Chapter 6

Oral Health Care for Patients with Fanconi Anemia

Introduction

The health of the mouth and surrounding craniofacial structures is central to overall health. All patients with Fanconi anemia (FA), regardless of age, should seek professional dental care and perform adequate oral hygiene practices at home to prevent and control oral and craniofacial diseases, conditions, and injuries. With a few exceptions, dental treatment is similar for FA patients and individuals in the general population. This chapter provides guidance on dental care and oral health maintenance for patients with FA and educates dental practitioners about particular aspects of FA that can impact dental treatment.

Importance of Oral Hygiene

Good oral hygiene lowers the risk of oral health problems such as tooth decay, gingivitis, and periodontitis. Several reports have suggested that good oral hygiene also reduces the risk of cancers such as head and neck squamous cell carcinoma (HNSCC) [1] and esophageal cancer [2], although the evidence is not yet conclusive. The incidence of HNSCC in patients with FA is 500- to 700-fold higher than the general population (see Chapter 5). Therefore, it is important that patients with FA maintain the recommended oral hygiene and professional dental care routines summarized in this chapter.

The oral cavity harbors a variety of microorganisms, also known as oral microbiota. This community of microorganisms is composed predominantly of bacteria, although fungi and viruses also can be present. There is increasing evidence for the potential contribution of oral microorganisms and oral inflammation in HNSCC development in the general population [3-7]. Elevated levels of bacteria species, such as *Helicobater pylori*, *Neisseria*, *Veilonella*, and *Fusobacteriam nucleatum*, have been associated with cancers, including gastric, esophageal and colon cancer [8-10]. Furthermore, periodontitis, which is mediated by oral bacteria and inflammation, has been suggested as a possible risk factor for HNSCC [5]. Even though these associations do not imply causation, it is prudent to control the circumstances that may lead to gingivitis and periodontitis through adequate and routine oral hygiene practices.

Toothbrushing

Dental plaque on the surface of teeth contains a thick film of bacteria that can be removed only by a dental professional or by brushing with a toothbrush. The surface of the tongue also is heavily populated with microorganisms, which can contribute to halitosis and gum diseases. For home care, twice daily toothbrushing and daily tongue cleaning is the most effective method to remove plaque and bacteria to prevent gum diseases and tooth decay. Manual and electric toothbrushes are overall equivalent in their ability to remove plaque. If an individual has physical limitations that can impact his or her physical ability to hold onto and use a toothbrush, adaptive aids may need to be employed. Parents of young children with FA should brush the child's teeth until the child can competently do so independently.

The frequency of toothbrushing should be increased in patients who have a high risk for caries, such as individuals with reduced salivary flow, known as xerostomia. Xerostomia can occur in FA patients [11] and may develop as a side effect of certain medications, stress, anxiety, diabetes, dehydration, graft-versus-host disease (GvHD), or radiation therapy for head and neck tumors.

Toothpastes

Patients should use a toothpaste that contains fluoride, which is the most effective agent for preventing dental decay. Many natural toothpastes do not contain fluoride and therefore do not help to reduce the risk of caries. Some toothpastes contain the antimicrobial, triclosan, which also is used in a number of skin cleaners and scrubs. An increasing number of studies suggest that triclosan may alter hormone regulation, and there are concerns about the emergence of triclosan-resistant bacteria. Although the potential detrimental effects of triclosan remain inconclusive, patients with FA are advised to avoid products containing triclosan due to their predisposition to endocrine disorders.

Some whitening toothpastes contain abrasive agents and chemical additives, such as sodium bicarbonate or sodium pyrophosphate, to help break down and remove surface

stains. Whitening toothpastes might also contain bleaching agents, such as hydrogen peroxide or carbamide peroxide, which may be a concern for patients with FA due the potential carcinogenic effects of peroxide. Therefore, whitening toothpastes are not worth the potential health effects that might be caused by exposure to hydrogen peroxide.

Plaque Removal Devices

Plaque that forms between teeth is virtually unreachable by toothbrushing, but should be removed at least once daily by flossing to prevent gum disease and cavities. Various plaque-removal devices are available, including floss, tape, electric interdental cleaners, wooden sticks, and interdental and end-tufted brushes. The choice of device should be based on the anatomy of the teeth and the dexterity of the patient; therefore, patients with FA who have hand and arm abnormalities may need to experiment to find a device that works well and is easy to manipulate.

