Literature Review

An Overview of Chronic Oral Graft-Vs-Host Disease Following Pediatric Hematopoietic Stem Cell Transplantation

Marcio A. da Fonseca, DDS, MS[1] • Catherine Hong, BDS, MS[2]

Abstract: *Hematopoietic stem cell transplant (HSCT) is the treatment of choice for many hematologic, genetic, oncologic, and immunologic diseases. It is also one of the most aggressive treatments among the different cancer therapies, however, and is associated with severe conditioning-related toxicity, profound neutropenia, a high level of prophylactic immunosuppression and graft-vs-host disease (GVHD). Even with GVHD prophylaxis, chronic GVHD remains a significant complication of HSCT and is a frequent reason for nonrelapse morbidity and mortality following allogeneic HSCT. It primarily targets the skin, gastrointestinal tract, and liver. Approximately 20% of patients who receive matched sibling transplants and 40% of matched unrelated donor recipients will develop chronic GVHD. Risk factors include: (1) history of acute GVHD; (2) hematologic malignancy; (3) female donor to male recipient; (4) use of total body irradiation; (5) donor age of ≥5 years; and (6) recipients >10 years of age. The purpose of this paper was to review the pathogenesis, prevention, and treatment of pediatric chronic graft-vs-host disease, with a focus on its oral manifestations and the dental management of affected children and adolescents. (Pediatr Dent 2008;30:98-104) Received April 6, 2007 / Last Revision June 14, 2007 / Revision Accepted June 15, 2007.*

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Hematopoietic stem cell transplantation (**HSCT**) is the treatment of choice for patients with hematologic, oncologic, genetic, and immunologic diseases and conditions for which conventional treatment modalities are likely to result in less successful disease-free survival (**DFS**).[1] Even when both the donor and the recipient are fully matched at the human leukocyte antigen (HLA) major histocompatibility loci, minor antigens not detectable by current typing technology make all allogeneic recipients at risk for development of graft-vs-host disease (**GVHD**). GVHD occurs in both an acute and chronic form, each with different kinetics and distinctive pathology.[2]

Although development of chronic GVHD (**cGVHD**) is associated with fewer relapses after allogeneic HSCT, it is the most frequent reason for poor long-term outcome and quality of life (**QoL**). The disease is the major cause of nonrelapse morbidity and mortality following allogeneic transplantation, becoming the primary limitation to its wider use.[2-4] The incidence of cGVHD is lower in children than in adults, but the number of patients developing the disease is rising due to the use of alternative stem cell sources and attempts to modulate the immune system to improve DFS.[5,6] Currently, there is minimal data on the long-term effects of cGVHD in pediatric subjects, but one can speculate about the deleterious effects of the disease itself and its treatment on a growing organism.[5] As more children and adolescents survive HSCT, pediatric dentists face a significant challenge in treating its oral complications and sequelae and modifying their approach to the dental care of these patients.

The purpose of this paper was to review the pathogenesis, prevention, and treatment of pediatric chronic GVHD, with a focus on its oral manifestations and the dental management of affected children and adolescents.

Pathogenesis, clinical manifestations, incidence, and risk factors. Although progress has been made in the understanding of the mechanisms of acute GVHD (**aGVHD**), the basic pathophysiology of cGVHD remains poorly defined.[2,3,5,6] aGVHD describes a distinctive syndrome of dermatitis, hepatitis, and enteritis developing within 100 days of allogeneic HSCT. cGVHD, on the other hand, tends to be a more pleiotropic syndrome that generally develops after day 100 although it can be seen prior to that.[5,7] In humans, it seems to be caused by the aberrant recovery of the immune system, primarily involving T-lymphocyte imbalances leading to a loss of normal regulation and, hence, to the recognition of T cells as foreign.[5,6] The clinical manifestations of cGVHD

[1]*Dr. da Fonseca is clinical associate professor, Department of Pediatric Dentistry, The Ohio State University College of Dentistry, Nationwide Children's Hospital, Columbus, Ohio; and* [2]*Dr. Hong is an assistant professor, Department of Oral Medicine, Section of Pediatric Dentistry, Carolinas Medical Center, Charlotte, NC. Correspond with Dr. da Fonseca at Marcio.DaFonseca@nationwidechildrens.org.*

