ORAL HEALTH CARE OF THE PATIENT RECEIVING CHEMOTHERAPY AND/OR BONE MARROW TRANSPLANTATION.

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ORAL HEALTH CARE OF THE PATIENT RECEIVING CHEMOTHERAPY AND/OR BONE MARROW TRANSPLANTATION.

A thesis submitted to the Faculty of Dentistry of the University of the Western Cape in partial fulfillment of the requirements for the degree M.Sc (Dent) in the discipline of Oral Medicine.

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Declaration

I, Charlene S. Solomon declare that "Oral health care of the patient receiving chemotherapy and/or bone marrow transplantation" is my own work and that all sources have been indicated and acknowledged by means of references.

Signed: C S Solomon

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Dedication

I dedicate this work to:

- my parents, John and Leonora Williams, for their sacrifices, support and guidance which made my education possible.

- my husband, Ashley, whose constant inspiration and encouragement gave me the confidence to finish this research and present it as a written report.

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SUMMARY

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Between September 1992 and August 1995, all patients with haematological malignancies who were treated as in-patients in the Haematology Unit at Groote Schuur Hospital received a twice weekly, oral and perioral examination. Sixty patients were monitored while following the traditional hospital oral care protocol (chlorhexidine, hydrogen peroxide, sodium bicarbonate, thymol glycol, benzocaine mouthrinse and nystatin). The mouth care protocol was then changed (protocol A = chlorhexidine, benzocaine lozenges, amphotericin B lozenges) and patients monitored until the sample size matched that of the hospital mouth care regimen (n = 60). A further 60 patients were then monitored using a third protocol (protocol B = benzydamine hydrochloride, chlorhexidine, benzocaine lozenges, amphotericin B lozenges). A statistically significant reduction in oral complications was found upon introduction and maintenance of protocols A and B. The findings of this study suggest that improved oral care and a structured oral care routine reduces the number of oral complications associated with chemo- and radiotherapy.

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OPSOMMING

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Alle binne - pasiënte in die Hematologiese Eendheid van Groote Schuur Hospitaal wat aan hematologiese maligniteite gely het, is gedurende September 1992 en Augustus 1995 twee - weekliks binnensmonds en buitensmonds ondersoek. Sestig pasiënte is gemonitor en die tradisionele mondsorg protokol (chlorheksidien, waterstofperoksied, natriumbikarbonaat, timolglikol, bensokaïen mondspoel en nistatien) is gevolg. Hierna is die mondsorg protokol verander (protokol A = chlorheksidien, bensokaïen suigtablette en amfoterisien B suigtablette) en pasiënte gemonitor totdat die grootte van die proefgroep dieselfde was as die hospitaal mondsorg regimen (n = 60). ħ Verdere 60 pasiënte is toe gemonitor volgens ħ derde protokol (protokol B = bensiedamien hidrochloried, chlorheksidien, bensokaïen suigtablette, amfoterisien B suigtablette). ħ Statistiese betekenisvolle afname in mondkomplikasies is gemerk na die aanvang en handhawing van protokolle A en B. Die bevindinge van hierdie studie dui daarop dat verbeterde mondhigiëne en ħ gestruktureerde mondsorgroetine die aantal mondkomplikasies geassosieer met chemo- en radioterapie, verminder.

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INTRODUCTION

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There are approximately 17 000 new cases of haematological malignancies reported in the United Kingdom each year (Campbell, 1995). It has been estimated that in Western countries one person in 100 will be affected by a haematological malignancy at some time in their life. These conditions are relatively common in young people and there are approximately 450 cases of childhood leukaemia in Britain each year. Approximately 90% of cases of leukaemia and related diseases occur in adults. Chronic lymphocytic leukaemia occurs almost exclusively late in life. Acute lymphocytic leukaemia shows a peak incidence in childhood, but the incidence of all other forms increases with age (Campbell, 1995).

The Haematology Unit at Groote Schuur hospital admits approximately 38 new patients with haematological malignancies annually. Seventy seven percent of these patients suffer from acute leukaemia and non-Hodgkins lymphoma, while 23% of patients are admitted with chronic leukaemia.

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Management of haematological malignancies requires various forms of cancer treatment which may include chemotherapy and/or bone marrow transplantation. All bone marrow transplant procedures include a preoperative conditioning therapy. This conditioning therapy includes a combination of chemotherapy and radiotherapy (Dahllöff et al, 1989; Nikoskelainen, 1990; Wingard, 1991; Schubert, 1994).

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CHEMOTHERAPY

Chemotherapeutic regimens are used to destroy rapidly proliferating tumour cells. However, because chemotherapeutic agents are non-specific, they also adversely affect host cells that have a high mitotic index. Normal cells that are susceptible to this adverse effect include those of the oral and gastrointestinal mucosa, and the haemopoeitic system.

Malignant and normal cells undergo five phases of development (Figure 1) (Naylor and Terezhalmy 1988). During each phase, specific metabolic activities occur that promote tissue growth. The G0 phase is a latent or resting phase. Although the cell is at rest in this phase, all biochemical activities are performed except for those related to cell reproduction and proliferation. After the cell becomes activated, it enters the G1 phase, in which it synthesizes ribonucleic acid (RNA) and other proteins in preparation for deoxyribonucleic acid (DNA) synthesis. In the S phase, DNA is synthesized. During the G2 phase, RNA and other proteins are continually synthesized in preparation for mitosis. In the M or mitotic phase, two daughter cells containing all genetic material are produced. From this phase, the daughter cells may enter the G0 phase or repeat the cell cycle by entering the G1 phase.

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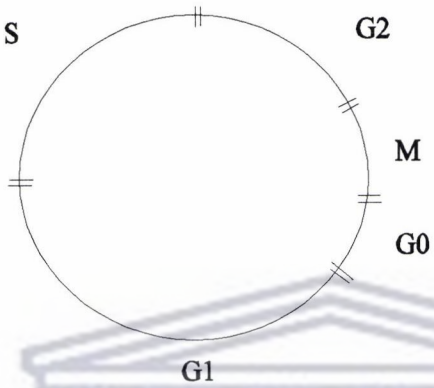
Fig 1. The cell cycle



Key: G0 = Latent Phase G1 = RNA synthesis G2 = RNA synthesis

S = DNA synthesis M = Mitotic Phase

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Chemotherapeutic agents may be cell-cycle dependent or independent. Cell-cycle dependent agents are effective only at specific intervals of the mitotic phase, while cell-cycle independent agents are effective in all phases of the cell cycle.

There are several classes of chemotherapeutic agents namely:

- alkylating agents,
- antimetabolites and
- antimitotic agents.

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The **alkylating agents** (e.g. cyclophosphamide) affect the DNA in all phases of the cell cycle by preventing cell reproduction. Alkylating chemotherapeutic agents are cell-cycle independent and are most effective in the treatment of chronic leukaemia, lymphoma, multiple myeloma, and carcinoma of the breast and ovary, but may also cause significant bone marrow suppression (Naylor and Terezhalmy, 1988).

The **antimetabolites** (e.g. methotrexate, azathioprine, cytarabine and fluorouracil) resemble normal metabolites of nucleic acid synthesis and interfere with the biosynthesis of purines and pyrimidines. Antimetabolites block the biosynthetic pathway in the S phase and are cell-cycle dependent. The antimetabolites have been used to treat many different malignancies and may cause bone marrow and gastrointestinal side effects.

The **antimitotic agents or plant alkaloids** (e.g. vincristine and etoposide) disrupt the microtubules during the metaphase in the M phase and are cell-cycle dependent. These drugs may cause bone marrow depression and neurotoxia. The antitumorigenic antibiotics (e.g. bleomycin) inhibit both RNA and DNA and are cell-cycle independent. These agents are used in the treatment of solid tumours and may cause bone marrow depression and gastrointestinal side effects. The hormones and miscellaneous agents may be cell-cycle independent or dependent.

Chemotherapeutic agents are often used in combination. Each agent has its own mechanism of action and characteristic toxicity. Therefore, combination chemotherapy often increases the effectiveness of treatment; distributes the side effects among various organ systems, which allows for better host cell tolerance; and decreases the likelihood that resistant cancer cells will develop (Naylor and Terezhalmy, 1988).

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BONE MARROW TRANSPLANTATION (BMT)

A BMT is a procedure whereby bone marrow from a donor is infused into a patient whose haematological disorder is refractory to chemotherapy alone. This treatment is used in the management of acute and chronic leukaemias, hairy cell leukaemia, preleukaemic states, lymphoma, multiple myeloma, neuroblastoma, selected solid tumours, aplastic anaemia, Fanconi's syndrome, thalassaemia and sickle cell anaemia (Maxymiw and Wood, 1989).

There are three sources of BMT grafts:

- **allogeneic** (allografts), in which bone marrow from a histocompatible donor (usually a sibling) is utilised,
- **syngeneic**, where the bone marrow is drawn from an identical twin, and an
- **autologous** when the patient's own cryopreserved marrow is used.

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According to Maxymiw and Wood (1989), allogeneic sibling grafts with high dose chemoradiotherapy provide the highest prospect of eliminating leukaemia (70-80% disease-free state), if the transplant is performed during the first remission. This figure is reduced to 30-50% if the BMT is done during a second remission.

The BMT procedure consists of two stages. The first stage involves a thorough evaluation of the family for histocompatibility between patient and potential donor. Histocompatibility utilises two tests: Human Leucocyte Antigen (HLA) and the Mixed Lymphocyte Culture (MLC). Human leucocyte antigen refers to the proteins found on leucocytes and occurs on all cells with a nucleus.

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This represents tissue typing for each individual. Human leucocyte antigen typing only identifies four of the known five foci. The last locus is determined by the MLC technique. This technique incorporates the mixing of lymphocytes of the donor and the recipient. If incompatibility exists, the lymphocytes will react. Although ABO blood groupings are important for compatibility, it is not crucial for a BMT.

BMT conditioning

The second stage of the BMT includes chemotherapy and total body irradiation (doses of 500 to 1200 cGy) to render the patient free of malignant marrow cells and receptive to the marrow transplant. This is termed bone marrow conditioning. Treatment protocols for BMT conditioning may vary according to the haematological malignancy, the dosage radiation employed and chemotherapy agent/s used.

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At the Haematology Unit at Groote Schuur hospital, radiotherapy for aplastic anaemia is limited to the immune system and is known as total lymphoid irradiation (TLI). In the cases of leukaemia, additional treatment is given to the rest of the body, known as total body irradiation (TBI). Allografting incorporates cyclophosphamide, TBI and/or TLI, while autologous marrow grafting uses minor variations of combinations consisting of nitrosurea, cylcophosphamide, and cytosine arabinoside (Maxymiw and Wood, 1989). Other agents have also been introduced to improve the antitumor efficacy (e.g. etoposide). Etoposide has excellent antitumor and immunosuppressive activity although not as much as cyclophosphamide (Wingard, 1991). The chemotherapy and radiation usually take place 5-10 days prior to the BMT and recipients are usually immunosuppressed for 6 - 12 months after their BMT.

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At transplantation, 500-1000ml of donor marrow is infused intravenously. Signs of a successful BMT engraftment are an increase of granulocytes to 500 per cubic millimetre. These are monitored over the next 30 - 60 days, while the patient is in isolation, a procedure necessary to prevent opportunistic infections.

SUSCEPTIBILITY OF THE ORAL CAVITY TO RADIO- AND CHEMOTHERAPY

Most cancer treatments affect normal as well as neoplastic cells and tissues. As treatments become more intensive and successful, the effects on normal tissues increase (Rosenberg, 1990; Holmes, 1991). The oral cavity is a frequent site of such side effects. Antineoplastic agents mainly disrupt cellular growth and proliferation. Therefore, the rapidly dividing basal layer of epithelial cells is particularly sensitive to chemotherapy. Persistent blood and tissue levels of cytotoxic agents further delay re-epithelization. The onset of chemotherapy-induced stomatitis usually occurs within 3 to 7 days of drug administration. The duration may also vary from several days with single-agent therapy to several weeks with combination-drug or combined chemoradiation therapy. The soft tissue of the lip, labial and buccal mucosa, tongue, soft palate, and pharyngeal mucosa are the most frequently involved. The keratinized tissues of the gingiva and palate are less involved because the thicker layer of epithelium resists coalescence of the ulcerations (Rosenberg, 1990).

In addition, chemotherapy affects the salivary glands, acting initially to stimulate salivation, resulting in excessive drooling and sialorrhoea, followed by complete dysfunction of the acinar cells, producing delayed xerostomia.

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Radiotherapy relies on the use of ionizing radiation to induce specific and predictable effects in exposed tissue. As radiation passes through the tissues, some of its energy is transferred to the cells causing ionization and producing highly reactive free radicals within them. These, in turn, cause physical and chemical changes altering cellular structure and function(s) through interactions with DNA and RNA or intracellular enzymes causing faulty transcription, defective repair, metabolic disturbance, accelerated ageing and mutations (Holmes, 1991). Since radiation cannot discriminate between normal and malignant cells, both cell populations are vulnerable to damage. The effect of radiotherapy on the oral tissues is an acute epithelial response (mucositis). Since cellular replication is inhibited, inadequate numbers of cells are available to maintain mucosal integrity. Therefore, the mucosal tissues becomes thin and inflamed.

The effects of radiation depend on both the type of radiation delivered and the number/type of cell(s) affected. The oral morbidity during radiotherapy to the head and neck is a consequence of damage to salivary glands, oral mucosa, mandibular bone and blood vessels.

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Oral complications of cancer therapy

Joyston-Bechal (1992) has summarized and classified the oral manifestations of radio- and chemotherapy according to acute and chronic effects (Tables 1 and 2).

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Table 1. Oral manifestations of radiotherapy (after Joysten-Bechal, 1992):

ACUTE EFFECTS	CHRONIC EFFECTS
Mucositis	Osteoradionecrosis
Salivary gland dysfunction	Salivary gland dysfunction
Changes in oral flora	Dental caries
Loss of taste	Periodontal disease*
Sensitivity to strong flavours, heat and cold	Candidiasis
	Trismus

* Joysten-Bechal (1992) refers to periodontal disease without detail of conditions e.g., gingivitis, periodontal disease, etc.

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Table 2. Oral manifestations of chemotherapy (after Joysten-Bechal, 1992):

ACUTE EFFECTS	CHRONIC EFFECTS
Mucositis	Infections (opportunistic)
Bleeding	Bleeding tendencies
Infections	Systemic and local effects may predispose
Sensitivity to heat and cold	patients to nutritional disorders
Salivary gland dysfunction	

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At the very least, these oral complications are painful, diminish the quality of life, and may lead to significant compliance problems, often discouraging the patient from continuing treatment. The oral cavity may also act as a port of entry for systemic infections (Heimdahl et al, 1989). Various treatment regimens for the management of the above mentioned oral complications have been proposed by numerous authors (Naylor and Terezhalmy, 1988; Touyz et al, 1991; Marciani and Wonby, 1992 and Joyston-Bechal, 1992). Although some guidelines exist concerning dental management prior to and following antineoplastic therapy, the literature is not clear about specific agents to be employed or the frequency of oral care procedures for immunocompromised patients.