Mouth Rinses and Topical Fluoride Treatments

Mouth rinses containing fluoride can be used to prevent tooth decay, rinses containing antimicrobials can prevent both tooth decay and gum disease, and both types of rinses can be used to improve breath odor. However, many mouth rinses contain alcohol, with concentrations ranging from 6-26.9%. Alcohol is known to increase the risk of HNSCC (see Chapter 5) and it is recommended that patients with FA avoid the use of mouth rinses that contain alcohol. Alcohol-free mouth rinses are available and appear to be as effective as their alcohol-containing counterparts [12].

Mouth rinses that contain compounds to kill bacteria, including chlorhexidine (CHX) or other anti-microbials, can provide effective plaque removal in circumstances where mechanical plaque removal is not possible, such as after oral surgical procedures. In the U.S., mouth rinses that contain antibiotics are available by prescription only and generally need to be mixed by a pharmacist. Mouth rinses that contain povidone-iodine should not be used by patients who are allergic to iodine, children under 6 years of age, patients with thyroid disorders, or patients taking lithium.

A number of over-the-counter mouth rinses are available to help control plaque accumulation. Some products contain 0.05% cetylpyridinium chloride, a compound that kills bacteria, or phenolic essential oils, which also reduce plaque and gingivitis. However, patients should be aware that many of these formulations have an alcohol content of 20% or greater, and should be avoided. Alcohol-free formulations are available and appear to be equally as effective [13].

Topical fluoride treatments are available over-the-counter or by prescription, and are suitable for use in children as well as adults. Topical fluoride treatments can be self-applied using gels, mouth rinses, or varnishes. The application method should be selected based on the patient's ability to use the method of application.

Professional Oral Health Care

All FA patients require professional dental care. The dental health care team should include a dentist and a dental hygienist who are aware of the complexities of the oral health issues in patients with FA and, when needed, can include other dental specialists. When appropriate, the dental health care team will work in close collaboration with the primary FA health care specialist to provide coordinated, comprehensive care.

Oral Examinations

Individuals should receive routine oral and dental examinations every six months. Examinations can occur more frequently if changes occur in the patient's medical and/or dental conditions, such as the development of periodontitis, diabetes, or xerostomia. In addition, FA patients have increased risk for developing HNSCC or oral cancer; therefore, the primary objectives of professional oral exams include the prevention and early detection of oral diseases such as dental caries, gingivitis, periodontitis, and oral cancer. Oral examination methods for cancer detection in patients with FA and recommendations for biopsy are discussed in Chapter 5.

During an exam, the dentist should evaluate the inside of the mouth as well as the soft tissues of the head and neck; any unusual findings should be further investigated. Caries can be detected by the clinical and radiographic examination of tooth surfaces and restorations. Changes in the color, consistency, and contour of the gums can reveal the development of gingivitis and periodontitis. Furthermore, gingival inflammation and plaque accumulation are involved in the development of periodontal disease, which has been associated with an increased risk of head and neck cancer. Thus, visits to the dentist also allow the dental team to evaluate the patient's oral hygiene practices and reinforce self-performed plaque control.

Radiographs

Many oral diseases cannot be detected with a visual or physical exam. Dental x-rays can help the dentist find cavities between teeth or under fillings, diagnose gum and bone diseases and some types of tumors, and better plan surgical interventions. These images can help detect and treat these hidden problems at an early stage before more extensive treatment is necessary. Radiographs and other imaging modalities are used to diagnose and monitor oral diseases, as well as to monitor dentofacial development and the progress or prognosis of therapy. However, x-rays should only be taken when there is an expectation that the additional information they can provide might result in improved patient care. Thus, the dentist must weigh the benefits of a radiographic examination against the risk of exposing a patient to x-rays, the effects of which accumulate from multiple sources over time. Based on the patient's health history and vulnerability to oral disease, the dentist may make this assessment in the interest of each patient.

