

Once diagnosed, treatment is carried in distinct phases. The purpose is to induce a remission and maintain this with appropriate supportive care such as the management of anemia, bleeding and infection. Treatment also involves the eradication of malignant cells from extra-medullary sites, such as the central nervous system, and the testes in boys (Xavier and Hegde, 2010).

The treatment of leukemia depends on factors such as type and subtype of the disease, risk factors, and age. In general, the recommended treatment is chemotherapy with or without adjuvant treatments. Hematopoietic stem cell transplantation (HSCT) is generally performed in the acute forms of the disease and some cases of chronic myeloid leukemia (Zimmermann *et al.,* 2015).

The treatment of ALL is based on clinical risk and is usually divided in four phases (Padmini and Bai, 2014; Xavier and Hegde, 2010; da Fonseca, 2004; Barbería *et al.,* 2008):

Remission induction - generally lasts 28 days and consists in a combination of 3 or 4 drugs (cytostatics and imunosupressants – the most commonly used are vincristine, prednisone, and L-asparaginase) A 95% success rate is frequently achieved. The remission is a known pre-requisite for prolonged survival.

CNS preventive therapy/prophylaxis - CNS can act as a sanctuary site for leukemic infiltrates because systemically administered chemotherapeutic drugs are not able to cross the blood-brain barrier. Cranial irradiation and/or weekly intrathecal injection of a chemotherapeutic agent (usually methotrexate) are used. This presymptomatic treatment can be done in each phase as well.

Consolidation or intensification - in an attempt to kill any remaining leukemic cells, it is designed to minimize the development of drug cross-resistance through intensified

treatment. Commonly used drugs include: imunosupressants, antimetabolites and alkylating agents (eg. 6-mecaptopurine, cytarabine and cyclophospamide). This phase lasts for 4 weeks.

Maintenance - The purpose is to suppress leukemic growth through continuous administration of cytotoxic drugs (namely methotrexate and 6- mercaptopurine). The optimal length of this phase has not been established yet but usually lasts from 2.5 to 3 years.

II. 3. Post-treatment oral effects

The oral mucosa is highly susceptible to the effects of chemotherapy and radiotherapy due high mitotic activity and is the most frequently documented source of sepsis in the immunosuppressed pediatric leukemic patients. Existing lesions that might normally lie dormant can flare up and become life threatening once the child is immune suppressed (Padmini and Bai, 2014).

II. 3.1. Early Oral complications of antineoplastic treatment

Oral complications at this stage often include: mucositis, gingival bleeding, xerostomia (Lowal *et al.*, 2015; Padmini and Bai, 2014) opportunistic infections (Zimmermann *et al.,* 2015).

Mucosal ulceration is one of the most frequent oral problem encountered (Padmini and Bai, 2014; Harris et al., 2014) and has a significant impact on patients quality of life and treatment plan (Cawley & Benson, 2005; Rubenstein et al).

Figliolia and colleagues (2008) examined 169 ALL pediatric patients and the association of oral mucositis (OM) with age, gender and leucocyte count were assessed (Figliolia *et al*. 2008). Forty-six percent of patients developed OM during chemotherapy. The study also showed that 48% of patients <9 years old and 39% of the patients between 10 and 18 years old developed OM . One study conducted by Pels (2012) reported that OM was present prior to anticancer therapy in 5% of a group of 78

pediatric patients with ALL. Sixty two percent of these patients manifested OM after the induction of chemotherapy with average time of 10-16 days of chemotherapy (Pels, 2012).

Xerostomia or reduced salivation and dysguesia, is a frequent effect of radiotherapy in the head and neck region. A variety of drugs other than chemotherapeutics like sedatives, opiates, antidepressants, antihistamines, diuretics may also be responsible to induce xerostomia. (Gupta, Epstein & Sroussi, 2006).

In a cross sectional study done by Dholam and colleagues (2014) 33 pediatric patient (5-15 years old, both gender) undergoing chemotherapy (induction phase particularly) were observed and they found that the oral health status, DMFT index and gingival findings were significantly deteriorated following the induction phase. This can be explained by the change in quality and quantity of saliva due to anticancer treatment (Dholam *et al.* 2014). Other study reported by Azher and Shiggaon (2013) similar results were found (Lowal *et al.*, 2015).