Current oral care procedures appear to be largely based on tradition or subjective evaluation with little reference to existing medical/dental literature. These procedures may be inadequate in the provision of optimal care for these patients. The National Health Consensus Statement (NHCS, 1989) and Holmes (1991) emphasize the need to develop protocols for the prevention of oral complications in immunocompromised patients. This study was conducted to address the aforementioned concerns by instituting and assessing the efficacy of specific oral care regimens in the prevention of oral complications in patients receiving antineoplastic therapy.

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REVIEW OF THE LITERATURE

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I. ORAL MANIFESTATIONS OF CHEMO- AND RADIOTHERAPY

a. Fungal infections

Introduction

Oropharyngeal candidiasis is an extremely common complication in patients with haematological disorders, who are receiving chemotherapy and/or bone marrow transplants. These patients are at higher risk for oral candidiasis because of the extensive use of broadspectrum antibiotics and chemotherapy-associated immunosuppression (Redding et al, 1988). Candidal species of major importance include *Candida albicans* (*C. albicans*) and *Candida tropicalis* (*C. tropicalis*). Although *C. albicans* is the most common colonizer of oral mucosal surfaces, *C. tropicalis* is a more common cause of systemic infections in immunocompromised patients even though it is isolated from the mouth less frequently (Thurmond et al, 1991).

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Prevalence

The prevalence of candidiasis in the immunocompromised patient is difficult to assess due to the variability in patient samples, age, underlying disease and therapy reported in the literature. Wahlin and Matsson (1988) observed candidiasis-like changes in 31% of leukaemic patients during induction therapy, whereas Redding and coworkers (1988) found fungal infections accounted for only approximately 15% of all infections that develop in leukaemic patients receiving chemotherapy. Dahllöf and partners (1989) reported a 15% prevalence in paediatric patients (below the age of 12 years) who were treated with allogeneic bone marrow

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transplantation.

Haematological Profile

The most important defence against the development of candidiasis is adequate numbers of functioning neutrophils and a normal interaction between lymphocytes and monocytes. Both of these defences are depressed by antineoplastic drugs. When candidiasis is present, the neutrophil counts are generally found to be lower (Beiraghi and Sanders, 1988; Williams and Martin, 1992).

Clinical presentation

The National Health Consensus Statement (NHCS, 1989) describes various clinical appearances for candidal infection in the immunocompromised host. Lesions may present as pseudomembranous candidiasis (removable white plaques), chronic hyperplastic candidiasis (leucoplakia-like plaques that do not rub off), chronic erythematous candidiasis (patchy or diffuse mucosal erythema), or angular cheilitis.

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Candidal infections mostly occur superficially involving oral and pharyngeal tissues, but may invade local tissues and cause widespread systemic infection (Seto and Tsutsui, 1986). Superficial candidal infection may spread to involve the oesophagus or lungs (via a break in the mucosal barrier) and eventually affects all organ systems. Once this occurs, superficial techniques for culturing and treatment are inadequate.

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Candidiasis in children occurs most frequently on the buccal mucosa, tongue, gingiva, and pharynx. Erythematous candidiasis involves the tongue and is associated primarily with the extensive use of broad-spectrum antibiotics (Simon and Roberts, 1991).

Laboratory diagnosis

The most common technique used for the diagnosis of oral candidiasis is microscopic examination of exfoliative cytology from the tongue and buccal mucosa (Stinnet et al, 1992). Cytological smears are stained using the Periodic Acid-Schiff (PAS) method, Gram stain or wet mount preparation in 10% potassium hydroxide (Stinnet et al, 1992). While this is a time-efficient and reliable method, it cannot identify different candidal species.

Direct culturing is a simple and reliable method of detecting oral candidal carriage (Heimdahl and Nord, 1990; Stinnet et al, 1992; Allen, 1992). According to Silverman and coworkers (1990) the imprint cultures designed by Arendorf and Walker (1979) are the most sensitive method for assessing frank infection and detecting candidal carriage. However, it is not cost effective and therefore not suitable for routine use in a hospital setting. The concentrated oral rinse technique described by Samaranayake and coworkers (1986) is simple to perform and less time-consuming. The greatest advantage of using culture techniques is the ability to speciate organisms (Stinnet et al, 1992).

To aid in the diagnosis of locally invasive *C. albicans* infections, Seto and Tsutsui (1986) recommend a biopsy of the lesion with PAS staining. However, in severely compromised patients excision of tissue specimens may pose a serious risk for the patient (Heimdahl and Nord, 1990).

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In these cases, the clinician has to rely on cultivation and clinical observations only.

Serologic determination of circulating antibodies against fungi is used mainly to detect invasive infections. Methods employed are the immunofluorescence measure of antibodies against cell surface components, immunodiffusion tests using cytoplasmic candidal antigens, and enzyme-linked immunosorbent assay (Heimdahl and Nord, 1990). Immunocompromised patients often have a decreased ability to produce antibodies, and interpretation of the serologic response is therefore complicated.

Identification of candidal species depends on the morphological features and physiological characteristics. Morphological tests for the identification of candidal species include direct microscopy, water mount/wet film, potassium hydroxide technique, the germ tube test and chlamydospore formation (Silverman et al, 1990). The direct examination of smears stained with Gram stain, shows characteristic rounded, or oval budding cells of yeast blastospores with or without the hyphal phase. A water mount can be prepared from a pure culture to examine the yeast blastospores, to observe the type of budding and to determine the shape and average size of cells. For viewing living (wet) preparations of microorganisms, the phase contrast microscope is best suited. This scope reveals clearly the shape, the size, certain internal structures and motility of unstained microorganisms (Nolte, 1982). Potassium hydroxide (KOH) can be used for direct examination of mucosal scrapings. KOH eliminates most debris and intensifies the contrast of fungal cultures. The germ tube test is a rapid screening procedure for differentiating *C. albicans* from other candidal species. A germ tube is a filamentous, cylindrical outgrowth from the yeast cell with no constriction present at the base (Silverman et al, 1990). Chlamydospore formation is a property unique to *C. albicans* and to very rare isolates of *C.tropicalis.* The chlamydospore

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is a thick-walled non-deciduous intercalary or asexual spore formed by the rounding off of a cell or cells. Chlamydospore growth can be observed by direct microscopy (Silverman et al, 1990).

Management

Clinical management of oral candidiasis consists principally of antifungal agents. The medicament and route of administration is determined by the severity of the infection. Topical forms of therapy for oral candidiasis include chlorhexidine (refer to agents for oral care, P. 49), nystatin and amphotericin B. Nystatin is poorly absorbed systemically (Lewis et al, 1991) and is mostly used as a topical medicament, especially in the management of mild candidal infections (Beiraghi and Sanders, 1988). Multiple daily doses are necessary which could result in poor patient compliance (Allen, 1992). Prolonged contact between the medication and the infected surfaces seems to increase its effect. Therefore nystatin suspension given in the form of ice cubes or antifungal lozenges instead of a suspension may be more effective (Naylor and Terezhalmy, 1988; Toth et al, 1990). However, its unpleasant flavour, may cause nausea (Lewis et al, 1991).

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Like nystatin, amphotericin B is not absorbed from the gut, but it can be given intravenously or intrathecally for systemic candidiasis in cases of unresponsive and disseminated candidiasis (Lewis et al, 1991). Serious side effects may occur with its use including azotaemia (an excess of urea or other nitrogenous bodies in the blood) and nephrotoxicity (Simon and Roberts, 1991; Lewis et al, 1991)..

Other recommended antifungals include the azole-derivative antimicrobials such as clotrimazole, miconazole, ketoconazole, fluconazole and itraconazole (Wray and Dagg, 1990; Lewis et al,

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1991). These azole-derivatives, which block the synthesis of the ergosterol component of the fungal cell wall, appear to be a better and safer option for systemic use (Lewis et al, 1991). Miconazole is bacteriostatic and fungicidal and therefore suitable for the treatment of angular cheilitis when a mixed bacterial/fungal flora is present (Lewis et al, 1991).

Ketoconazole has been shown to have excellent absorptive properties because of its capacity to reach therapeutic blood levels when given orally. It is used widely in the management of chronic mucocutaneous candidiasis, gastrointestinal candidiasis, and candidiasis in immunocompromised patients (NHCS, 1989; Lewis et al, 1991). However, it does have several side effects, including endocrine disturbances, hepatitis and interaction with cyclosporin (Heimdahl and Nord, 1990).

Fluconazole and itraconazole has been shown to eliminate oropharyngeal and oesophageal candidiasis effectively in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex (De Wit et al, 1989; Heimdahl and Nord, 1990; Redding et al, 1992). Fluconazole is now considered to be a safe alternative to amphotericin B in treating candidaemia in patients without neutropaenia (Meunier, 1994).

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Systemic therapy may be supplemented with topical debridement (e.g. with swab, sponge, gauze, washcloth, etc.) as this increases the exposure of the fungi to antifungal agent(s) and disrupts the organization of the infection (Seto and Tsutsui, 1986).

Management of denture stomatitis

Wray and Dagg (1990) recommend that denture patients do not wear their dental prostheses (except for eating) and store prostheses in an aqueous chlorhexidine solution. In the presence of candidiasis, dentures should also be scrubbed under running water before insertion and the fitting

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surfaces coated with antifungal cream. Amphotericin B treatment includes lozenges and applying amphotericin B cream to the fitting surface of the denture. Bissell and coworkers (1993) demonstrated that systemic fluconazole is as effective as topical amphotericin for the treatment of denture stomatitis. The therapeutic effect of fluconazole on superficial mucosal lesions is dependent on the presence of saliva on the fitting surface of the denture. Therefore, Bissell and coworkers (1993) recommend removing the dentures at night as an adjunct to fluconazole treatment. Other antifungal agents recommended for denture stomatitis include ketaconazole and clotrimazole.

Iacopino and Wathen (1992) reported on the efficacy of a denture-soak solution containing benzoic acid which completely eradicates *C. albicans* from the denture surface. Benzoic acid is taken up into the resin and eliminates the organism from the fitting and the external surface of the prosthesis. Additionally, they suggest that the denture be relined with a soft base. This should be done by first removing about 1mm of the internal base acrylic resin; thus removing acrylic that has been penetrated by the fungus.The soft base can then be changed frequently as these soft liners do not inhibit candidal growth.

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b. Viral infections

Viral infections are a significant cause of morbidity and mortality in immunosuppressed patients. Herpes simplex virus (HSV) and herpes zoster virus (HZV) are the most common viral pathogens associated with oral lesions in patients receiving myelosuppressive chemotherapy and/or bone marrow transplants (BMT). Other viral pathogens potentially of concern in the immunocompromised patients are Epstein-Barr virus (EBV), cytomegalovirus, human papilloma and enteric viruses (Schubert, 1991). Chemotherapeutic medications have cytotoxic and cytostatic effects on lymphocytes and disrupt cytokine production and therefore increase the risk of viral infections.

Herpes Simplex Infection

The most common risk factor in developing oral HSV infection in immunocompromised patients is the presence of latent virus as indicated by detection of HSV antibodies. Immunosuppression is responsible for the reactivation of the latent virus in this group of patients.

Incidence

Approximately 50 to 90 percent of BMT patients who are seropositive for HSV will develop HSV infections (Schubert et al, 1990; Schubert, 1991). Montgomery and coworkers (1986) reviewed various dental and medical literature on the incidence of HSV. Their study demonstrated many discrepancies in the criteria used for the diagnosis of HSV, e.g., it is possible that some oral and throat lesions are less obvious and therefore not routinely cultured in contrast to lesions of the

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lips. In this way some HSV infections may not be identified. Distortion of incidence rates may also occur due to subclinical viral shedding and differences in therapeutic regimens.

Clinical presentation

Oral HSV infections in immunocompromised patients are severe and may be sites of potential secondary bacterial and fungal infection. It can also lead to a disseminated viral infection with severe organ involvement.

As mentioned earlier, herpetic lesions in immunocompromised patients may be atypical in appearance and location. The "normal transition" of these lesions from red papules to vesicles to ulcer is rarely seen. Schubert (1991) suggests an accelerated, maturational process as lesions frequently first appear as ulcerations. Lesions also tend to be more extensive and aggressive, slow or nonhealing, and extremely painful. Oral pain is frequently severe enough to limit oral intake and speech, predisposing patients to dehydration and nutritional insufficiency. There is also a clear tendency for lesions to occur more frequently on keratinized gingival and palatal tissues than on the buccal mucosae and the lateral margins of the tongue (Schubert, 1991). Extraoral HSV infections often become secondarily infected and appropriate antibiotics can prevent this.

Diagnosis

Epstein and coworkers (1990) demonstrated that the low and normal blood levels of lymphocytes and monocytes relate significantly to the onset and recovery respectively of HSV lesions. The onset of oral HSV infection in patients receiving chemotherapy is most likely to occur when

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absolute lymphocyte and monocyte counts drop below 600cells/mm^3 and 250 cells/mm^3 respectively and subsequent recovery may not occur until counts recover to above these levels, despite the use of acyclovir (Schubert, 1991).

The diagnosis of HSV infection based on clinical criteria is often misleading because of the variation in its clinical presentation in this patient population. Hence, laboratory testing is recommended for all lesions for accurate diagnosis. Numerous laboratory methods are available, namely, electromicroscopy, serologic diagnosis, tissue cultures and fluorescent assay (Zysset et al, 1986). These procedures vary in accuracy, rapidity and cost of diagnosis. Tissue culture is most commonly employed because of its accuracy, ease of use, cheapness and rapidity. Flaitz and Hammond (1988) compared the Papanicolaou and immunoperoxidase methods. The latter technique was shown to be a faster, simpler, and less expensive tool for diagnosing intra-oral HSV. In addition, it provides a permanent record of the infected cells, reveals cellular morphology, and uses standard light microscopy.

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Herpes Zoster Infection

Varicella zoster infection is rarely seen as a primary infection, and the herpes zoster lesions involving cranial nerves can cause significant morbidity, including postherpetic neuralgia, corneal scarring, cranial nerve palsies and deafness (Schubert, 1991). Herpes zoster is characterized by painful, unilateral vesiculation that may follow the distribution of a branch of the trigeminal nerve. These lesions may coalesce and form large ulcerations that may persist for weeks.

Cytomegalovirus infection

Cytomegalovirus (CMV) infection is more frequently seen in immunocompromised patients including those who receive immunosuppressive therapy, those with AIDS, and those who receive bone marrow or organ transplantation (Epstein et al, 1993). The incidence of infection is increased in patients who are CMV seropositive and in patients who are seronegative and their donor seropositive. In the immunosuppressed patient, this infection can vary from asymptomatic shedding of the virus (the most common presentation), to systemic disease.

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Oral lesions associated with cytomegalovirus infection are rarely seen, but may present as granulomatous ulcerations and/or CMV oesophagitis associated with odynophagia (pain on swallowing). Epstein and coworkers (1993) described CMV ulcerations in AIDS patients as large, single shallow ulcers which demonstrate intranuclear and cytoplasmic CMV inclusions on electron microscopy. Citing a case report, these authors also suggest a possible role of CMV in gingivitis in the immunosuppressed patient .