The American Dental Association and the U.S. Food and Drug Administration have devised recommendations for the selection of patients for dental radiographic examinations [14], which can serve as a framework for dentists who treat FA patients. According to this document, the dentist is advised to conduct a clinical examination, consider the patient's signs, symptoms, and oral and medical histories, as well as consider the patient's age and vulnerability to environmental factors that may affect oral health. This diagnostic and evaluative information may determine the type of imaging to be used or the frequency of its use.

Once the need for radiographs is determined, a conscious effort should be made by the dentist to reduce the radiation risks of dental x-rays, including limiting the number of radiographs, using protective gear (e.g., leaded aprons and thyroid collars), and using faster speed films and digital imaging.

Radiation Exposure From Dental Radiographs

When taken properly, dental radiographs provide limited radiation exposure (Table 1). In fact, natural sources of radiation can provide more radiation exposure than dental x-rays. For instance, a panoramic dental x-ray exam may expose a patient to only about 1 millirem, whereas a cross-country flight exposes an individual to 5 millirem of cosmic radiation. Moreover, the National Council on Radiation Protection estimates that the average U.S. resident receives about 360 millirem of radiation every year. Exposure can be minimized even further with the use of digital radiographs [15].

Table 1. Effective radiation doses from various dental x-ray procedures [16].

Type of X-Ray	µSv	mSv	mrem
Panoramic	6–11	0.006-0.011	0.6-1.1
Cephalometric	6–11	0.006-0.011	0.6-1.1
TMJ tomogram	2	0.002	0.2
Full-mouth intraoral	10–15	0.01-0.015	1-1.5
Bitewings (4 x-rays)	2–3	0.002-0.003	0.2-0.3
Mandible CT	150–700	0.15-0.7	15-70
PA and lat. chest x-ray (for comparison)	170	0.17	17
Background radiation per year (for comparison)	3,600	3.6	360

Restorative Dental Treatments

Fillings and Restorative Materials

Dental fillings can be used to restore function to teeth that have become damaged or decayed. There are several dental filling materials available. Amalgam fillings, which are made of mercury, silver, tin, copper, and other trace metals, have been used extensively for many decades. Amalgam fillings are easy to place, strong, and have good longevity. However, it remains unclear whether the mercury in amalgam fillings is harmful to health [17]. Therefore, the use of amalgam fillings in patients with FA should be limited until further research is available.

Tooth-colored, synthetic resins known as composite resins can be used as a restorative material or adhesive. Composite resins are approved for use in all teeth and can replace the use of amalgam in molar teeth. However, patients should be warned that composite fillings are associated with an increased occurrence of secondary decay and tooth sensitivity. Composite resins may be of potential concern for FA patients due to the presence of bisphenol A (BPA), which may have endocrine-disrupting, estrogenic properties. However, the potential harmful effects of BPA remain controversial and no unacceptable risks for the patient have yet been recognized [18]. Furthermore, BPA exposure can be reduced by cleaning and rinsing surfaces of sealants and composites immediately after placement [19].

The best way to avoid the need for any restorative materials is to decrease the patient's risk for caries. This can be achieved by aiming for optimal oral hygiene at home, following a balanced diet (low in sucrose), and having access to fluoride as appropriate.

Orthodontic Treatment

The use of braces to reposition the teeth should not pose a problem for patients with FA who are not neutropenic or otherwise immunocompromised. However, the brackets and wires on the braces can cause trauma and chronic inflammation in some patients. Because chronic physical irritation has been reported to be associated with oral cancer in clinical studies [20, 21], efforts should be made to prevent such irritation in FA patients. Recently, new orthodontic treatment methods using clear aligners have been developed that obviate the need for traditional brackets and wires in certain cases.

Dental Implants

Dental implants are titanium cylinders that are implanted into the jaw bone to replace missing teeth. They act as artificial roots to hold crowns or dentures in place. It should be noted that FA is not a contraindication for dental implants. A patient with FA should be stable (i.e., non-immunocompromised and non-thrombocytopenic) and meet all the

routine requirements for implants, such as sufficient bone volume and the ability to maintain good oral hygiene.