(Table 1) closely resemble those of autoimmune diseases, thus suggesting a similar pathophysiology.[2,4,6] The disease is associated with significant immunodeficiency because of impaired T and B cell production, altered T cell function, impaired antibody production, and functional asplenia, which are all aggravated by immunosuppressive medications used to treat it.[3] The disease may occur by itself ("de novo"), present after resolution of aGVHD ("quiescent" or "interrupted"), or evolve from aGVHD ("progressive").[3,4,7] The most commonly used clinicopathological staging divides the disease into limited or extensive. The significant heterogeneity in GVHD prophylaxis and in the stem cell source in the pediatric population makes it difficult to quantify its true incidence.[5] CGVHD presents between 3 and 14 months post-HSCT in approximately 20% of matched sibling transplants and in 40% of matched unrelated donor recipients.[8] The most significant risk factors for developing cGVHD are: 1) patient age 10 years or older; 2) donor age 5 years or older; 3) female donor to male recipient; 4) use of total body irradiation as part of the transplant conditioning regimen; 5) diagnosis of hematologic malignancy; and 6) previous aGVHD.[9,10]

There is a low rate of GVHD following cord blood transplants, possibly due to a decreased reactivity of the donor T cells or other cells within the cord, lower age of the recipient, and use of antithymocyte globulin and steroids as part of the conditioning.[5]

Table 1. CLINICAL MANIFESTATIONS OF CHRONIC GRAFT-VS-HOST DISEASE [4-6,8,13]

Eyes	Sicca syndrome, burning, irritation, pain, photophobia, cataracts, conjunctivitis, corneal ulceration
Liver	Cholestatic abnormalities, cirrhosis, portal hypertension, liver failure
Skin	Epidermal atrophy, dermal fibrosis, generalized scleroderma leading to contractures, hyper- or hypopigmentation, poikiloderma
Hair, nails	Alopecia, thin, brittle hair, premature graying of the hair, nail loss, vertical ridging, fragile nails
Pulmonary	Obstructive lung disease, cough, wheezing, bronchiolitis obliterans
Gastrointestinal	Difficulty or pain with swallowing, heartburn, weight loss, malnutrition, decreased appetite, nausea, vomiting, diarrhea, abdominal pain, esophageal web, strictures, abnormal motility, malabsorption
Oral cavity	Decreased salivary flow, sensitivity to acidic or spicy foods and drinks, pain, atrophy, erythema, lichenoid lesions, mucoceles, ulcerations, pseudomembranes, soft tissue growths
Musculoskeletal	Arthralgias, arthritis, myalgias, weakness, contractures
Immune system	Sepsis with encapsulated micro-organisms, sinopulmonary infections, pneumocystis pneumonia, late cytomegalovirus and herpes zoster infections
Other	Vaginitis, vaginal strictures, bradycardia, chest pain, proteinuria, sensory and motor neuropathies, immune thrombocytopenic purpura, neutropenia, autoimmune hemolytic anemia, loss of sweat glands, cystitis

cGVHD diagnosis, course, and prognosis. The similarities between cGVHD and a normal immune response make it difficult to use biologic markers for diagnosis and response.[4] Viral infections and drug reactions may also confound the diagnosis. If the classic manifestations of the disease are not present, a tissue biopsy, particularly from the oral mucosa and skin, is necessary to aid the diagnosis and to determine if infection is present.[4,7] Close monitoring of post-transplant patients is critical to establish an early and correct diagnosis of cGVHD in order to prevent late complications and disability.[7] The disease course is determined mainly by its extent and the severity of the associated immunosuppression.