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Epstein - Barr Virus (EBV)

Epstein-Barr virus infection is frequently noted in immunosuppressed patients but oral manifestations are rare. The majority of infections are asymptomatic and are detected only by recovery of virus from body fluids or subsequently rising anti-EBV antibody titers. When the disease is clinically evident, patients are noted to have a mononucleosis-like syndrome with fever, lymphadenitis, pharyngitis, tonsillitis, splenomegaly, and icterus. Atypical symptoms can include jaw pain, arthralgias, joint space effusions, diarrhoea, skin rash, encephalitis and pneumonitis (Schubert, 1991).

Management

The management of viral infections is mainly palliation and the prevention of secondary bacterial infection. Antiviral drugs have proven to be effective in the treatment of herpesvirus, zoster infections and in the prevention of reactivation of the latent virus. When HSV lesions are diagnosed, acyclovir is the preferred drug for treatment. It is a potent inhibitor of herpes simplex DNA polymerase and induces early DNA chain termination, thereby inhibiting viral DNA replication. Potential side effects of intravenous administration include encephalopathy secondary to renal insufficiency and nephropathy. Adverse effects encountered with oral administration include headaches and nausea.

Occurrence of HSV infection, despite the prophylactic use of acyclovir, has been reported in less than one percent of patients (Epstein and Scully, 1991; Peterson et al,1992). These resistant strains are generally found in patients who have had multiple recurrences of infection treated on

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several occasions. Fortunately, many of these infections will respond to trisodium phosphonoformate hexahydrate (Foscarnet®[1]) and should be used if acyclovir therapy is not effective (Epstein and Scully, 1991; Peterson et al, 1992). Trisodium phosphonoformate hexahydrate inhibits virus-specific DNA polymerase and has potent *in vitro* effects against HSV, with low toxicity to mammalian cells.

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[1] Not presently available in South Africa.

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c. Bacterial infections

Aetiology

The majority of bacterial infections that occur are due to gram positive cocci such as *Streptococci, Staphylococci* and aerobic gram negative bacilli namely *Pseudomonas, Klebsiella, Serratai, Enterobacter, Proteus, and Escherichia*. However, in the immunocompromised patient, gram negative infections predominate (Holmes, 1991; Beck, 1992).

Clinical presentation

Bacterial organisms in the mouth can cause localized infections, including sialadenitis of major salivary glands, periodontal abscess, pericoronitis or other dental infections (NHCS, 1989). Chemotherapy related oral infections may involve or originate from the teeth, gingiva or mucosa (Marques and Walker 1991).

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In the myelosuppressed patient, the normal signs of infection are not always obvious. The most consistent signs are pain, fever and the presence of a lesion (Naylor and Terezhalmy, 1988).

Management

Penicillin is the drug of choice for the treatment of gram-positive microorganisms. Due to a myelosupressed state, the mouth may be inoculated by enteric gram negative microorganisms. These bacteria are resistant to penicillin and cephalosporins and thrive in a hospital environment.

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A combination of trimethoprim and sulphamethoxazole with nystatin has been recommended by Naylor and Terezhalmy (1988). Bacterial infections are generally treated with broadspectrum antibiotics (e.g. vancomycin, ceftazidime and metronidazole) such as as prescribed by Marques and Walker (1991). However, vancomycin should be used with great caution. Naylor and Terezhalmy (1988) advocate culture and sensitivity testing before antibiotics are prescribed.

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d. Mucositis

Definition

Mucositis induced by irradiation is an inevitable but transient side effect defined as the reactive inflammatory-like process of the oropharyngeal mucous membrane following therapeutic irradiation of patients who have head and neck cancer (Spijkervet, 1989).

Aetiology

Classically, mucositis is associated with irradiation, but it is also associated with cytotoxic therapy. Ulcerative mucositis occurs in approximately 75% of bone marrow transplant recipients in the absence of herpes simplex infection (Woo et al, 1993). According to Seto and coworkers (1985), oral mucositis during bone marrow transplantation is multifactorial in origin, resulting from the toxicity of chemotherapy, radiotherapy, infection, graft-versus-host disease or trauma.

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Chemotherapeutic agents frequently associated with mucositis include antimetabolites and in particular methotrexate, fluorouracil and cytarabine, anti-tumor antibiotics such as daunorubicin, dactinoymycin, doxorubicin, bleomycin, cyclophosphamide and hydroxurea (Rosenberg, 1990; Simon and Roberts, 1991). A high incidence of mucositis is also found with mitoxanthrone and high-dose etoposide (O'Brien et al, 1991). When chemotherapy drugs are used in combination, the frequency and severity of mucositis increases (Rosenberg, 1990).

The conditioning regimen appears to be the most significant factor contributing to the severity of

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ulcerative mucositis (Woo et al, 1990; Schubert, 1994). Spijkervet (1989) showed an association between mucositis and oral gram negative bacilli (GNB). These researchers demonstrated that with the effective elimination of GNB from the oral cavity, the formation of pseudomembranous lesions (associated with GNB) is significantly prevented.

The role of gram-negative bacilli

The treatment of cancer radically changes the mucosal flora, the opportunistic enterobacteria and pseudomonas predominate. The presence of GNB represents opportunistic colonization associated with "abnormal" carriage and may contribute to morbidity and mortality. Live GNB can cause infection of any oral site where a break in the mucosa exists and may complicate oral healing (Martin and van Saene, 1992).

Spijkervet (1989) did extensive studies to evaluate whether selective elimination of oral flora reduced the severity of mucositis. Their results were remarkable, because the most severe sign of mucositis (pseudomembrane formation) was completely prevented and the mucositis scores significantly reduced after three weeks of therapeutic irradiation. Additionally, the generalized side effects of weight loss and nasogastric tube feeding were also completely prevented.

Spijkervet (1989) further implicated endotoxins (released by colonizing GNB) as the mediator between oral GNB and mucositis. They had strong supportive arguments to validate their hypothesis. They reasoned that firstly, endotoxins are potent inducers of inflammation. Secondly, the time of onset of the most severe signs of mucositis corresponds with the time that increased permeability of the mucous membranes is caused by irradiation. The increased permeability allows

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endotoxins to pass through and to induce the cascade of inflammatory processes. Polymyxins were also shown to be effective endotoxin neutralizers both *in vitro* and *in vivo.*

Clinical Features

The early effects of chemoradiotherapy are seen on nonkeratinized mucosal surfaces, but may progress to include keratinized mucosa (Seto et al, 1985). When trauma or infection contributes to mucositis, keratinized and/or nonkeratinized tissues may be involved. These also tend to occur later in the course of disease (Seto et al, 1985). Simon and Roberts (1991) describe the first sites of mucositis involvement to be the soft palate, pharynx, buccal mucosa, and sublingual tissue.

According to Spijkervet (1989), the first clinical signs of mucositis appear at the end of the first week of a six week conventional radiation protocol (daily dose of 2 Gray, five times a week). Wingard and coworkers (1991) found mucositis occured between days 2 and 18, with a median onset of 4 days in the bone marrow transplant treatment. Chemotherapy-induced mucositis is reported to develop on days 3 to 7, or may be delayed if a boost is given after the initial chemotherapy course. Important to note is that these findings may differ due to variation in treatment protocols (Zerbe et al, 1992).

Reported initial symptoms of mucositis include a burning sensation, dryness of the mouth, tingling of the lips and pain (Simon and Roberts, 1991). However, some controversy exists about the first clinical sign of mucositis. Some authors describe a white mucosal appearance which, according to Spijkervet (1989), is an expression of a higher degree of hyperkeratinization. Others consider the first reaction to be erythema (Simon and Roberts, 1991), due to vascular dilatation

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(hyperaemia) or obstructive changes in arterioles (Spijkervet, 1989). More severe symptoms of mucositis include the formation of pseudomembranes and ulcerations which tend to appear after three weeks of radiation (Spijkervet, 1989).

Severe pain is often associated with the later stages of mucositis manifesting as ulceration and pseudomembranes. This often requires oral or intravenous administration of analgesics including morphine (Simon and Roberts, 1991). Severe mucositis may result in poor nutrition, prolonged hospitalization and an increased risk of patients developing a life-threatening septicaemia (Walsh et al, 1990).

Mucositis Scoring

Scoring mucositis is necessary for proper communication among clinicians about the severity of mucositis and related generalized complaints, for research purposes and to evaluate preventive or therapeutic measures (Spijkervet, 1989). Several approaches to scoring oral mucositis have been described in the literature.

Ideally, accurate, quantifiable, and reproducable criteria are needed to grade mucositis. Some systems only grade the severity of oral ulceration, while others include an evaluation of local signs of mucositis such as erythema and pseudomembranes. In addition, an assessment of oral symptoms may also be incorporated (Walsh et al, 1990). The practical applicability of scoring systems to dentists, physicians and nursing staff responsible for day to day care of bone marrow transplant patients is still uncertain. Existing scoring systems are infrequently used by medical staff which makes these systems of no value to assist in making clinical decisions with regard to oral

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hygiene measures.

Spijkervet (1989) developed his own scoring system and evaluated and compared his system with three other systems used. He concluded that mucositis scores developed by Van der Schueren and Spijkervet, cited by Spijkervet (1989), were research techniques to evaluate dose-response relationships and the effects of preventive measures on mucositis. The World Health Organisation and Hickey method described by Spijkervet (1989) was suggested for clinical use only. Both systems use a simple four-point scale to assess mucositis recording quantitative and qualitative data.

A 21 point scale scoring system was introduced by Walsh and coworkers (1990) to evaluate signs and symptoms of mucositis. Their extended range allowed subtle variations to be reflected. The oral assessment record permitted rapid transfer of medically important information between medical staff without the need for lengthy or obscure descriptions of signs and symptoms. This scoring system is reported to be suitable for use by nondental members of the health team. The tested interexaminer variation was found to be within acceptable limits.

The routine use of the oral mucositis scoring system for the evaluation of bone marrow transplant patients and other haematology/oncology patients, has increased the awareness of both the relationship between oral and general health and the importance of regular oral hygiene measures.

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Management

No specific therapy is available to prevent mucositis, but several palliative rinses have been advocated. Most of these contain topical anaesthetic and anti-inflammatory agents. Combinations of topical agents have been reported to be effective (Simon and Roberts, 1991).

Ingredients used in multi-agent topical mouthrinses include aluminum and magnesium hydrochloride (protects mucosa and promotes healing), tetracycline (antibacterial), diphenhydramine hydrochloride (antihistamine and topical anaesthetic), sucral sulphate (promotes healing), dyclonine hydrochloride, nystatin (antifungal), hydrocortisone (anti-inflammatory), sorbitol and lidocaine hydrochloride (topical anaesthetic) (Simon and Roberts, 1991). The ingredients and formulae may vary, although most regimens have the same therapeutic goal. The use of multi-agent regimens has largely declined in favour of 0.12 percent chlorhexidine mouthrinse. Chlorhexidine has most of the properties of multi-agent regimens, except analgesia (Simon and Roberts, 1991).

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While chlorhexidine was considered to be one of the most promising single agents for prevention and management of oral complications, many authors disputed this fact. Raether and coworkers (1989) showed that the use of 0.12 percent chlorhexidine could not prevent or control oral mucositis in paediatric bone marrow transplant patients. This was confirmed by Spijkervet (1989) whose study also failed to show a reduction in mucositis with a 0.1 percent chlorhexidine mouthrinse. Chlorhexidine also failed to eliminate GNB from the oral cavity.

Similar findings were obtained in a study by Foote and coworkers (1994) who failed to

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demonstrate any benefit of chlorhexidine mouthwash (concentration was not specified) for radiation-induced mucositis. These authors conducted a multi-institutional study with different examiners which reduced the inter-examiner reliability. The chlorhexidine mouthwash used in this study contained a 12% alcohol vehicle and was compared to a non-alcohol containing placebo mouthwash. The conclusions of this study are suspect because an alcohol-containing mouthwash would be more damaging to mucositis compared to a non-alcohol containing mouthwash.

Recently, prostaglandin E2 was found to be of local benefit in radiochemotherapy-induced mucositis. Prostaglandins are potent locally acting substances and are used with clinical benefits in the gastrointestinal tract (Matejka et al, 1990). In this study, patients were given a topical application of prostaglandin E2 tablets, 0.5mg four times a day at 4-hour intervals. Excellent results were obtained demonstrating patients to be free of bullous or desquamating inflammatory lesions in the oral cavity. Prostaglandin E2-treatment at a local level was shown to be a promising and effective therapeutic approach without any potential side effects.

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Epstein and Stevenson-Moore (1986) proposed the use of benzydamine hydrochloride (BZH) in prevention and management of oral pain in oral mucositis associated with radiation therapy. No studies that asses the efficacy of BZH in the management of oral complications in the chemo- and radiotherapy patient are available. However, a study by MacD and Hunter (1978) reports good results in the management of pain in patients following oral surgical procedures. Fewer patients required systemic analgesics and patient compliance was good.

Spijkervet's (1989) theory of eradicating oral GNB from the oral cavity to reduce the severity of mucositis was assessed using lozenges containing 2mg of polymyxin and 1.8mg of tobramycin.

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Amphotericin B (10mg) was added as prophylaxis for candidal infection. Patients were given this combination 4 times daily from the first day of irradiation, for five consecutive weeks. The eradication of GNB in 15 irradiated head and neck cancer patients was found to be associated with a significant reduction in mucositis.

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e. Salivary changes and xerostomia

Aetiology

The salivary glands are highly sensitive to radiation and may display progressive inflammatory and degenerative changes in both acinar and ductal cells as well as alterations to the vascular supply. The salivary function can be reduced or even destroyed as the quantity of saliva is decreased and its chemical composition changed (Holmes, 1991; Martin and van Saene, 1992; Jones et al, 1992). The magnitude of salivary flow reduction seems to be related to the radiation dosage and the amount of salivary gland tissue in the radiation field (Liu et al 1990; Atkinson and Wu 1994). Following a dose of 10 Gray, the saliva becomes viscous, losing its lubricating qualities and it adheres to the teeth. Chemotherapy-induced xerostomia may be caused by hyperthermia, mouth breathing, oxygen therapy or the chemotherapeutic agent. Significant xerostomia, however, is not frequently encountered in patients treated with chemotherapy (NHCS, 1989).

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Qualitative changes in saliva

Mansson-Rahemtulla and coworkers (1992) analyzed salivary components in stimulated whole saliva from patients with acute leukaemia who were undergoing chemotherapy. They found that treatment with cytotoxic agents results in a decrease in the enzyme, thiocyanate, in association with a granulocytopenia. The salivary peroxidase system (a non-immunoglobulin defence system) is impaired by the decrease in thiocyanate, which the aforementioned authors believe may be a contributing factor to some of the oral complications that occur in patients undergoing chemotherapy.

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Funegård and coworkers (1994) did a similar study, but they investigated the composition of parotid saliva during and after irradiation in patients treated for malignancies in the head and neck region. Their results showed that, in addition to the secretion of water, the biosynthesis and secretion of proteins also changes following radiotherapy. However, these changes were shown to vary between patients. The authors concluded that the increased concentrations of the total amount of protein and hexosamine, and low secretory rates may explain why saliva becomes thick and sticky following radiotherapy (Funegård et al, 1994).