Prolonged bleeding in childhood malignancy may be caused by chemotherapy induced myelosuppresion, certain medications and disorders of clotting and platelets related to the baseline disease (Xavier and Hegde, 2010).

Fungal infections (Candida) of the oral mucosa are common and can cause burning sensation, distortion of taste and problems with swallowing. Viral infections especially the re-activation of herpes simplex virus type I (HSV-1) is serious because they can cause pain and problems with hydration and nutrition (Xavier and Hegde, 2010).

The leukemic child may be at high risk for dental caries from a dietary standpoint for a number of reasons as patients are prescribed daily nutritional supplements rich in carbohydrate to maintain or gain weight and oral pediatric medications contain high amounts of sucrose (e.g., nystatin) which makes them prone for dental caries. (Padmini and Bai, 2014).

Some patients may complain of paresthesias caused by leukemic infiltration of the peripheral nerves. Others may report dental pain mimicking irreversible pulpitis in the absence of a dental/periodontal infection. (da Fonseca, 2004)

Oral complications of treatment of leukemia in children such as; leukemic infiltration in the mandible, trismus, mucormycosis and oral aspergillosis could be found (Lowal *et al.*, 2015).

For pediatric patients who are undergoing bone marrow transplant and radiotherapy, they may develop graft-versus-host disease (GVHD) 2-3 weeks after the transplantation , and it's induced by the cytotoxic effect of the donor T lymphocytes in the receiver tissues. Those patients may manifest oral signs such as: erythema, erosion, ulceration of the mucosa, lichenoid changes and xerostomia. (Lowal *et al*., 2015)

II. 3.2. Late and long term effects of antineoplastic treatment

The most common changes are microdontia, agenesis of teeth, change in crown or root shape, defective mineralization of the dental structure, and delayed tooth eruption (Padmini and Bai, 2014).

Direct radiation of the jaw, face and head can promote the most serious side effects in children which includes incomplete development of the jaws, arrested tooth development which can cause small teeth, atrophy of the overlying soft tissue; enamel malformation and incomplete calcification of teeth (Xavier and Hegde, 2010).

Some cross-sectional studies correlate ALL treatments and dental anomalies frequency (Minicucci, Lopes & Crocci, 2003; Maciel *et al*., 2009; Khojastepour, Zareifar & Ebrahimi, 2014). The clinical and radiographic examination showed that 82%, 80% and 28% of the same patients had at least one dental anomaly, respectively. Moreover, Maciel *et al.* 2009 reported that agenesis, microdontia, tapering roots and short roots was considerably greater on the same group Vasconcelos *et al.* 2009 stated that ALL treatment does affect the dental age maturity of the involved patients compared to their healthy counterparts. (Vasconcelos *et al.,* 2009; Lowal *et al.,* 2015)

A study conducted by Sonis et al. in 97 children to evaluate craniofacial development in long term survivors of acute lymphoblastic leukemia found that craniofacial effects of therapy were observed in only those children who received 2400 cGy before 5 years of

age. Ninety percent of children in this group had diminished mandibular growth that was determined by cephalometric analysis (Padmini and Bai, 2014).

Another similar study conducted by Guyuron et al., has shown that among 41 patients who received irradiation to the head and face during growth thirty-eight of them had soft tissue or bony deformities. (Padmini and Bai, 2014). A study done by Minicucci and colleagues (2003) showed delays in dental development, hypoplasia, and microdontia in children receiving chemotherapy. (Minicucci, Lopes & Crocci, 2003; Padmini and Bai, 2014).

Some studies also refer the risk of developing of mucoepidermoid carcinoma in previously treated leukemic children (Boccon *et al*., 2005; Sandoval and Jaybose, 2001; Cheuk *et al.,* 2008) and squamous cell carcinoma secondary to allogenic bone marrow transplant. (Lowal *et al*., 2015).