Overall survival and DFS at 6 years post-HSCT in a recent pediatric study was 67% and 57%, respectively.[11] Mortality is increased in subjects with: 1) extensive disease; 2) progressive-type onset; 3) thrombocytopenia; 4) impaired performance status; 5) involvement of the skin, gastrointestinal tract, and oral cavity; 6) weight loss; and 7) HLA-nonidentical donors.[6,7,12,13]

This shouldn't be a paragaraph; it's a continuation of the paragraph above The lowest mortality rates are seen in patients with limited disease and/or "de novo" onset, which occurs in 20% of the cases.[3,5-7] The major cause of death is infectious complications, followed by progressive organ failure from GVHD involvement.[5,7] A study of 52 pediatric allogeneic HSCT survivors showed that cGVHD subjects had lower QoL scores than those without it, especially in self-esteem and general health.[14]

The disease and the drugs used for its prevention and treatment, pretransplant conditioning with irradiation, and altered immune functions are strongly related to the risk of new solid cancers, mainly squamous cell carcinomas of the skin and oral cavity.[15] The risk is higher for HSCT recipients younger than 10 years of age at the time of transplant, particularly males and those who receive high-dose total body irradiation, have cGVHD, and/or receive prolonged immunosuppressive therapy.[15,16] In general, patients who survive HSCT for at least 10 years have a significantly higher risk (8.3 times) of new solid cancers than the general population.[16]

cGVHD prevention and treatment. The best approach to reduce GVHD-related mortality is to prevent the disease from developing. There are 4 principal overlapping prevention strategies[17]:

1. interference with T cell activation and function–cyclosporine and tacrolimus are the most common agents used to prevent the disease;
2. interference with T cell proliferation–methotrexate and mycophenolate mofetil (**MMF**) are most commonly used for this purpose;
3. reduction of T cell numbers–agents such as alemtuzumab and antithymocyte globulin are used in vivo, while monoclonal antibodies and some physical methods can be used in vitro;

4. interference with cytokine function–corticosteroids can be used for that purpose, but they increase the risk of infections; other agents have been used with minimal efficacy.

Unfortunately, prevention of aGVHD has not resulted in less cGVHD. The only successful strategies are T cell depletion and the use of umbilical cord blood as a stem cell source.[5]

The appropriate intensity and duration of treatment are not well-established, but should be done until all the clinical and pathological signs and symptoms have resolved which may take several years.[8] The benefit of eradicating the manifestations of cGVHD must be weighed against the complications of therapy.[4] Prednisone, alone or in combination with cyclosporine, remains the standard systemic therapy and the dose is tapered as tolerated, depending on the response.[4,5] Psoralen (methoxalen) plus ultraviolet A irradiation (**PUVA**) has a role in the treatment of skin cGVHD, while thalidomide and MMF have shown efficacy for steroid-resistant cGVHD in adults and children.[4,8] Extracorporeal photophoresis (**ECP**) has shown promising results in the treatment of cGVHD that is refractory to standard therapy. The procedure involves apheresis to collect leukocytes, which are incubated with methoxsalen (UVADEX®) or 8-methoxypsoralen and then exposed to ultraviolet light before being returned to the patient.[4,5,8] Other promising drugs, which can be used alone or in combination, are currently at different levels of clinical trials, including: hydroxychloroquine, sirolimus, oral beclomethasone for intestinal cGVHD, tacrolimus ointment, rituximab, infliximab, denileukin diftitox, pentostatin, clofazimine, etanercept, daclizumab, and high-dose methylprednisolone.[4,8,18]

Supportive care includes:

1. local measures—physical therapy to reduce contractures, deep tissue massage for deep cutaneous sclerosis, optimal oral care with fluoride, etc;
2. prophylaxis against infections;
3. protein and carbohydrate dietary supplements to prevent weight loss due to increased metabolic activity and diminished intestinal absorption; and
4. use of sunblock to avoid activation of GVHD by sun exposure.[4]

Oral and dental aspects. The mouth can be the primary or only site of cGVHD and may present persistent activity after resolution of the disease in other areas of the body.[19] Therefore, prompt diagnosis and treatment are important to limit disease severity and to increase the patients' QoL.[4] Diagnosis of oral symptoms and findings in children can be more complex than in adults, given that tissue biopsies and even clinical examinations can be difficult is certain cases.[20] Oral cGVHD usually starts with xerostomia and/or oral sensitivity (to acidic and spicy foods, acidic drinks, carbonated beverages, heavily flavored products such as toothpastes, etc) and may be overlooked or confused with other problems, such as fungal colonization or residual effects of high-dose chemotherapy.[4,19,21] Close monitoring by a dental professional must continue for life because these patients are at risk for development of oral squamous cell carcinomas.[16] These patients should be counseled to avoid exposure to carcinogens such as tobacco and alcohol.