Clinical presentation

There is an early loss of serous secretions since the serous acinar cells of the parotid glands are generally more affected than the mucous acinar cells in other areas of the mouth. Later, in the absence of mucin, a reduction in saliva flow occurs, resulting in xerostomia which makes swallowing, talking and oral hygiene difficult and painful. These clinical changes correspond to microscopic evidence of structural intracellular damage. Intracellular damage and mitotic death lead to hypoplasia. The loss of bacterial components and self-cleansing action of saliva results in plaque accumulation and alterations in the normal oral flora, caries and oral infection. In addition to this, the salivary pH gradually falls increasing the patients' risk to dental caries.

Chemotherapy-related xerostomia is a transient development, but its effect may be devastating in the presence of mucositis. Xerostomia may be confirmed by milking salivary glands and then evaluating quantitative and qualitative changes in saliva (Naylor and Terezhalmy, 1988). The oral mucosa may appear shiny, atrophic, and desiccated. Xerostomia also promotes the accumulation of plaque, bacteria and materia alba, which increases the patient's susceptibility to caries and

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periodontal disease.

Management

Management is usually directed towards temporary relief by rinsing with normal saline or by using an artificial saliva substitute. The lubricating ingredient in artificial saliva is either carboxymethylcellulose or mucin (Atkinson and Wu, 1994). These agents keep the mucosa moist and free of debris and reduce patient discomfort. In addition, friction between teeth and mucosa, or mucosa and mucosa, is minimized, preventing a more severe mucositis. Johannes's-Gravenmade and Vissink (1993) recommend the use of mucin lozenges for the treatment of oral symptoms of xerostomia. Epstein and coworkers (1994a) demonstrated increased saliva production with bethanechol in patients with xerostomia following radiation therapy. Bethanechol possesses muscarinic and nicotinic-cholinergic activity and is not associated with any significant side effects.

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If patients are still able to produce saliva, they may benefit from agents that stimulate the remaining functional secretory tissue. The stimulus may be mechanical, such as chewing; gustatory, such as citrus-containing beverages and sugarless hard sweets; or pharmacologic (Atkinson and Wu, 1994). They also reported the successful use of pilocarpine, a systemic pharmacologic stimulant for patients with Sjögren's syndrome and radiation xerostomia.

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f. Taste alterations/ dysgeusia

Chemotherapy and irradiation may markedly affect gustatory sensation. It may be so severe that extreme taste aversions may be present, thus predisposing the patient to malnutrition. Radiation therapy is also associated with specific changes in taste acuity.

Mattsson and coworkers (1992) investigated the influence and changes in taste experience and taste acuity in bone marrow transplant patients followed over a period of one year. They found that following bone marrow transplantation, there was a significant hypogeusia of all four taste modalities compared to a healthy control group. Some normalization of taste threshold was registered 3-6 months after transplantation, but most subjects still experienced dysgeusia. Taste acuity was normal after a 2-5 year period. An important finding of this study was that taste perception is only temporarily impaired and can regenerate. This confirmed a study done previously (Tomita and Osaki, 1990).

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g. Dental caries, gingivitis and periodontitis

The reduced volume and altered composition of saliva, combined with its reduced lubricating and cleansing activity, results in adherence and stagnation of both saliva and food debris around the teeth and the emergence of a highly cariogenic microflora, increasing the vulnerability to decay (Holmes, 1991). Radiation induced mucositis aggravates this problem as the inflammatory exudate clings to the teeth/gingiva and the pain/tenderness inhibits effective oral hygiene. Effective oral hygiene may also be inhibited by hypersensitivity of the cervical areas of the teeth. In the presence of a reduced salivary buffering capacity, demineralisation of the enamel is enhanced. Demineralisation may particularly affect the gingival margins as they are continuously bathed in an acidic saliva. Such effects involve any teeth, whether or not they are included in the radiation field (Holmes, 1991). Typically, radiation caries affects the necks of teeth, usually at the labial surface of the incisors and canines.

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Periodontal tissues directly in the radiation field may be significantly damaged, displaying disorganization of the ligamentous fibers, thickening of membranes and loss of vascularity, reducing the capacity to repair and regenerate and probably accounting for the resultant mobility and/or loss of teeth (Holmes, 1991). In addition, periodontally diseased teeth within the radiation treatment field may predispose the patient to osteoradionecrosis, especially if the dose to the bone is high (Fattore et al, 1987). During chemotherapy, induced granulocytopaenia results in a decrease or disappearance of inflammatory responses in general. The absence of clinical symptoms may therefore mask the periodontal infection (De Beule et al, 1991). The latter study showed that prophylactic measures prevent a measurable periodontal degradation, even in the presence of pre-existing periodontal disease.

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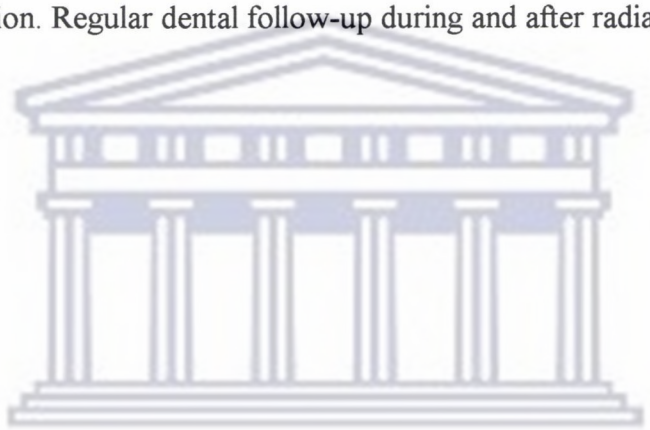
Management

Fattore and coworkers (1987) recommend conservative treatment of periodontal disease in patients receiving radiation therapy for head and neck cancer. These recommendations may also apply to other radiation therapy patients. Before radiotherapy treatment, teeth with significant periodontal disease should be extracted. After radiation treatment, advancing periodontal disease should be managed with conservative treatment, tetracycline, scaling and root planing, curettage, and oral hygiene instruction. Regular dental follow-up during and after radiation therapy is also advised.



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h. Additional dental problems in children

Radiotherapy and chemotherapy may affect tooth development and result in various dental abnormalities. The degree and severity of the disturbances are related to the child's age at the time of treatment, the treatment modalities used, and the dose and field of radiation (Dahllöf et al 1994). During the period of tooth development, radiation and chemotherapy may affect crown and root formation and/or result in delayed tooth eruption. Therefore, clinical and radiographic examination may show missing teeth, enamel opacities, hypocalcifications and thin shortened roots (NHCS 1989; Joyston-Bechal 1992).

The development of facial bones may be retarded, giving rise to orofacial asymmetry and malocclusion (Dahllöf et al, 1991). Disturbances in mineralisation induced by chemotherapy are limited to bands of hypomineralisation; hypoplasias are rarely found. Vincristine (an antimicrotubular drug that reduces both mitogenic and secretory activity in different cell types) may be responsible for these disturbances (Dahllöf et al, 1994). The latter authors concluded that chemotherapy mainly induces qualitative disturbances (hypoplasia) in both dentine and enamel, whereas total body irradiation induces both qualitative and quantitative changes e.g. short roots, microdontia, etc. Radiation affects radiosensitive cells (e.g. actively dividing cells) resulting in cell death. Hypoplasia may therefore be due to the direct effect of radiation on the odontoblasts and ameloblasts, and/or due to the indirect effects on the fibrovascular tissue stroma (Dahllöf et al, 1994). General management of children is similar to that outlined for adults, but they may require orthodontic and prosthetic procedures in the long term. Regular dental supervision is recommended every 3 to 4 months (Joyston-Bechal, 1992).

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II. ORAL CARE

Oral health care measures are of vital importance in preventing infections and thereby further damage to the oral tissues (Wright et al, 1985; Sonis and Kunz, 1988; Naylor and Terezhalmy, 1988; Joyston-Bechal, 1992). However, there seems to be no clear guidelines about the frequency of oral care and agents to be employed for patients receiving antineoplastic therapy. Before selecting one of the many oral hygiene agents available, one must establish the patient's needs, and secondly, have a knowledge of the agents' characteristics, mechanisms of action and interactions in various situations. The following section summarizes the guidelines for oral care measures as proposed in the medical and dental literature.

a. Purpose of oral care

The ultimate goal of oral hygiene is a comfortable, functional oral cavity, which is necessary for nutrition, emotional expression, and verbal communication. According to Daeffler (1981) and Holmes (1991) the purpose of oral hygiene measures may be summarized as follows:

1. To keep the oral mucosa clean, soft, moist and intact, thereby preventing infection in the oral cavity - xerostomia may cause communication difficulties and contribute to halitosis.
2. To keep the lips clean, soft, moist and intact - dry lips may crack and bleed causing discomfort and pain, and affect self-image.
3. To prevent caries and gingivitis and periodontal diseases by removing food debris and plaque without damaging the mucosa.
4. To alleviate oral pain and discomfort and thereby facilitate oral intake.

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5. To prevent halitosis, leave a fresh feeling in the mouth, and thereby stimulating the appetite.

b. Agents for oral care

Various agents are described and proposed in the literature. These agents may be classified according to purpose e.g., cleansing agents, pain-relievers, lubricating agents. However, some of them serve multiple purposes while others are not easily categorized. This section will only include agents that are commonly used and those that are of potential value to the immunocompromised patient. These agents are discussed in alphabetical order.

Antibiotic mouthwashes: Mycostatin (Nystatin®) is an antifungal antibiotic that is used in an oral suspension of 100,000 units per ml in a vehicle containing 50% sucrose and 1% alcohol. Mycostatin is also available in oral tablets (500,000 units) and vaginal tablets. It is recommended for the treatment of Candida infection in dosages of 5 ml suspensions q.i.d. The rinse and swallow suspension is widely used for candidiasis, mouth ulcers and sometimes as a prophylactic measure. The vaginal tablet is also used orally for local application (Daeffler, 1980b).

Artificial saliva: This product is used for xerostomia, most commonly caused by radiation therapy. These substances physically resemble saliva but do not provide the antibacterial and immunological protection of saliva (Holmes, 1991). It is usually "prepared on demand" and its ingredients may vary from one institution to another. Ingredients may include: carboxymethylcellulose, polyethylene oxide, sorbitol, flavouring agents, glycerine and normal saline (Daeffler, 1980b; Epstein and Stevenson-Moore, 1992). The pH of artificial saliva varies

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around 7. Normal saliva is slightly acidic with a pH of 6.6 - 6.9. Patients' preference of products depends on effect, duration, lubrication, taste, delivery system and cost (Epstein and Stevenson-Moore, 1992). A minimum volume is needed to maintain internal lubrication; one to two milliliters often maintains lubrication for up to 12 hours (Holmes, 1991). However, none of these artificial salivas have the quality of substantivity.

Benzydamine hydrochloride (Andolex®): Benzydamine hydrchloride (BZH) is a nonsteroidal drug that reportedly possesses analgesic, anaesthetic, antiinflammatory, and antimicrobial properties (Beck, 1992). The action of BZH is believed to be mediated by the prostaglandin system. The drug may affect formation of thromboxanes and alter the rate of prostaglandin production, inhibiting platelet aggregation and stabilizing cell membranes. A double-blind clinical trial by MacD and Hunter (1978) showed a decrease in the severity of post-operative pain with the use of BZH for patients undergoing surgical removal of impacted lower third molar teeth. In a study conducted by Epstein and Stevenson-Moore (1986), benzydamine hydrochloride rinse was found to reduce pain associated with radiation mucositis. However, a burning discomfort was associated with the use of the rinse when mucositis developed and this, according to the authors, was probably related to the 10 percent alcohol content. These symptoms may be reduced or prevented when it is diluted with water. However, in a study by Samaranayake and coworkers (1988), comparing BZH and chlorhexidine, no significant difference in its effectiveness was found. This efficacy was measured on the basis of mucositis and overall pain scores and yeast and bacterial species isolated.

Cetylpyridium chloride (Cepacol®): This mouthrinse is widely used in hospitals. Cepacol® is not advised for patients with stomatitis because of its drying and astringent effect and because of its

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alcohol content. It is generally accepted for routine mouthcare, but not advised for leukaemic patients or patients receiving chemotherapy that affects the oral mucosa. See further discussion under "Commercial Mouthwashes" (P. 50).

Chlorhexidine digluconate (Hibident®; Corsodyl®): The use of Chlorhexidine gluconate (CHX) in the prevention and management of oral complications in immunocompromised patients is well documented in both the medical and dental literature. CHX has been recommended for plaque removal by means of 0.2% chlorhexidine digluconate mouthrinse in the immunocompromised patient (Barkvoll and Attramadal, 1989; Meurman et al, 1991; Simon and Roberts, 1991;Toljanic et al, 1992). The success of chlorhexidine can be partly ascribed to its capacity to remain active in the mouth for at least 4 hours, providing antibacterial action in the oral cavity (Toljanic et al, 1992). Dramatic reductions in both incidence and severity of mucositis and oral Candida infections have been reported with the use of CHX in chemotherapy and bone marrow transplant patients (Ferretti et al, 1987; Rutkauskus and Davis, 1993). Bergman and coworkers (1992) demonstrated that chlorhexidine only reduced gingival inflammation when it was preceded by mechanical removal of plaque and calculus. They therefore only advocate the use of chlorhexidine following initial dental treatment. Chlorhexidine gel was also found to reduce the caries risk in patients treated with radiation therapy (Epstein et al, 1991).

On the contrary, Raether and coworkers (1989) found that a lower concentration of chlorhexidine (0.12%) did not reduce the development of bacteraemia in bone marrow transplant patients and suggest that it only be used to augment oral hygiene care. Another study by Wahlin (1989), using a 0.2% chlorhexidine mouthwash, showed no significant reduction in the number of oral lesions, plaque scores, gingival bleeding scores or occurrence of candidiasis in leukaemia

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patients. This study does not support the use of chlorhexidine in patients who are able to maintain good oral hygiene by mechanical means. According to Barkvoll and Attramadal (1989) and Simon and Roberts (1991), nystatin and chlorhexidine should not be used simultaneously, as combining these agents results in the formation of chlorhexidine-nystatin complexes that appear to be ineffective against Candida.

Adverse effects include: altered taste sensation, superficial desquamation, brownish dicoloration of the tongue and teeth, and increased calculus formation. Chlorhexidine has also been associated with potential anaphylactic reactions which may either be an immediate- or delayed-type hypersensitivity reaction (Gagari and Kabani, 1995). Therefore, chlorhexidine should be administered with caution in patients with a history of multiple drug reactions.

Commercial mouthwashes: Depending on their constituents, these may cause irritation and hypersensitivity stomatitis manifested by erythema, ulceration, or epithelial sloughing (Daeffler, 1980b; Holmes 1991). White lesions of the gingiva have also been reported following the excessive application of isopropyl alcohol, with remission of lesions after discontinuation (Daeffler, 1980b; Gagari and Kabani ,1995). These reactions are related to constituents such as menthol, thymol, methylsalicylates and alcohol. White lesions were reported with the use of Listerine®, a commercial mouthwash containing 25.0 - 26.9% alcohol, thymol, eucalyptol, methylsalicylate, menthol, benzoic acid, and boric acid (Gagari and Kabani, 1995). The latter authors also cited a study which showed that regular users of mouthwashes containing concentrations of alcohol greater than 25% had a greater risk of oral and pharyngeal cancer.