Oral Surgery

Oral and maxillofacial surgeons are involved in the diagnosis and management of diseases, injuries, and defects of the oral and maxillofacial region. Common reasons to visit the oral surgeon include tooth removal (including removal of the third molars), treatment of dental infections, biopsy of oral lesions, or reconstruction with dental implants. Patients also may need to see an oral surgeon for the treatment of trauma to the oral region or facial bones. The majority of procedures can be safely and comfortably done in the oral surgeon's office, where sedation is often used. The sedation techniques used in an oral surgery office are very similar to those used during an FA patient's bone marrow aspirate or biopsy. Patients with FA who are non-immunocompromised and non-thrombocytopenic usually can be treated in a routine fashion. The oral surgeon may need to consult with the patient's hematologist about any questions or concerns.

Oral Manifestations Associated with Fanconi Anemia

Fanconi anemia can manifest in numerous ways in the oral cavity of patients with the disease. Many of these manifestations also occur in healthy children, so it remains unclear whether they are associated with FA itself or rather with treatments for bone marrow failure (BMF), such as chemotherapy and radiation used during hematopoietic cell transplantation (HCT), which are known to adversely affect the development of teeth and jaws in children younger than 12 years. Regardless, it is important that FA patients be evaluated for dental and skeletal developmental issues that include:

- Agenesis, microdentia, or micrognathia
- Supernumerary teeth or delayed development of permanent teeth
- Changes in the color of the tooth enamel or abnormal tooth shape, rotation or position
- Delayed development of teeth (usually permanent teeth), including delayed loss of primary teeth and eruption of permanent teeth compared with healthy peers

Oral Ulcers

Oral ulcers occur frequently in patients with FA and can cause anxiety due to the high risk of oral cancer in these individuals. Oral ulcers or any oral lesions that do not resolve need to be assessed by a health care professional. The most serious oral lesion associated with FA is oral cancer (see Chapter 5).

It is extremely important for clinicians to differentiate between canker sores, ulcerations caused by a condition known as aphthous stomatitis, and oral ulcerations due to other potential causes.

Canker sores are lesions that often develop after a relatively mild trauma and heal within approximately 4-7 days. Aphthous stomatitis is characterized by multiple ulcers that occur simultaneously and can recur as often as once a month (just as the previous ulcers are healing). Most cases of aphthous stomatitis can be treated with topical steroids applied directly to the ulcer (Table 2).

Table 2. Management of recurrent ulcerations.

Treatment	Dose and Treatment Schedule
Topical anesthetics	2% viscous lidocaine; doxepin solution
Topical coating agents	Hydroxypropylcellulose film (Zilactin)
Topical corticosteroids	0.05% clobetasol gel; 0.05% flucinonide gel; 0.1 mg/ml dexamethasone elixir; budesonide inhaler
Intralesional injection	40 mg/ml triamcinolone (0.1 - 0.3 ml)
Systemic therapy	0.5-1 mg/kg prednisone; thalidomide

Neutropenic Mouth Ulcers

Patients who have neutropenia can develop oral ulcers that are clinically indistinguishable from canker sores. Such neutropenic ulcers can develop spontaneously or after a mild trauma (such as a mild bite injury), but tend to worsen and become painful. Neutropenic ulcers can be an early indication of bone marrow diseases, such as aplastic anemia or leukemia, though additional systemic signs and symptoms of bone marrow disease often will be present. Additionally, cancer therapies such as chemotherapy can cause severe neutropenia and neutropenic ulcerations.

Viral-Induced Mouth Ulcers

Recurrent herpes simplex virus (HSV) infections can cause ulcerations of the oral mucosa and lip. These lesions often are associated with the immune dysfunction that often accompanies severe aplastic anemia, myelodysplastic syndrome, and leukemia. The lesions also can arise after high-dose chemotherapy or hematopoietic cell transplant (HCT).

Oral Health Problems Associated with Bone Marrow Failure

Bone marrow failure (BMF) contributes to significant oral health problems including increased bacterial, viral, and fungal infections, gum enlargement, bleeding, pain and other facial neuropathies. Table 3 describes the underlying causes of these oral health issues in patients with FA and provides recommendations for management.

Table 3. Management of oral health problems during bone marrow failure.