Although some cGVHD patients are admitted to the hospital for treatment of the disease and its sequelae, most are seen on an outpatient basis. Therefore, all pediatric dentists must be able to recognize and treat the oral manifestations. Schubert et al[19] studied 60 patients (between 3 to 41 years old) and found that the most common presentations were atrophy and erythema or lichenoid lesions of the buccal mucosa (Figure 1) and labial mucosa (Figure 2). Oral pain was also frequently seen and not limited to patients with ulcerations. Erosive lesions, which were usually covered with a heavy grayish pseudomembrane, were often associated with severe lichenoid abnormalities of the lateral tongue (Figure 3) and the posterior buccal mucosa. They also observed xerostomia and mucoceles, and patients who presented with severe liver dysfunction and elevated bilirubin levels showed a marked icteric coloration in the oral mucosa. Lichenoid changes result from focal hyperkeratinization and appear as white striae or plaques.[4,7]

The predictive value for cGVHD approaches 100% when results of the oral examination and the labial mucosa biopsy are combined.[19,21-23] Patients are anesthetized using a unilateral mental block, and an elliptical incisional biopsy specimen measuring approximately 6 x 3 mm in size is taken from the inner lower labial mucosa 10 mm beneath the vermilion border. The tissue is fixed in 10% neutral buffered formaldehyde solution and sent to the pathology lab for analysis.[19] Histological findings include ductal necrosis, sialoadenitis, epithelial lymphocytic infiltration, and acinar destruction in the labial salivary glands.[19,22]

Few studies have been performed on pediatric oral cGVHD.[20,24,25] An evaluation of 22 children diagnosed with the disease found that most lesions were erythematous, followed by reticular and ulcerative forms. Patients reported mouth pain, xerostomia, and avoidance of certain foods (eg, spicy and acidic foods and drinks) because they caused discomfort.[20] Other significant presentations were atrophic glossitis, gross caries, soft tissue fibrosis and mucoceles. Patients with sclerodermatous changes may present decreased oral opening due to perioral fibrosis (Figure 4) and limited mobility of soft tissue structures, including the tongue.[26]

The presence of salivary gland dysfunction is associated with the severity of the disease and seems to be less prevalent in children than in adults.[20,27] Sialochemistry changes include: (1) elevated salivary sodium and lysozyme; (2) decreased phosphate and secretory IgA concentrations; and (3) diminished salivary flow rates. These changes affect the preservation of oral homeostasis, decreasing the protection of the mucosal integrity, defense against opportunistic infections, and caries protection.[19,27] Worsening of xerostomia can be associated with the

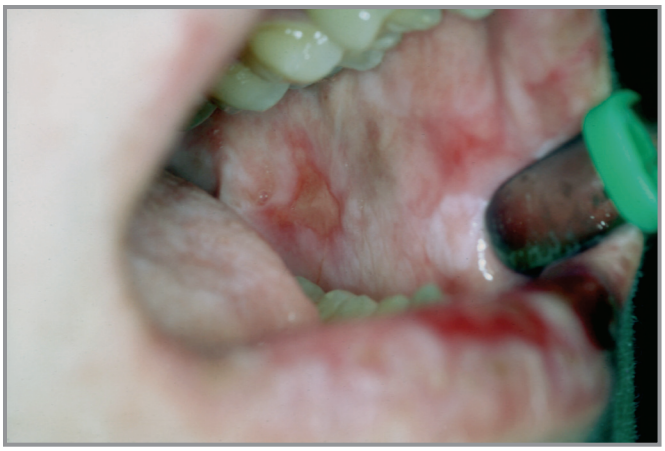

Figure 1. Buccal mucosa: atrophy, erythema, lichenoid lesions, pseudomembrane covering ulceration in a 15 year old adolescent with oral chronic graft-vs-host disease