In the light of the vulnerability of the oral mucosa in many patients with cancer, the following

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guidelines for the use of commercial mouthwashes are proposed (Daeffler, 1980b): Commercial mouthwashes may be used by patients (a) whose oral mucosa has a healthy appearance, (b) who are neither receiving nor have received radiation therapy to the head or neck area, (c) who are neither receiving nor have received chemotherapy with drugs that affect the gastrointestinal mucosa for the previous 2 weeks, (d) whose neutrophil and lymphocyte count are within normal limits, and (e) who do not have leukaemia.

Fluoride: The role of fluoride both in treatment of early caries and prevention in radiation therapy patients is well documented in the literature (Naylor and Terezhalmy ,1988; Marciani and Wonby, 1992 and Joyston-Bechal, 1992). Daily application of fluoride is recommended for radiation therapy patients (Holmes, 1991; Marciani and Wonby, 1992). It is important to note, that fluoride is only effective on clean teeth and cannot substitute for brushing or other oral hygiene measures.

Hydrogen peroxide: This is a known germicidal agent which rapidly decomposes forming oxygen and water when in contact with the enzyme catalase that is found in blood and tissues. This released oxygen has some mechanical cleansing (due to the effervescence) and antibacterial effects (Daeffler, 1980b; Holmes, 1991; Beck, 1992). Hydrogen peroxide is diluted with one or more parts of water immediately prior to use as a mouthwash since it rapidly decomposes in water. The foaming effect of this mouthwash may however be dangerous for patients with compromised coughing reflexes unless assistance with suction is readily available. According to Daeffler (1980b), hydrogen peroxide should not be used when the patient has fresh granulation surfaces in the mouth since it tends to break down the new tissue. Its use in gingivitis and stomatitis may irritate the tongue and buccal mucosa. It is also reported to cause a deepening of fissures and overgrowth of papillae of the tongue which will form an excellent medium for candidiasis.

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Although it is not a mouthwash of choice for patients with stomatitis, it may be useful in loosening crusting and debris from mucosal surfaces.

Magnesium hydroxide (Milk of Magnesia®): This is an antacid which is a white, opaque 7.5% suspension of magnesium hydroxide. It has a soothing effect, reduces oral acidity and dissolves mucin films. The antacid effect is short in duration and does not cause systemic alkalosis. Milk of Magnesia® has a saliva-stimulating effect and should be swabbed in the mouth and left for 15-20 minutes before it is washed out. Adverse effects include an intolerable taste to some patients; the unabsorbed magnesium salt exerts an osmotic effect which may dry the oral mucosa (Daeffler, 1980a).

Orabase: Is an oral protective paste that is available with or without an analgesic (benzocaine) or an antiinflammatory agent (Kenalog®, with hydrocortisone) and combines gelatin, pectin, and sodium carboxymethylcellulose in a hydrocarbon gel. The hydrocarbon gel contains mineral oil. This paste is recommended for temporary relief and protection of minor irritations of the mouth and gingiva. It is not intended for use in infections.

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Petroleum (mineral jelly, petroleum jelly, yellow soft paraffin, Vaseline®): This is a purified mixture of semisolid hydrocarbons obtained from petroleum. It is used as an ointment base and as a protective dressing and soothing application to the skin. Vaseline® is commonly used as a lip lubricant for dry, sore or cracked lips. Vaseline® forms a protective film on the lips, preventing evaporation of moisture through the skin on the lips, and thereby, drying.

Phenol (Chloraseptic®): This is an alkaline solution containing phenol and sodium phenolate with

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a menthol or cherry flavour. It is available as a mouthwash, lozenges, gel and a spray. The spray contains compressed nitrogen as a propellent. It is an antiseptic, anaesthetic and deodorizing solution. According to the manufacturers (Pharmatec), it provides prompt temporary relief of discomfort after oral surgery, aphthae, and infectious stomatitis, gingivitis, and many other conditions. The use of Chloraseptic® for leukaemic patients is rejected because its phenol content promotes mucosal ulceration.

Saline (sodium chloride solution): Warm saline rinses have been recommended as a palliative treatment for 'leukaemic gingivitis' and for patients having head and neck irradiation (Daeffler, 1980b). It is thought to aid in the formation of granulation tissue and promote healing. It is safe, effective, economical and readily available. Although there is no evidence to support this, anectodal evidence suggests that normal saline solution may be the least damaging mouthwash available.

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Sodium Bicarbonate ($NaHCO_3$): Sodium bicarbonate is known as an effective cleansing agent that may be used in the presence of oral ulcers. Its main function is to dissolve mucins and loosen debris. In the absence of oral crusts, there is no indication for its use. Adverse effects include a burning sensation and an unpleasant taste.

Topical anaesthetics (Cepacaine®, Lidocaine®, Xylocaine®): These products are commonly used for painful oral lesions. The anaesthesia may decrease the potential nutritional complications of stomatitis if given 15-20 minutes before meals, decreasing the pain with swallowing. Benzocaine is available in a water soluble base, which has been found to be safe and effective. It is marketed in South Africa as both a mouthrinse and lozenges (Cepacaine ®). The onset of action of

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benzocaine is quick, approximately 30 seconds, and the duration is from 5 to 15 minutes (Beck, 1992). This effect may also be unpleasant for some individuals as patients may dislike the feeling of numbness. Lidocaine has a longer duration of action, approximately 40 minutes; however, it is absorbed systemically and has been associated with cardiac and central nervous system complications (Beck, 1992). It is also reported to mask sensitivity to hot foods (Daeffler, 1980b).

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c. Tools for oral care

Toothbrush: Some clinicians are not in favour of toothbrushing in the presence of mucositis and especially during aplasia (Seto et al, 1985; Maxymiw and Wood, 1989; Beck, 1992); the main reason being that it may give rise to infectious and hemorrhagic complications. As an alternative to toothbrushing, Beck (1992) recommends sponge-tipped oral swabs (the Toothette®). Borowski and coworkers (1994), in a randomised controlled clinical study, compared a limited oral hygiene care regimen (preventive dental treatment; gingival and toothbrushing) and an intensive oral hygiene care (initial dental treatment; tooth and gum brushing during aplasia) in bone marrow transplant candidates. They found that septicaemia was not significantly higher in the intensive oral care patient group, and suggested that the ban on toothbrushing during aplasia be lifted. Beck (1992) recommended brushing with a soft, multitufted toothbrush 30 minutes after eating and at bedtime.

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Epstein and coworkers (1994b) demonstrated that the use of a foam brush saturated with chlorhexidine is equally as effective in reducing plaque levels and gingivitis as a toothbrush. They therefore recommended the use of a foam brush soaked in chlorhexidine as an alternative if a toothbrush cannot be used in hospitalized patients.

Toothettes®: Daeffler (1980b) and Beck (1992) describe the use of Toothettes® which are foam sticks that may be available with or without a dentifrice. It is less traumatic and less effective than a toothbrush; it is hygienic (disposable) and effective in stimulating the gingiva and palate, but they are ineffective at cleaning all tooth surfaces (Holmes, 1991).

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Water Pic®: This is a water irrigation device frequently used by patients at their bedside. The oral cavity is irrigated with an antiseptic solution (often chlorhexidine) under a pressure spray. Suction equipment may be necessary for patients who are unable to expectorate. The Water Pic® is ideal for the removal of sloughing in mucositis; it is convenient as the patient can use it at his/her bedside and no clinical assistance is needed except for suctioning.

Lemon-glycerine swabs: These swabs are medicated instruments and are used to clean the mouth and stimulate saliva production. The lemon juice contains a citric acid that may irritate the mucosa and glycerine is a trihydric alcohol that absorbs water (Holmes, 1991; Beck,1992). According to Daeffler (1980a), these devices are not recommended for patients with stomatitis for the following reasons: (1) it is ineffective in removing tooth debris, (2) its acidity may decalcify teeth, (3) it may cause pain in the presence of mucositis and (4) it is an ineffective salivary stimulant that should not be used in dehydrated patients. Frequent usage as a salivary stimulant may also result in reflex exhaustion. Holmes (1991) and Beck (1992) agree that these swabs have little value in either cleaning or moisturizing the oral cavity.

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Electric toothbrushes: These are widely available and have different types of brushing motion, head design and bristles. However, according to Holmes (1991), head design and bristles are manufactured to make the head last longer, but they are rarely of ideal shape/ texture for thorough cleaning of the teeth and gingiva. Holmes (1991) further reports on the superiority of electric toothbrushes in the physically and mentally handicapped patient, but their efficacy remains to be proven in the cancer patient.

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III. MANAGEMENT OF ORAL COMPLICATIONS

There appears to be general agreement that oral health care measures are important in preventing infections in the immunocompromised patient (Wright et al, 1985; Sonis and Kunz, 1988; Naylor and Terezhalmy, 1988 and Joyston-Bechal, 1992). Preventive oral hygiene also reduces infectious periodontal complications during aggressive antineoplastic therapy (De Beule et al, 1991). Maxymiw and Wood (1989) emphasize comprehensive dental examinations for bone marrow transplant patients prior to treatment.

Various treatment regimens for the management of the abovementioned oral complications have been proposed (Naylor and Terezhalmy, 1988; Touyz et al, 1991; Marciani and Wonby, 1992, Joyston-Bechal, 1992). The authors, however, seem to separate treatment protocols for chemotherapy and radiotherapy patient groups. The following is a summary of their proposed regimes.

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a. Treatment regimens for patients receiving radiation therapy:

Radiation causes tissue injury that may present in the form of xerostomia, indurated tissues, facial hair loss, skin pigmentation, mucosal redness and thinning, cutaneous flaking and taste loss. The aforementioned factors result in mucositis, increased caries risk, overgrowth of candidal fungus, periodontitis and secondary infection of traumatic microabrasions (Touyz et al, 1991).

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Pre-treatment strategies include:

- Careful examination and assessment with appropriate radiographs
- All teeth with infection or with a questionable prognosis should be extracted (if patients' blood count and overall condition permit)
- Teeth which can be saved should be restored or dressed
- All teeth should be scaled and polished and oral hygiene instructions given
- Fluoride treatment and follow-up care
- Possible elimination of tori and other alveolar irregularities
- Removal of inflamed redundant fibrous tissue and other soft tissue irregularities
- Charting of impacted teeth
- Diagnosis and treatment of benign cysts and odontogenic tumors
- When deep scaling and root planing are done, 7 to 10 days (postsurgically) should be allowed for healing before irradiation.

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Post-irradiation treatment includes:

(i) Control of gingivitis and periodontitis

- Treatment of mucositis
- Chlorhexidine mouthrinse to reduce risk of infection and to maintain a clean mouth in the absence of oral hygiene
- Patients should be monitored closely every 3 to 4 months when oral hygiene

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instructions are reinforced and scaling carried out when necessary

- Routine prophylaxis
- Review and reinforce oral hygiene home care

(ii) Control of caries

- Monitor salivary flow
- Stimulated flow rates should be measured every 3 to 4 months in order to establish the level of caries risk
- Dietary advice
- Chlorhexidine and daily fluoride treatments to reduce radiation caries
- Limit or avoid crown and bridge reconstruction and endodontic therapy

(iii) Management of dry mouth

- Salivary substitutes

(iv) Extractions

- Must be carried out as atraumatically as possible (without periosteal elevation; surgical site to be closed with sutures and patient covered with antibiotics, Touyz et al, 1991)

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(v) Edentulous patients

- May be necessary to construct new dentures
- Relining of denture with soft lining materials
- Rinse with chlorhexidine (10ml) twice daily to keep mouth "fresh"
- Candidiasis to be treated appropriately

b. Treatment regimens for patients receiving chemotherapy

Pretreatment examination and management

- Thorough oral examination with radiographic analysis
- Oral hygiene instructions given
- If patient's haematologic status and time permits, optimal dental treatment should include:

  a. prophylaxis

  b. restoration of carious teeth

  c. replacement of faulty restorations

  d. smoothening of rough enamel or restored surfaces

  e. elimination of ill-fitting prosthesis

  f. extractions if necessary

  g. when surgical treatment is done, chemotherapy should be delayed for at least 1 week, but 2 weeks are preferred

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According to Naylor and Terezhalmy (1988), patients who have undergone these prophylactic measures and maintained a healthy mouth have had fewer chemotherapeutic-related oral complications.

Dental management following chemotherapy (Joyston-Bechal, 1992):

- Existing periodontal disease should be treated and carious teeth restored if the patient was not made dentally fit before chemotherapy
- A regimen to control caries, gingivitis and periodontal disease is desirable; using chlorhexidine gel
- Fluoride mouthrinse daily (0.05 percent sodium-fluoride)
- Patient should be monitored every 4 to 6 months, when oral hygiene instructions and dietary advice can be reinforced
- Measure salivary flow

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There are no specific preventive and therapeutic oral care regimens in the management of oral complications for patients receiving chemo- and radiotherapy. The literature suggests many oral care agents, and with the exception of chlorhexidine, no other oral medicament has proven to be effective for these patients. Jansma and coworkers (1992) did a survey on the prevention and treatment regimens for oral complications in Dutch radiotherapy institutions. They found great diversity in the preventive approach of head and neck patients in the various institutions. The authors suggested that this diversity is mainly due to: (1) lack of well-defined guidelines, (2) absence of a dental team in some centers, (3) absence of an oral hygienist in some dental teams and (4) patients not being referred to the dental team. The authors concluded that there was a

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need to develop a general protocol for the prevention of oral complications in all radiotherapy institutions.

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MATERIALS AND METHOD

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STUDY POPULATION

Between September 1992 and August 1995, all patients with haematological malignancies who were treated as in-patients in the Haematology Protected Unit at Groote Schuur Hospital, Cape Town were monitored. Their treatment included chemotherapy or bone marrow transplantation. Bone marrow transplant recipients received a combination of chemo- and radiotherapy. All patients received nystatin and acyclovir prophylactically as follows: 100, 000 units nystatin 4 hourly and 200mg acyclovir 5 times daily or 5mg/kg every 8 hours intravenously. Oral acyclovir therapy continued for 90 days. From the first day of admittance until their discharge, patients were kept in an isolation room. Patients who had succumbed to the disease and not completed their antineoplastic therapy were excluded.

DATA COLLECTION

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An examination form was devised to record and summarize data for each patient (Appendix 1). All eligible patients were interviewed and given an oral and perioral examination before receiving antineoplastic treatment. Visual examination was done with aid of a dental mirror and probe using the hospital auditory torch provided for the ear, nose and throat specialists. The patients' oral status was assessed twice weekly by a single skilled examiner (dentist) during therapy until their discharge. Diagnoses for oral candidiasis and herpes simplex infection were confirmed by cultures obtained from mouth and throat swabs. Oral microbial cultures were done only when an oral infection was suspected.

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CRITERIA FOR ASSESSMENT

There are no clear guidelines for the accurate assessment of oral complications associated with cancer therapy. The criteria used for the assessment of oral lesions in the medical, dental and nursing literature vary from one study to the other. The following assessment guides were used based on previous reported studies.