Children undergoing an allogenic bone marrow transplant (BMT) often develop Graft-versus-Host-Disease (GVHD) and oral cavity may be the first or only site showing GVHD. An increasing level of xerostomia and/or generalized stomatitis which appear hundred or more days after the BMT are indicators of chronic GVHD. The younger the child, the greater is the risk for craniofacial and developmental abnormalities (Xavier and Hegde, 2010).

III. Discussion

Despite the increased incidence of neoplastic malignancies, a higher survival has been reported - early diagnosis and improved treatments share important contributions (Barbosa *et al.,* 2010; Silva *et al*., 2012; Lim &Kim., 2014). ALL is associated with general and common signs and symptoms with frequent oral expression (Francisconi *et al*., 2016; Stafford *et al*., 1980). A depth knowledge and careful attention to such signs and symptoms allow the dental clinician to contribute for an early diagnosis, improving survival.

Oral mucosa is highly susceptible to the effects of chemotherapy and radiotherapy and it is a frequent source of sepsis in the treatment phase - lesions that might normally lie dormant can flare up. Such oral complications often compromise chemotherapy protocols, leading to a decreased dose administration, changes in the protocol treatment, or even discontinuation of antineoplastic therapy – these changes affect directly both patient survival and its quality of live (Padmini and Bai, 2014; Zimmermann *et al.*, 2015). Dental professionals should be able to promote adequate oral care during treatment, in order to prevent its compromise, and thus, contribute to both survival and quality of live related to oral health.

Several studies support the reduction of the amount of microbial flora, reduction pain and bleeding, and prevention infection and reduces the risk of dental complications provided by oral care (Cawley & Benson, 2005; Rubenstein *et al*, 2004). OM is one of the most frequent complications and it can be highly severe and aggressive. Harris and colleagues (2008) reported an evidence-based intervention consisting on adherence to a oral care regimen can reduce the duration and severity of OM, although oral care has not been demonstrated to completely prevent OM, (Harris *et al,* 2008). Furthermore, Cheng and colleagues (2001) found a 38% decrease in OM incidence in children supervised with oral care when compared to a control group (without oral care supervision). Moreover, both pain and OM severities were also significantly reduced (Cheng, Molassiotis, Chang, Wai, & Cheung, 2001; Cheng, Chang, & Yuen, 2004). These results reinforced the importance of oral care in ALL children along treatment.

Leukemia treatment may exert an adverse influence on odontogenesis and growth centers, affecting maturation of craniofacial complex and resulting in asymmetrical facial growth and malocclusion (Padmini and Bai, 2014). There is also risk involving the development of mucoepidermoid carcinoma in leukemic patients and a squamous cell carcinoma secondary to allogenic bone marrow transplant as reported by (Lowal *et al*., 2015). These abnormalities may have a significant impact on aesthetic and may also cause functional and occlusal disturbances A relapse of ALL is also possible, associated with and again, oral manifestations. The long-term monitoring of these patients, by the

dentist, allows an earlier detection and therefore an earlier treatment/management of such anomalies.

IV. Conclusions

The dental clinician should be aware and capable to recognize the general and oral signs and symptoms of ALL, contributing to an early diagnosis, and therefore, to higher survival rate.

During antineoplastic treatment, dentists should be able to provide adequate and proper oral care to patients, in order to prevent and minimize the oral complications associated to treatment - minimizing the possibility of treatment compromising - improving the general and oral quality of life of the patient, contributing to a higher success of the antineoplastic treatment and again, to a higher survival rate.

After treatment, the dentist should provide a long-term follow-up, treating and managing all the manifestations that can appear. Relapse of the disease should also be considered. It is of great importance that caregivers advise and guide the patients for a good oral hygiene and oral care.

The dental clinicians may contribute to a higher survival rate and improved oral related quality of life in ALL patients since they might enable an early diagnose, support antineoplastic treatment success and monitoring treatment of long-term effects. Dentists shall, therefore, be a critical element of the multidisciplinary team in hematology-oncology context.