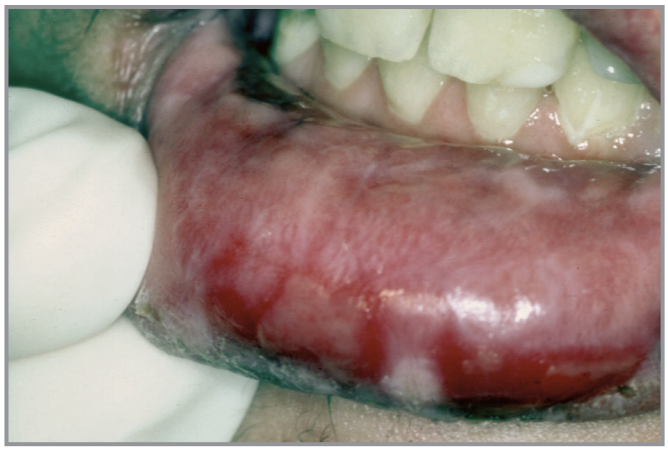

Figure 2. Lower labial mucosa: atrophy, erythema and lichenoid lesions in a 12 year old patient with oral chronic graft-vs-host disease

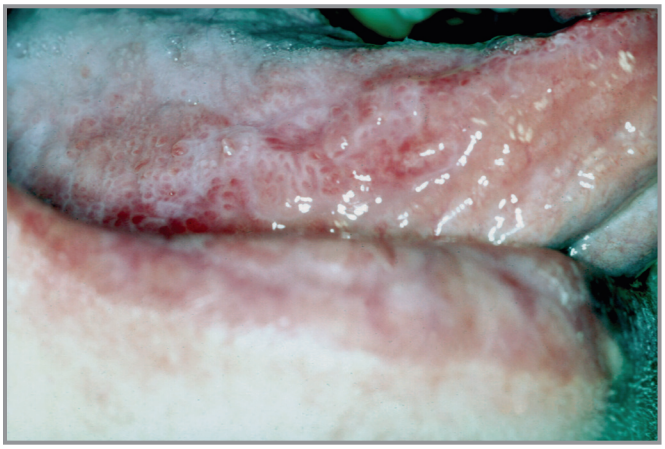

Figure 3. Right lateral tongue: severe lichenoid changes, atrophy and erithema with loss of tongue architecture in a 12 year old patient with chronic graft-vs-host disease

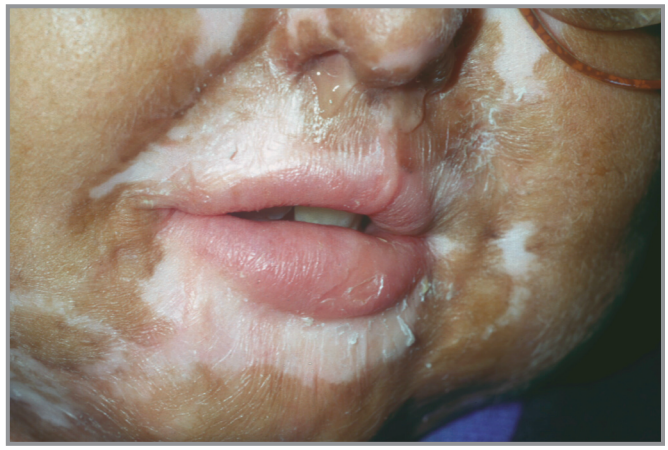

Figure 4. Severe perioral fibrosis and areas of hypo/hyperpigmentation in a 7 year old child with severe chronic graft-vs-host disease

onset or a flare-up of cGVHD and is a simple way for the pediatric dentist and hygienist to monitor the disease.[19] Oral pain and xerostomia can easily interfere with oral hygiene and the patient's ability to speak and eat, causing weight loss and reduced body mass index which is a predictor for mortality in these patients.[12]