Herpes simplex (HSV) infection: Reactivation of HSV was considered when typical HSV mucosal or lip lesions were observed or when HSV was demonstrated in swabs taken from blister walls (Dahllöf et al, 1989). Diagnosis was made using tissue culture techniques.

Candida infection: Clinical signs including those for erythematous candidiasis had to be present, such as bleeding and the formation of distinct microbiologically proven colonies on mucous membranes, including erythematous candidiasis. Identification of *Candida* spp. was done by means of the germ tube test (Silverman et al, 1990).

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Oral ulceration: All types of mucosal ulcers that were not considered as being caused by HSV infection were included in this group. These ulcers were most likely to be caused by trauma, cytotoxic therapy or infection (Dahllöf et al, 1990).

Mucositis: Diagnosed by the presence of mucosal erythema, ulcerations and/or pseudomembranous lesions associated with pain following chemo- or radiotherapy (Spijkervet, 1989).

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Gingivitis: Only a clinical diagnosis based on the appearance of the gingiva, e.g. erythema, oedema and/or bleeding, was made for gingivitis. Probing was attempted during the pilot study but caused distress to the patients and was therefore discontinued.

Angular cheilitis: Defined as inflammation or ulceration of the commissures of the lips (Dahllöf et al, 1989).

Hairy Tongue: was defined as brown hair-like extensions of the filiform papillae on the dorsum of the tongue (Dorland, 1974).

ORAL CARE

Sixty patients were monitored while following the traditional hospital oral care regimen (Table 3a) The medications included: chlorhexidine, hydrogen peroxide, sodium bicarbonate, thymol glycol and nystatin. Patients rinsed with a single mouthrinse every two hours without any specific sequence. Brushing was encouraged but not included in this regimen. Due to the absence of a structured routine in the hospital mouth care regimen, patients tended to choose their own medication of preference of which a number were available.

The mouth care regimen in the unit was then changed to protocol A, consisting of chlorhexidine and amphotericin B lozenges only (Table 3b). Amphotericin B lozenges replaced nystatin oral suspension as it provided prolonged mucosal contact. For the same reason, benzocaine lozenges were prescribed to replace the benzocaine mouthrinse. Patients were monitored until the sample

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size matched that of the traditional oral regimen. A further 60 patients were monitored after adding benzydamine hydrochloride to protocol A, which was designated protocol B (Table 3c). A structured routine for both protocols A and B (Tables 3b and 3c) was implemented to prevent a reduced efficacy of chlorhexidine as a result of combining with other oral medications (Barkvoll and Attramadal, 1989).

Oral hygiene instructions were given to all patients. All mouth care regimens were followed from the first day of the conditioning regimen until their discharge from the unit.

Table 3(a): Hospital Oral Care Regimen

MOUTHRINSES	INSTRUCTIONS
Chlorhexidine Hydrogen Peroxide Sodium Bicarbonate Thymol Glycol Nystatin Benzocaine Mouthrinse[a]	Rinse mouth on a two hourly basis, rotating the listed rinses.

[a]Benzocaine mouthrinse was included when mucositis was present.

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Table 3(b): Protocol A

MOUTHRINSES AND ROUTINE			INSTRUCTIONS
7H30	-	Brush Teeth	
8H30	-	Amphotericin B lozenge	
11H30	-	Brush Teeth	
12H30	-	0.2% Chlorhexidine	Rinse with 10ml for 30seconds
16H30	-	Amphotericin B lozenge	
17H00	-	Brush Teeth	
20H00	-	0.2%Chlorhexidine	Rinse with 10ml for 30seconds
Benzocaine lozenges[b]			

[b]Benzocaine lozenges were included when mucositis was present.

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Table 3(c): Protocol B

MOUTHRINSES AND ROUTINE			INSTRUCTIONS
7H30	-	Brush Teeth	
		Benzydamine Hydrochloride	Rinse with 15ml for 30 seconds
8H30	-	Amphotericin B lozenge	
11H30	-	Brush Teeth	
		Benzydamine Hydrochloride	Rinse with 15ml for 30 seconds
12H30	-	0.2% Chlorhexidine	Rinse with 10ml for 30seconds
16H30	-	Amphotericin B lozenge	
17H00	-	Brush Teeth	
		Benzydamine Hydrochloride	Rinse with 15ml for 30 seconds
20H00	-	0.2% Chlorhexidine	Rinse with 10ml for 30seconds
Benzocaine lozenges[c]			

[c]Benzocaine lozenges were included when mucositis was present.

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DATA CAPTURING AND STATISTICAL ANALYSIS

All the data were captured on a database in the DBASE IV data capturing programme. The statistical analysis of the data were carried out on the Epi Info 5 statistical package. The Wordperfect 6.0 word processing package was utilised for preparing the written report. p - Values of less than 0.05 were regarded as statistically significant.

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RESOURCES

Dental mirrors and probes for the oral assessment of patients were provided by the Haematology Unit, Groote Schuur Hospital. Except for benzydamine hydrochloride, which was provided by 3M Dental Company, all oral medications were supplied by the hospital pharmacy. Microbial cultures from oral lesions were analysed by the microbial laboratory at Groote Schuur Hospital and the results obtained from computers within the haematology ward. All stationery, computer and literature resources for this study was acquired from the Faculty of Dentistry, University of the Western Cape.

ETHICAL CONSIDERATIONS

Consent from the superintendents and consultants of the relevant hospital ward (F4) and co-operation of the staff in the clinic was obtained. An explanatory outline for consent and possible short and long term benefits of the changed protocols to the patients was presented and accepted by all the role players. Participants were assured of confidentiality, report back (if desired), right of refusal of treatment or referral for any manifestations observed.

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RESULTS

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1. PATIENT POPULATION

The sample consisted of 180 patients with haematological disorders. Table 4 describes the demographic characteristics of the three groups. The patients' ages ranged from 4 to 68 years, with a mean of 32 years.

Table 4. Patient Characteristics

PATIENTS	HOSPITAL REGIMEN n = 60	PROTOCOL A n = 60	PROTOCOL B n = 60
Age			
Mean	31.7	30.5	36.0
Range	12 - 68	4 - 67	12 - 67
Gender			
Male	41 (68.3%)	35 (58.3%)	42 (70.0%)
Female	19 (31.7%)	25 (41.7%)	18 (30.0%)
Diagnosis			
Acute leukaemia	44 (71.0%)	38 (66.7%)	47 (78.3%)
Chronic leukaemia	8 (12.9%)	3 (5.3%)	-
Aplastic anaemia	2 (3.2%)	4 (7.0%)	5 (8.3%)
Multiple myeloma	2 (3.2%)	1 (1.8%)	2 (3.3%)
Non-Hodgkins	4 (6.5%)	7 (10.5%)	4 (6.7%)
lymphoma	-	-	-
Other[a]	1 (1.6%)	5 (8.8%)	2 (3.3%)

[a] Includes: Myeloproliferative syndrome, Fanconi' anaemia and Promyelocytic leukaemia.

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The majority of patients suffered from acute leukaemia (71.0%, 66.7% and 78.3% in the hospital regimen, protocol A and B respectively). Other diagnoses included: chronic leukaemia, aplastic anaemia, multiple myeloma, non-Hodgkins lymphoma, Fanconi's anaemia and promyelocytic leukaemia. No significant differences between the three patient groups with respect to medical diagnoses ($p > 0.05$) were found.

2.1 ANTINEOPLASTIC TREATMENT

Patients entering the unit received either chemotherapy, a bone marrow transplantation or merely observation (Table 5). Bone marrow transplant recipients received a combination of chemo- and radiotherapy. The majority of patients entering the unit received chemotherapy followed by bone marrow transplantation. Various chemotherapy modalities were used, the majority of chemotherapy patients receiving a combination of etopiside, daunorubicin and cytosine arabinoside. No significant differences between the three groups with respect to type of medical treatment received and specific chemotherapy modalities ($p > 0.05$) were found. Some patients received more than one course of chemotherapy and therefore may have entered the unit for their 2nd, 3rd or 4th course. No significant differences between the three patient groups with respect to the chemotherapy course received was found ($p > 0.05$).

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Table 5: Treatment modalities in each group by percentage

	HOSPITAL REGIMEN n = 60	PROTOCOL A n = 60	PROTOCOL B n=60
Treatment			
Chemotherapy	41 (68.3%)	37 (61.7%)	35 (58.3%)
Bone marrow transplant	13 (21.7%)	15 (25.0%)	18 (30.0%)
Observation	5 (8.3%)	3 (5.0%)	6 (10.0%)
Other[a]	1 (1.7%)	5 (8.3%)	1 (1.7%)
Chemotherapy Type			
Etoposide, daunorubicin	25 (56.8%)	23 (62.2%)	29 (82.9)
and cytosine arabinoside	-	-	-
Cytosine arabinoside,	7 (15.9%)	7 (18.9%)	6 (17.1%)
methotrexate and	-	-	-
epipodophyllotoxin	-	-	-
High-dose	6 (13.6%)	4 (10.8%)	-
cyclophosphamide	-	-	-
Other[b]	6 (13.6%)	3 (8.1%)	-

[a]Includes: ALG (Antilymphocytic Globulin) and Retinoic Acid

[b]Includes: VAAP (vincristine, asparaginase, adriamycin and prednisone) and high-dose cytosine arabinoside

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2.2 BASELINE ORAL EXAMINATION

All patients received a baseline oral examination before their antineoplastic therapy (Table 6). Oral lesions encountered at baseline examination included angular cheilitis, ulceration, gingivitis, candidiasis and caries. No significant differences between the patient groups with respect to the oral complications encountered at baseline oral examination was found ($p > 0.05$).

Table 6: Frequency of oral complications at baseline examination.

	HOSPITAL n=60	PROTOCOL A n=60	PROTOCOL B n=60	*p* -value
Angular Cheilitis	1	0	0	0.220
Ulceration	2	0	1	0.477
Gingivitis	1	5	2	0.658
Candidiasis	0	1	0	0.220
Caries	3	4	3	0.703

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2.3 ORAL COMPLICATIONS DURING ANTINEOPLASTIC THERAPY

The frequencies of oral complications observed using the three mouth care regimens, were compared (Table 7, Figure 2). All oral complications were noted as single observations (Figures 3 to 7b). A statistically significant overall reduction in the oral complications with the use of protocols A and B ($p = 0.007$) was noted. Seventy five percent of patients developed oral lesions with the use of the hospital regimen, 65% of patients had oral lesions with protocol A and when protocol B was instituted, there was a further reduction in the oral lesions (48.3%). Except for gingivitis and hairy tongue (which remained at the same level), there was a reduction in every other oral complication.

Dual comparisons showed no statistically significant reduction in oral lesions when the hospital regimen and protocol A were compared. This was also the case when protocol A was compared with protocol B. However, when the hospital regimen was compared with protocol B, a statistically significant reduction was found in the overall number of oral lesions observed ($p = 0.004$).

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Table 7. Frequency of oral lesions observed during therapy.

	HOSPITAL Regimen n = 60	**PROTOCOL A n = 60**	**PROTOCOL B n=60**	***p*-value**
Pts[a] with lesions	45 (75%)	39 (65.0%)	29 (48.3%)	0.007*
HSV[b] lesions	7 (11.7%)	5 (8.3%)	2 (3.3%)	0.089
Angular cheilitis	2 (3.3%)	2 (3.3%)	1 (1.7%)	0.576
Ulceration	8 (13.3%)	4 (6.7%)	5 (8.3%)	0.350
Mucositis	22 (36.7%)	20 (33.3%)	19 (31.7%)	0.563
Gingivitis	12 (20.0%)	5 (8.3%)	5 (8.3%)	0.051
Hairy tongue	1 (1.7%)	1 (1.7%)	1 (1.7%)	1.000
Candidiasis	16 (26.7%)	13 (21.7%)	11 (18.3%)	0.273

[a] Patients

[b] Herpes simplex virus

* p - value <0.05 is statistically significant.

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Oral lesions during antineoplastic therapy