Oral Health Problem	Cause(s)	Management
Bleeding	Thrombocytopenia	Avoid oral trauma; prevent infection
Bacterial infections	Loss of white blood cells, especially neutrophils; secondary infection of traumatic oral lesions	Maintain excellent oral hygiene; antibacterial mouthwashes; systemic antibiotics for severe infections
Fungal infections (primarily yeast)	Loss of white blood cells, especially neutrophils; loss of salivary gland function; use of systemic antibiotics	Topical antifungals (nystatin or clotrimazole) for oral yeast infections; systemic antifungals for extensive infections
Viral infections *(herpes simplex virus, varicella zoster virus, cytomegalovirus or Coxsackie group viruses)*	Immune dysfunction, including neutropenia	Systemic antiviral drugs (acyclovir or valacyclovir)
Delayed healing of oral tissues	Loss of white blood cells, especially neutrophils, resulting in secondary infections; severe anemia	Obtain primary closure of extraction or surgical sites; reduce risk for trauma and irritation; prevent secondary infection
Gum enlargement, bleeding, and pain	Accumulation of leukemic cells in gum tissue, usually in response to gingivitis; medication-induced gum enlargement	Maintain excellent oral hygiene; treat the leukemic disease; consider medication modification
Facial and oral neuropathies (nerve damage)	Compression of nerve bundles by leukemic cells, resulting in numbness and tingling	Treat the leukemic disease

Oral Care Before and After Hematopoietic Cell Transplant

The treatment and management of BMF can result in a wide spectrum of oral complications for patients with FA. Preventing and controlling oral complications can improve the patient's quality of life and, in many instances, potentially improve the patient's treatment outcomes.

Pre-Hematopoietic Cell Transplant Oral Examination

Prior to treatment for BMF with HCT, patients should undergo a complete oral examination and dental evaluation. Dental care should focus on eliminating any oral and dental diseases that could contribute to oral complications during treatment. Teeth with a poor long-term prognosis due to periodontal disease and/or teeth deemed to be non-restorable should be extracted. In situations where extractions are not possible due to the patient's medical status, time-release antibiotics can be placed in deep periodontal pockets to reduce the levels of bacteria in the region for several weeks and, thus, hopefully reduce the risk of periodontal infections.

Patients must be informed of the potential oral complications of HCT, including the causes, prevention, and management of the complications. Patients must accept responsibility for maintaining the highest level of oral hygiene and adhering to protocols to reduce the risk of oral complications from BMF and HCT.

Post-Hematopoietic Cell Transplant Oral Care

Routine oral care after HCT is essential to help maintain oral health and prevent infections and bleeding problems associated with gingivitis and periodontal disease. Once dental examinations resume after HCT, the dentist should carefully examine the patient's teeth and periodontal tissues, and x-ray images should be obtained if pre-transplant images are not available. However, routine elective dental treatment, including dental cleanings and restorations, should wait until the patient's immune system has sufficiently recovered.

If a patient urgently needs dental treatment before the immune system has recovered, the dentist and physician should determine what additional supportive medical care is needed. Supportive care may include prophylactic antibiotics, immunoglobulin G administration, adjustment of steroid doses, and platelet transfusions if the patient has a significant risk for bleeding. Prophylactic antibiotic regimens appear to be efficacious, with regimens being extended if there is ongoing dental infection or if there is concern for delayed healing. Dentists should minimize the spray from dental equipment by using rubber dams and high-volume suction devices to reduce the chances that a patient recovering from HCT will inhale any infectious or dangerous substances during dental

treatment. The dental care team also should aim to reduce the complexity of treatments and shorten treatment times.

Summary

Patients with FA have an increased risk of developing head and neck squamous cell carcinoma (HNSCC). Several studies have highlighted the role of adequate oral hygiene in preventing HNSCC and although the evidence is not yet conclusive, it is recommended that all FA patients follow best practices for oral care and evaluation. All FA patients, including pediatric and adult, should be evaluated by a dental professional every six months. Oral examination for HNSCC should start no later than age 10 (see Chapter 5). Patients with FA are encouraged to develop excellent oral hygiene practices at home, which include twice daily brushing, removal of plaque between the teeth, and avoidance of toothpastes with triclosan or hydrogen peroxide and mouth washes with alcohol. Digital radiographs used for routine dental evaluations do not increase the risk of cancer and support comprehensive dental care for dental caries or additional oral issues common to FA patients. The oral health of FA patients undergoing HCT should be closely monitored before and after transplant.

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