Soft tissue growths, such as pyogenic granulomas, may occur possibly due to susceptible "responder" fibroblast subpopulations, adequate serum and tissue levels of cyclosporine, and the presence of local inflammation.[21,28] These growths are reactive proliferations of fibrous and granulation tissue that may exhibit rapid growth, raising concerns of a malignancy.[28] A very unusual periodontal presentation has been described in a 15-month-old girl with severe extensive cGVHD.[29]

Treatment of oral cGVHD and its sequelae. Research on the management of pediatric oral cGVHD is almost nonexistent. Treatment is based on adult therapies and is directed to: (1) treatment of specific lesions; (2) pain control; (3) relief of xerostomia; and (4) maintenance of oral health.[21] If the patient presents asymptomatic oral cGVHD, no treatment is necessary but regular follow-ups must be done

Table 2. MOST COMMONLY PRESCRIBED TOPICAL CORTICOSTEROIDS FOR ORAL CHRONIC GRAFT-VS-HOST DISEASE

Medication	Dose	Usage
Dexamethasone elixir	0.1-0.5 mg/ml	3-5 ml to swish or hold for 2 minutes, 3-6 x/day, limit use for 2 weeks, nothing to eat or drink for 30 minutes after use
Betamethasone elixir	0.6 mg/5 ml	
Fluocinonide	0.05%	Dry area; using a cotton tip, coat lesion with a thin film 1-2 times daily, limit use for 2 weeks, nothing to eat or drink for 30 minutes
Clobetasol	0.05%	
Tramcinolone acetonide	0.5%	

to monitor the oral tissues. Reticular lesions rarely require intervention, whereas erythematous and ulcerative lesions typically demand aggressive therapy.[20] Topical steroid preparations may be utilized for oral cGVHD when systemic immunosuppressive agents do not completely resolve severe atrophic and ulcerative lesions (Table 2).[20,21] For severe localized oral lesions, a potent corticosteroid such as fluocinonide 0.05% or triamcinolone acetonide 0.5% may be used once or twice daily.

Children require less topical steroids than adults because of their smaller body surface area; general guidelines suggest that infants be given one fifth of the adult dose, children be given two fifths, and adolescents two thirds.[30] Topical dexamethasone rinses may be prescribed for patients with severe generalized oral lesions. It is extremely potent, however, and may result in significant side effects in children; thus, consultation with the physician prior to its implementation is recommended. It is important to follow-up all patients on topical corticosteroids within 2 weeks of the beginning of usage to evaluate its efficacy and to monitor for adverse effects such as opportunistic fungal infections.

Patients and caretakers should be cautioned that the medication be used only for the length of time prescribed and discontinued once the condition has resolved. If no improvement is seen, reassessment is necessary in conjunction with the patient's physician. Rebound of the oral lesions may be avoided by gradual reduction of the dose and potency of the agent at 2-week intervals. Intralesional steroid injections with triamcinolone (40 mg/ml) may help in cases of 1 or 2 large lesions.[20,21] Anecdotal evidence suggests that patients who do not respond to systemic and/or topical steroids may benefit from the use of thalidomide.[21] Other agents that have been reported for intraoral use include 0.1% tacrolimus ointment, intraoral PUVA alone or in combination with topical steroids, CO_2 laser, budesonide rinses, cyclosporine rinses, ultraviolet B irradiation, azathioprine rinses, topical thalidomide, ECP, and topical cyclosporine in zilactin bioadhesive.[18,31-39] There is no evidence that any one therapy is superior, and the available evidence of efficacy for current topical treatments is weak.[18,40]