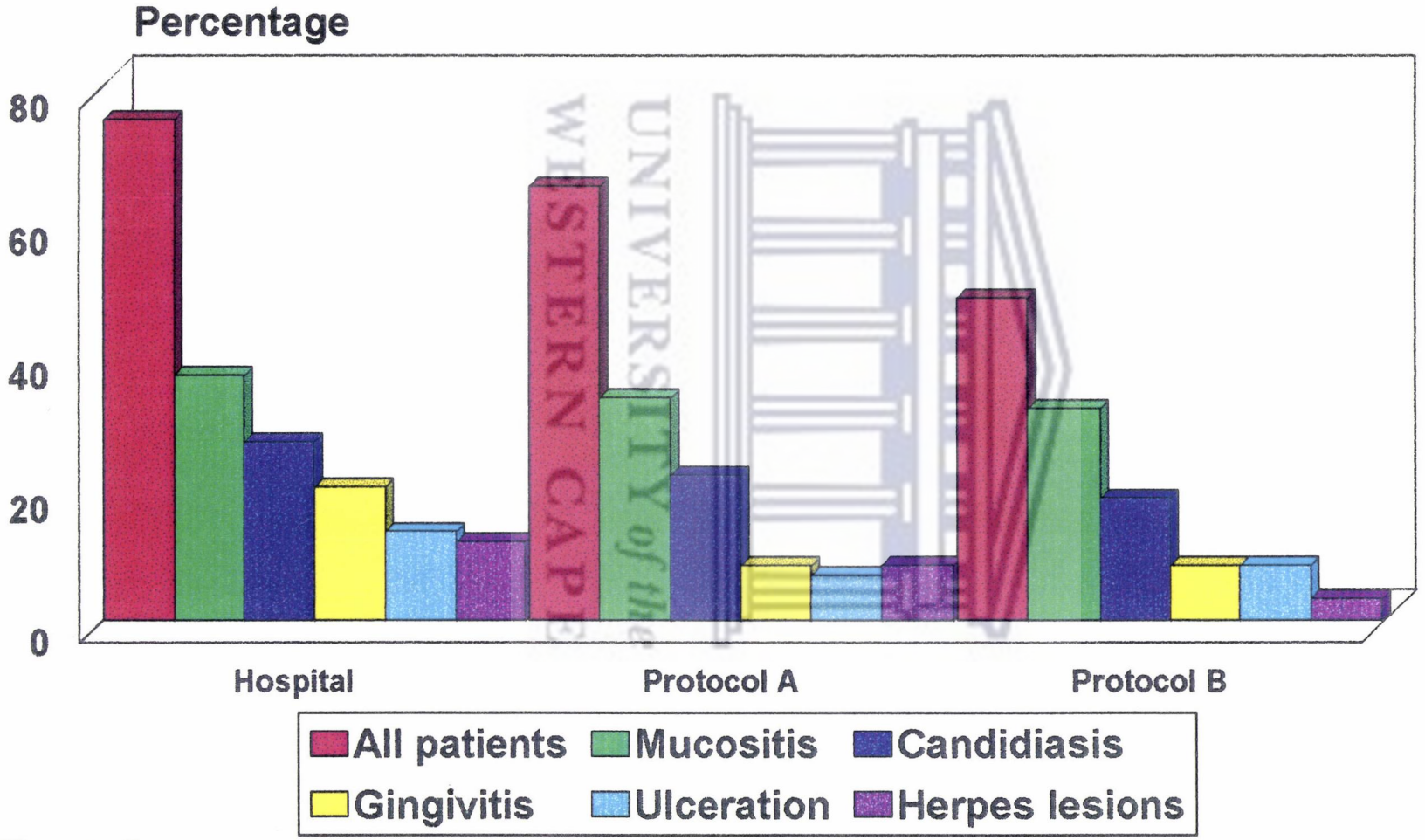

Figure 2

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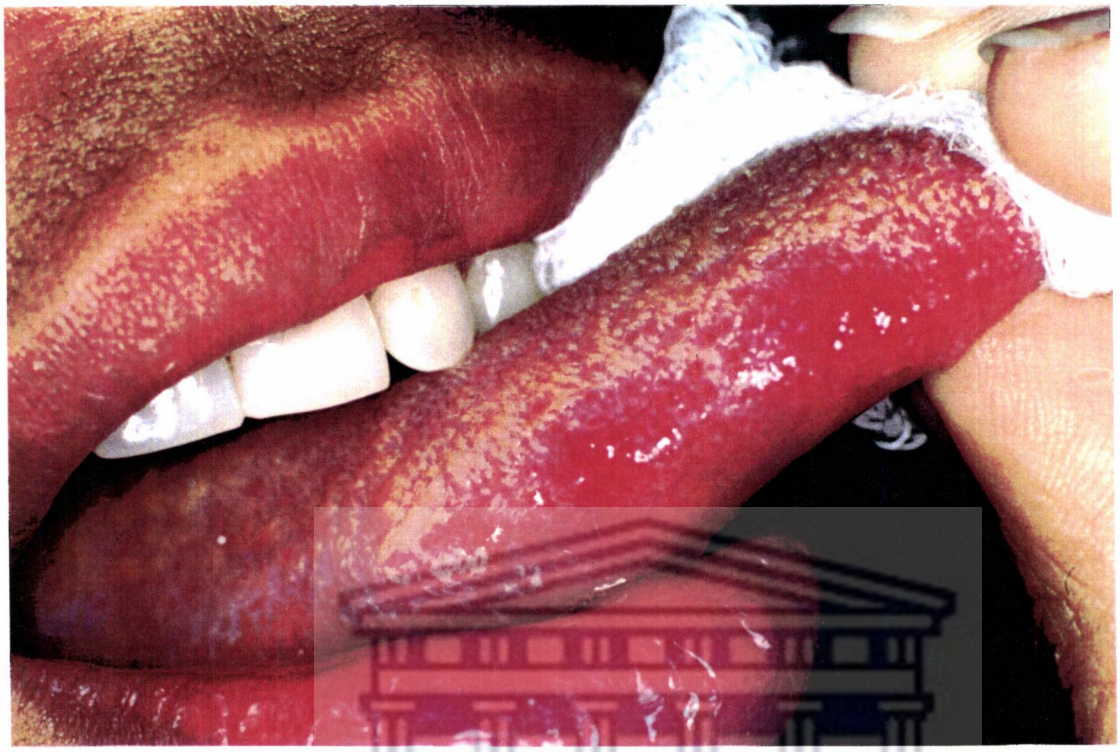

Figure 3. Herpetic ulceration on the lateral border of the tongue during chemotherapy.

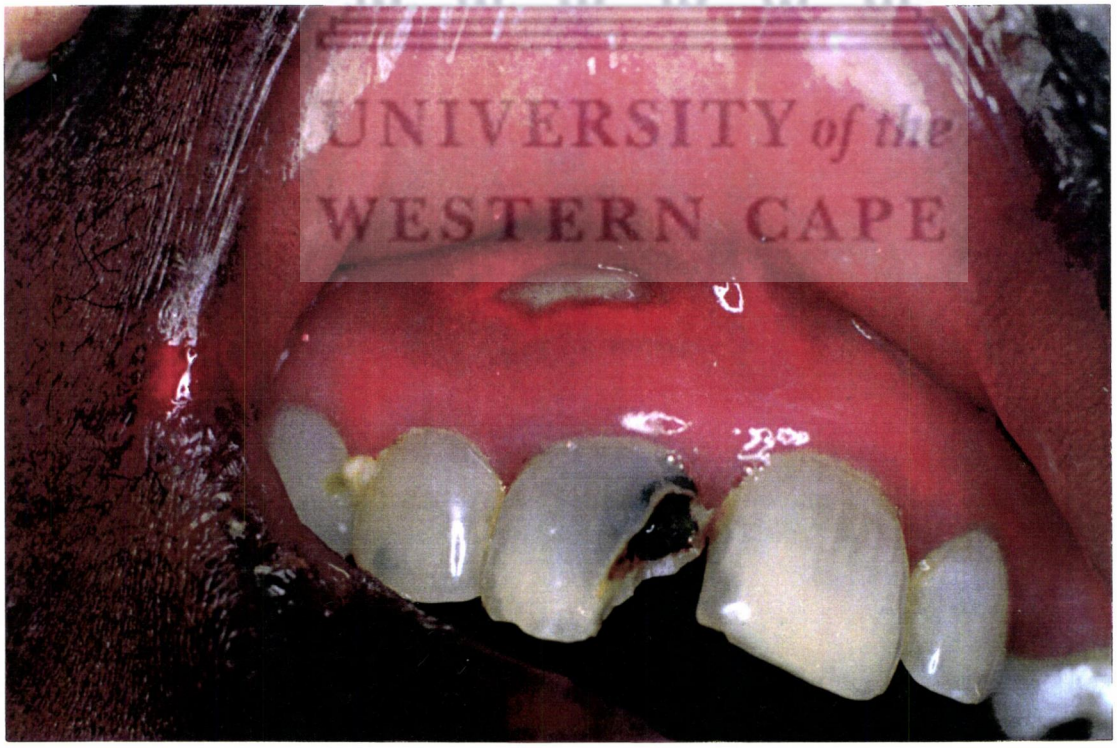

Figure 4. Patient admitted for chemotherapy with angular cheilitis, ulceration and visible caries.

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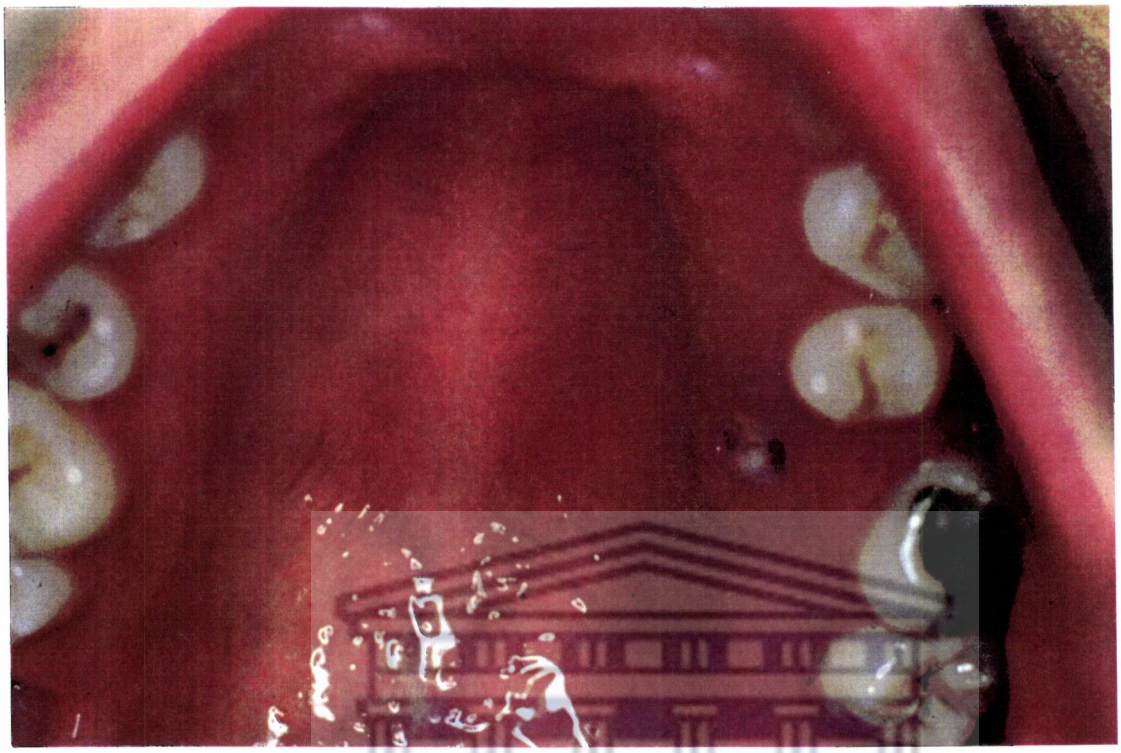

Figure 5. Ulceration in the hard palate during and following chemotherapy.

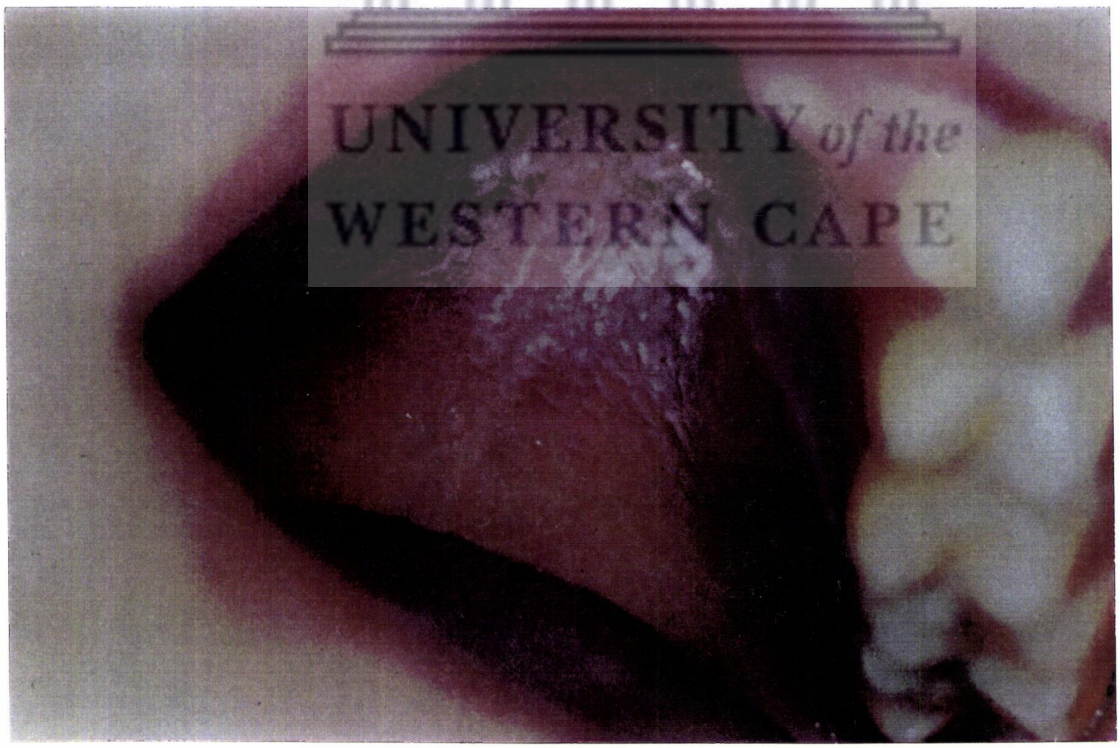

Figure 6. Pseudomembranous candidiasis on the hard palate duirng chemotherapy.

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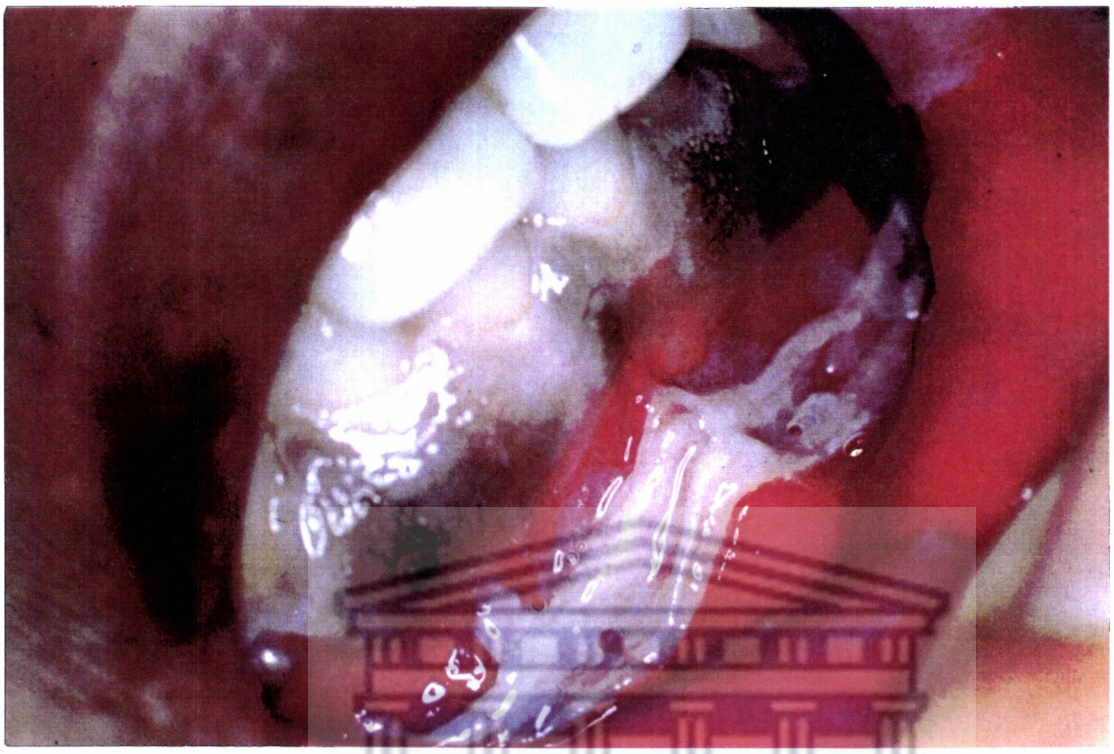

Figure 7a. Oral mucositis following bone marrow transplantation.