V. References

American Academy of Pediatric Dentistry. (2013). Guideline on Dental Management of Pediatric Patients Receiving Chemotherapy, Hematopoietic Cell Transplantation, and/or Radiation Therapy. *Reference Manual - Clinical Practice Guidelines,* 37(6), pp. 298-306.

Anirudhan D., Bakhshi S., Xess I., Broor S., Arya L.S. (2008). Etiology and outcome of oral mucosal lesions in children on chemotherapy for acute lymphoblastic leukemia. *Indian Pediatr.,* 45(1), pp. 47-51.

Aronovich S. and Connolly T.W. (2008). Pericoronitis as an initial manifestation of acute lymphoblastic leukemia: a case report. *J Oral Maxillofac Surg.,* 2008 66(4), pp. 804-808. doi: 10.1016/j.joms.2006.10.062.

Azher U. and Shiggaon N. (2013). Oral health status of children with acute lymphoblastic leukemia undergoing chemotherapy. Indian J Dent Res. , 24(4), pp. 523. doi: 10.4103/0970-9290.118371.

Barbería E., Hernandez C., Miralles V., Maroto M. (2008). Paediatric patients receiving oncology therapy: review of the literature and oral management guidelines. *Eur J Paediatr Dent.,* 9(4), pp. 188-94.

Barbosa, A., Ribeiro, D. & Caldo-Teixeira, A. (2010). Conhecimentos e práticas em saúde bucal com crianças hospitalizados com câncer. *Ciência & Saúde Coletiva,* 15(1), pp. 1113-1122.

Cawley, M.M., & Benson, L.M. (2005). Current trends in managing oral mucositis. *Clinical Journal of Oncology Nursing, 9*(5), pp. 584–592.

Cheng, K.K., Chang, A.M., & Yuen, M.P. (2004). Prevention of oral mucositis in paediatric patients treated with chemotherapy: A randomised crossover trial comparing two protocols of oral care. *European Journal of Cancer, 40*(8), pp. 1208–1216.

Cheng, K.K., Molassiotis, A., Chang, A.M., Wai, W.C., & Cheung, S.S. (2001). Evaluation of an oral care protocol intervention in the pre- vention of chemotherapy-induced oral mucositis in paediatric can- cer patients. *European Journal of Cancer, 37*(16), pp. 2056–2063.

Cho S.Y., Cheng A.C. and Cheng M.C. (2000). Oral care for children with leukemia. *Hong Kong Med J.*, 6(2), pp. 203-208.

da Fonseca M.A. (2004). Dental care of the pediatric cancer patient. *Pediatr Dentistry*, 26(1), pp. 53-57.

Declerck D, Vinckier F (1988). Oral complications of leukemia. *Quintessence Int*, 19, pp. 575-83.

Dholam K.P., Gurav S., Dugad J. and Banavli S. (2014). Correlation of oral health of children with acute leukemia during the induction phase. *Indian J Med Paediatr Oncol.,* 35(1), pp. 36–39. doi: 10.4103/0971-5851.133717

Figliolia S.L., Oliveira D.T., Pereira M.C., Lauris J.R., Maurício A.R., Oliveira D.T., Mello de Andrea M.L. (2008). Oral mucositis in acute lymphoblastic leukaemia: analysis of 169 paediatric patients. *Oral Dis.,* 14(8), pp. 761-766. doi: 10.1111/j.1601-0825.2008.01468

Francisconi C. *et al*, (2016). Leukemic Oral Manifestations and their Management, *Asian Pacific Journal of Cancer Prevention,* 17, pp. 911-915.

Gupta A., Epstein J.B, Sroussi H. (2006). Hyposalivation in elderly patients. *J Can Dent Assoc.*, 72(9), pp. 841-846.

Guyuron B., Dagys A.P., Munro I.R. and Ross R.B. (1983). Effect of irradiation on facial growth: a 7- to 25-year follow-up, *Annals of Plastic Surgery*, 11(5), pp. 423–427.

Harris D., Eilers J., Harriman A., Cashavelly B.J., Maxwell C. (2008). Putting evidence into practice: evidence-based interventions for the management of oral mucositis. *Clin J Oncol Nurs*, 12, pp.141-52.