The extensive use of systemic immunosuppression, topical steroids, and antibiotics, together with the presence of xerostomia and local tissue damage, create an ideal environment for the development of secondary infections. Close monitoring of the soft tissues by the dental professional will enable timely diagnosis and treatment of these infections, which have an atypical presentation in these patients.[25] Individuals treated for oral cGVHD with topical steroids should receive prophylaxis against candidiasis. Chlorhexidine may be prescribed prophylactically because of its mild antifungal properties. Nystatin rinses, which are not effective to prevent or treat candidiasis in immunocompromised patients,[41] and clotrimazole troches are rich in sucrose, thus predisposing the patient to dental caries. Systemically administered antifungal agents, such as triazoles (eg, itraconazole and fluconazole), have excellent safety profiles and are more effective than topical antifungal agents.[42,43] Because of their interaction with other drugs, selection of the appropriate antifungal agent should be done in conjunction with the patient's physician.

Oral pain can be controlled with soothing rinses (saline or sodium bicarbonate, for instance) and topical anesthetics such as 2% viscous lidocaine. The anesthetic, being a contact medication, must be held in the mouth for 1 to 2 minutes to be effective. Patients should be cautioned against gargling or swallowing the solution because it will cause loss of the gag reflex, creating an aspiration hazard. Pain medications should start with non-narcotics and progress to opiates containing codeine or hydrocodone to stronger opiates (dilaudid and morphine) as needed.[21]

Difficulty with eating and/or swallowing foods or constantly needing to wet the mouth may indicate oral dryness which can be alleviated with bland rinses (saline or sodium bicarbonate), sugarless candy or gum, special toothpastes, gels, mouthwashes, and saliva substitutes. Other home care regimens that may aid patients cope with the discomfort of xerostomia include the use of a bedside humidifier during the night, fresh and lightly acidic fruits, slices of cold cucumber or tomato, and thin slices of apple.[44] Vitamin C tablets and lemon can also stimulate the salivary flow, but both have erosive effects on dental enamel—therefore, they should not be used frequently.[44] Muscurinic agonists such as pilocarpine, carbamylcholine, bethanechol, and cevimeline cause an increase in salivary flow but they are not approved for use in children and are associated with a multitude of side effects (sweating, gastrointestinal problems, hypotension).[27,40,44]

Dental care. Patient education regarding the importance of good oral health and prevention of oral/dental infections is a must. cGVHD patients are at high risk for caries for many reasons, including: 1) hyposalivation; 2) loss of the protective properties of saliva; 3) perioral fibrosis limiting mouth opening and oral pain that prevent optimal hygiene; 4) high caloric diet due to weight loss; 5) decreased mobility of the tongue, making oral clearance difficult; and 6) frequent consumption of soft foods. Therefore, patients should receive an intensive caries prevention program. Maintenance of good oral hygiene is crucial, and the use of fluoride supplements (gels, pastes, etc) should be prescribed based on individual needs. Products containing xylitol, such as chewing gum and mints, help with salivary stimulation and provide protection against caries.

Patients should not resume routine dental treatment, including dental polishing and scaling, until they present adequate immunological reconstitution.[45] They can receive routine clinical examinations every 3 to 6 months, depending on their caries risk, to detect and prevent disease and to assess oral cGVHD. Radiographs can also be made. The presence of painful oral lesions, however, may preclude their use. If dental

treatment is imperative while the patient is immunosuppressed, the pediatric dentist must consult with the physician to determine what level of medical support is necessary for dental care (need for antibiotic and steroid supplementation, platelet transfusions, etc).[45] Admission to the hospital and treatment under general anesthesia must be considered if the patient has severe cGVHD in order to complete the dental treatment efficiently with appropriate supportive medical care. If the patient's oral cGVHD is asymptomatic and the systemic disease is under control, dental care can be done in the office.

Use of antibiotic prophylaxis due to the presence of a central line should be discussed with the physician since there is no convincing scientific evidence that micro-organisms associated with dental procedures cause infection of nonvalvular vascular devices at any time after implantation.[46] The American Heart Association does not recommend it routinely.[46] Other parameters, such as platelet and absolute neutrophil count, must be assessed before any invasive dental procedure. Also, the pediatric dentist should apply the same principles as those for dental care of immunosuppressed hematology/oncology patients which have been discussed extensively elsewhere.[47]

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