Javed F., Utreja A., Bello Correa F.O., Al-Askar M., Hudieb M., Qayyum F., Al-Rasheed A., Almas K., Al-Hezaimi K. (2012). Oral heath status in children with acute lymphoblastic leukemia, *Critical Reviews in Oncology Hematology*, 83, pp. 303-309.

Katz J., Peretz B. (2002). Trismus in a 6 year old child: a manifestation of leukemia? *Journal of Clinical Pediatric Dentistry*, 26, pp. 337-9.

Khojastepour L., S Zareifar S. and Ebrahimi M. (2014). Dental Anomalies and Dental Age Assessment in Treated Children with Acute Lymphoblastic Leukemia. *Iran J Ped Hematol Oncol.,* 4(4), pp. 172–177.

Lim H.C., Kim C.S. (2014). Oral signs of acute leukemia for early detection, J *Periodontal Implant Sci,* 44:293-299 http://dx.doi.org/10.5051/jpis.2014.44.6.293

Lowal K.A. et al., (2015). Dental Considerations for Leukemic Pediatric Patients: An Update Review for General Dental Patrictioner, Master Sociomed, 27(5), pp. 359-362

Maciel J.C., de Castro C.G. Jr, Brunetto A.L., Di Leone L.P., da Silveira H.E. (2009). Oral health and dental anomalies in patients treated for leukemia in childhood and adolescence. *Pediatr Blood Cancer,* 53(3), pp. 361-365. doi: 10.1002/pbc.22108.

Minicucci E.M., Lopes L.F., Crocci A.J. (2003). Dental abnormalities in children after chemotherapy treatment for acute lymphoid leukemia. *Leuk Res.,* 27(1), pp. 45-50.

Padmini C. and Bai K. (2014). Oral and Dental Considerations in Pediatric Leukemic Patient, *ISRN Hematology*, [Em linha] Disponivel em http://dx.doi.org/10.1155/2014/895721. [Consultado em 20/02/2017].

Pai A., Prasad S., Dyasanoor S. (2012). Acute leukemias: a dentist's perspective. *Minerva Stomatol*, 61, pp. 233-8.

Pels E. (2012). Oral mucositis in children suffering from acute lymphoblastic leukaemia. *Contemp Oncol,* 16(1), pp. 12–15. doi: 10.5114/wo.2012.27331

Rubenstein, E.B., Peterson, D.E., Schubert, M., Keefe, D., McGuire, D., Epstein, J., Elting L.S., Fox P.C., Cooksley C and Sonis S.T. (2004). Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer,* 100(9, Suppl.), pp. 2026–2046.

Silva B.A., Siqueira C.R., Castro P.H., Araújo S.S., Volpato L.E. (2012). Oral manifestations leading to the diagnosis of acute lymphoblastic leukemia in a young girl. *J Indian Soc Pedod Prev Dent.,* 30(2), pp. 166-168. doi: 10.4103/0970-4388.100003.

Sonis AL, Tarbell N, Valachovic RW, Gelber R, Schwenn M, Sallan S. (1990). Dentofacial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. *Cancer*, 66(12), pp. 2645-52.

Stafford R., Sonis S., Lockhart P. and Sonis A. (1980). Oral pathoses as diagnostic indicators in leukemia. *Oral Surgery, Oral Med, Oral Pathol*, 50(2), pp. 134-139.

Vasconcelos N.P.S., Caran M.M., Lee M.L., Lopes N.F., Weiler R.M.E. (2009). Dental maturity assessment in children with acute lymphoblastic leukemia after cancer therapy, *Forensic Science International,* 184, pp. 10-14.

Xavier A.M. and Hegde A.M. (2010). Preventive Protocols and Oral Management in Childhood Leukemia - the Pediatric Specialist's Role. *Asian Pacific Journal of Cancer Prevention,* 11, pp. 39-43.

Zimmermann, C., Meurer M., Grando L., Moral A.,Rath I. and Tavares S. (2015). Dental Treatment in Patients with Leukemia, *Journal of Oncology*. http://dx.doi.org/10.1155/2015/571739