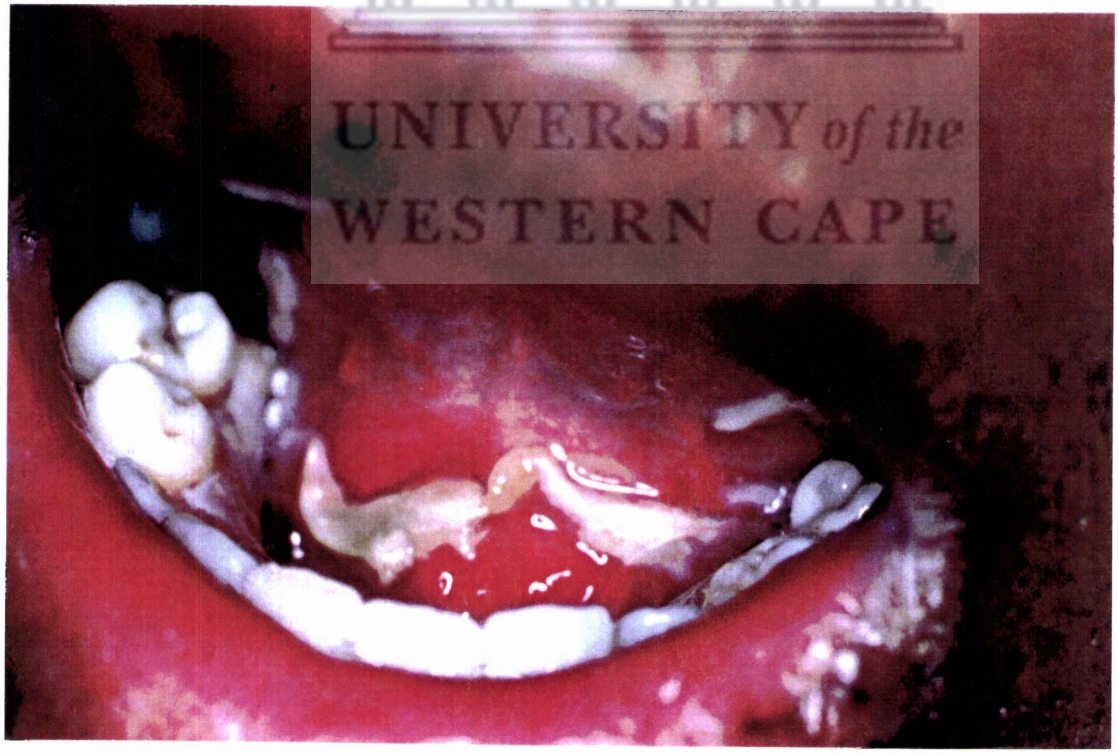

Figure 7b. Oral mucositis following bone marrow transplantation.

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2.4 TREATMENT VERSUS ORAL LESIONS

The frequencies of patients who developed oral lesions during the different treatment modalities were compared (Table 8).

Table 8. Frequencies of patients with oral lesions during different treatment modalities.

	HOSPITAL REGIMEN n = 60	PROTOCOL A n = 60	PROTOCOL B n = 60	*p* - VALUE
Chemotherapy	30	18	15	0.014*
BMT[a]	13	15	14	0.070
Observation	2	3	1	0.057
Other[b]	0	3	1	0.185

[a] Bone Marrow Transplant

[b] ALG (Antilymphocytic Globulin) and Retinoic Acid

* a *p* - value less than 0.05 is regarded as statistically significant.

In the chemotherapy patient group, a statistically significant reduction in the number of patients who developed oral lesions with the use of protocols A and B were found ($p = 0.014$). Further analysis showed that 39% percent of patients on their 1st course of chemotherapy developed some oral problem. This percentage increased to 40% of patients on their 2nd course and 45% of patients on their 3rd course of chemotherapy. However, this increase in oral lesions with multiple chemotherapy courses was not statistically significant ($p > 0.05$). The sample size of the

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chemotherapy patient group is too small to analyze the different chemotherapy courses versus the three oral care protocols. Therefore, more patients need to be monitored to be able to make any definitive conclusions in this regard.

In the bone marrow transplant patient groups, all patients following the hospital regimen developed mucositis. One patient had no mucositis with protocol A, and with the use of protocol B, two patients maintained healthy mouths and remained symptom free.

2.5 SPECIFIC ORAL LESIONS DURING DIFFERENT ANTINEOPLASTIC THERAPIES

Table 9 illustrates the frequencies of specific oral lesions observed during the different treatment modalities. Mucositis was significantly high in the BMT group of all three oral care regimens. This was expected as mucositis is considered an inevitable side effect of radiotherapy (Spijkervet, 1989). Gingivitis was also found to be significantly higher in the chemotherapy patient group using the hospital regimen, when compared with other treatment modalities ($p = 0.049$).

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Table 9. Frequencies of oral lesions observed during various treatment modalities.

		CHEMO[a]	BMT[b]	OBS[c]	OTHER[d]	*p*-value
HOSPITAL ORAL CARE REGIMEN n = 60	HSV[e]	5	1	1	0	0.921
	AC[f]	2	0	0	0	0.339
	Ulceration	6	1	1	0	0.729
	Mucositis	9	13	0	0	0.007*
	Gingivitis	11	1	0	0	0.049*
	Hairy Tongue	1	0	0	0	0.502
	Candidiasis	10	5	1	0	0.698
PROTOCOL A n = 60	HSV[e]	3	0	1	1	0.582
	AC[f]	0	1	1	0	0.074
	Ulceration	2	0	1	1	0.326
	Mucositis	5	14	1	0	0.002*
	Gingivitis	4	0	0	1	0.614
	Hairy Tongue	1	0	0	0	0.468
	Candidiasis	9	3	0	1	0.566
PROTOCOL B n = 60	HSV[e]	1	1	0	0	0.944
	AC[f]	1	0	0	0	0.411
	Ulceration	4	0	1	0	0.465
	Mucositis	4	15	0	0	0.003*
	Gingivitis	5	0	0	0	0.057
	Hairy Tongue	1	0	0	0	0.411
	Candidiasis	8	2	0	1	0.355

[a] Chemotherapy [b]Bone Marrow Transplant [c]Observation

[d] Treatment including ALG (Antilymphocytic Globulin) and Retinoic Acid

[e] Herpes simplex virus

[f]Angular cheilitis

**p*-values less than 0.05 are regarded as statistically significant.

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Apart from mucositis, oropharyngeal candidiasis was the most frequent oral problem observed. Sixty four percent of candidal swabs taken with the hospital regimen were positive, compared with 54% in protocol A and 42% in protocol B (Table 10). However, there was no statistically significance difference found in the reduction of candidiasis with the use of protocols A and B (p=0.273).

Table 10. Candidiasis

	HOSPITAL REGIMEN n = 60	PROTOCOL A n = 60	PROTOCOL B n = 60	p - VALUE
Swabs taken	25	23	26	0.085
Positive lesions	16	13	11	0.273
Positive lesions (%)	64%	56%	42%	

2.6 SYMPTOMS EXPERIENCED DURING ANTINEOPLASTIC THERAPY

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The majority of patients who developed oral symptoms are those who received bone marrow transplants (Table 11a.). Patients complained mainly of taste alterations (80%) and dry mouth (93%). These percentages were significantly higher when compared to the chemotherapy group ($p < 0.05$). Only 4% of the chemotherapy patient group developed taste alterations and 16% of patients complained of a dry mouth. With the implementation of protocols A and B, fewer patients experienced taste alterations and dry mouth (Table 11b). This reduction, however, was not statistically significant ($p > 0.05$).

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Table 11a. Oral symptoms experienced during different treatment modalities.

	CHEMOTHERAPY n = 113	BMT[a] n = 46	OTHER[b] n = 21	*p*-VALUE
Dysgeusia	5 (4%)	37 (80%)	-	0.000*
Dry Mouth	18(16%)	43 (93%)	3 (14%)	0.000*
Dental Pain	1 (0.00)	-	1 (4%)	0.390

[a]Bone marrow transplant

[b]Observation and other therapies including ALG (Antilymphocytic Globulin) and Retinoic Acid.

* p - values less than 0.05 are regarded as statistically significant.

Table 11b. Oral symptoms experienced during different oral care protocols.

	HOSPITAL REGIMEN n = 60	PROTOCOL A n = 60	PROTOCOL B n = 60	p - VALUE
Dysgeusia	15 (25%)	13 (22%)	13 (22%)	0.811
Dry Mouth	23 (38%)	21 (35%)	20 (33%)	0.568
Dental Pain	2 (3%)	0	0	0.082

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DISCUSSION

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With the current knowledge and techniques available, some damage to oral tissues during antineoplastic therapy is inevitable since even meticulous oral hygiene cannot prevent treatment induced inhibition of cellular replication. There is however, general agreement that appropriate oral care procedures which prevent secondary infection, gingivitis and periodontitis and dental caries may also reduce systemic infection (McElroy, 1984; Sonis and Kunz, 1988; Joyston-Bechal, 1992).

Many researchers have investigated the efficacy of a variety of mouthrinses for various oral conditions (MacD and Hunter, 1978; Ferretti et al, 1987; Samaranayake et al, 1988; Wahlin, 1989; Epstein et al, 1991; Bergman et al, 1992; Epstein and Stevenson-Moore, 1992; Rutkauskus and Davis, 1993). Although some guidelines exist concerning oral care prior to and during antineoplastic therapy, the literature is not clear about specific agents used for these patients. Additionally, there appears to be no specific protocol for the overall management of their oral problems. Oral care appears to be based on symptomatic relief and subjective evaluation with little or no reference to the existing lietrature.

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Holmes (1991) emphasizes the need for consistency with oral care and suggested that the time intervals for oral care be determined by doing further research. Some authors recommend a 3 hourly oral care routine for radio- and chemotherapy patients (Holmes, 1991; Carl, 1993). Although this may be adequate for reducing and/or preventing infection, Holmes (1991) believes that this may not enhance patient comfort and suggests more systematic and frequent care with 2 - 4 hourly intervals. Other researchers recommend that the frequency of mouth care be increased as the intensity of oral dysfunction increases (Daeffler, 1980a; Beck, 1992). Therefore, a 4 hourly mouth care routine may be reduced to an hourly routine in the presence of severe stomatitis.

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In the present study, the patients categorized as the hospital regimen group, rinsed with a single mouthrinse every two hours without any specific sequence. Brushing was encouraged but not included in the two-hour-mouth-care-regimen. Compliance was poor, probably due to the absence of a structured routine in the hospital mouth care regimen, where patients chose their medication of preference (e.g. according to taste) of which a number were available. The frequency of oral care in protocols A and B varies between 1 and 3 hourly care. These time intervals permit prolonged contact of medication (amphotericin B lozenges are kept in the mouth for a longer period of time compared to nystatin oral suspension). By making some allowance for the substantivity of chlorhexidine digluconate, the loss of efficacy of chlorhexidine that results from it combining with other oral medications, is reduced (Barkvoll and Attramadal, 1989; Simon and Roberts, 1991). The changed regimens were generally well accepted by patients and compliance was noticeably better.

The results of this study are difficult to compare with other mouthrinse studies because of differences in underlying disease, cancer therapy, antimicrobial prophylaxis, patients' ages, compliance, rinse concentrations and rinsing schedules. Chlorhexidine is one of the most intensely researched preventive agents in dentistry and its use has shown conflicting results with cancer patients (Ferretti et al, 1987; Raether et al, 1989; Meurman et al, 1991; Epstein et al, 1992). This study used a 0.2% chlorhexidine gluconate (Corsodyl® manufactured by SmithKline Beecham) which is widely available locally. Other workers have used a 0.12% solution (Ferretti et al, 1987; Meurman et al, 1991; Bergman et al, 1992). It has been reported to be effective in reducing bacterial and fungal pathogens in patients with haematological malignancies (Ferretti et al, 1987; Epstein et al, 1992) and therefore decreased plaque and gingivitis scores in these patient groups were expected (Ferretti et al, 1987; Meurman et al, 1991). Meurman and coworkers (1991) used

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chlorhexidine in a study of 51 patients suffering from Hodgkins and non-Hodgkins lymphoma. Visible plaque and gingival bleeding scores were significantly reduced after periods of rinsing with chlorhexidine solution ($p < 0.001$). Chlorhexidine gluconate also prevents periodontal destruction in patients with haematological malignancies even in the presence of pre-existing gingivitis and periodontal disease (De Beule et al, 1991).

Chlorhexidine gluconate was also successfully used in the management of mucositis and oral *Candida* infection (Ferretti et al, 1987; Rutkauskus and Davis, 1993). Dramatic reductions in both the incidence and severity of mucositis and oral *Candida* infections were found in patients receiving chemotherapy and bone marrow transplantation (Ferretti et al, 1987). Chlorhexidine rinse was prescribed twice daily for patients in this study as they were required to use several other oral medications. More frequent rinsing may have increased the risk of potential interaction and inactivation of chlorhexidine and nystatin (Barkvoll and Attramadal, 1989).

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Other studies failed to demonstrate a protective effect of chlorhexidine (Raether et al, 1989; Wahlin, 1989; Spjikervet, 1989). Although compliance was good, mucositis was not reduced in any patient group (Wahlin, 1989; Spjikervet, 1989). Both Spjikervet (1989) and Raether and coworkers (1989) used a 0.1% chlorhexidine concentration, whereas Wahlin (1989) used a 0.2% concentration. Wahlin (1989) reported on a randomized study of 28 patients with acute leukaemia. The median number of febrile days, mucosal ulceration, plaque scores, gingival bleeding scores, and candidiasis were not reduced in the chlorhexidine group. The author did not specify the rinsing schedule and patients were given nystatin oral suspension in addition to chlorhexidine. This factor is critical in the analysis of her results due to the potential nystatin-chlorhexidine interaction (Barkvoll and Attramadal, 1989).

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Samaranayake and coworkers (1988) studied the effects of chlorhexidine and benzydamine hydrochloride in 25 patients receiving radiotherapy for sqaumous carcinoma of the oral cavity. Their study showed little difference between the two mouthrinses in controlling pain and mucositis or in the oral carriage of *Candida* species. Other studies with benzydamine hydrochloride report a reduction in pain experienced in radiotherapy patients (Epstein and Stevenson-Moore, 1986) and a reduction in post-operative pain in patients who had impacted lower third molars removed (MacD and Hunter, 1978). Although various authors advocate the use of benzydamine hydrochloride for immunocompromised patients (Touyz et al, 1991; Beck , 1992; Fayle et al, 1994), no previous scientific studies exist that evaluate the efficacy of benzydamine hydrochloride on oral complications in immunocompromised patients. However, this study has done that and determined a beneficial effect. All the patients in protocol B enjoyed the taste of benzydamine hydrochloride. Although some burning discomfort was experienced when mucositis developed, none of the patients discontinued the use of the rinse. A few patients used the rinse diluted with water when severe symptoms developed. The complaint of burning with the use of this rinse probably relates to the 10% alcohol content.

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In addition to chlorhexidine, amphotericin B lozenges replaced nystatin suspension in protocols A and B to provide prolonged mucosal contact in an attempt to increase the effect of the medication. For this reason, benzocaine lozenges also replaced the benzocaine mouthrinse for patients with mucositis. Hydrogen peroxide was excluded from protocols A and B because it irritates the mucosa in the presence of stomatitis and because it causes an overgrowth of the papillae of the tongue (Beck 1992). Sodium bicarbonate was also eliminated from the protocols A and B as it causes a burning sensation, has an unpleasant taste and damages the oral mucosa (Daeffler 1980b).

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Early and aggressive dental treatment is recommended by many authors (Sonis and Kunz, 1988; Maxymiw and Wood, 1989; De Beule et al, 1991; Joyston-Bechal, 1992) to reduce the frequency of oral problems associated with antineoplastic therapy. At baseline examination, the prevalence of visible caries and other soft tissue pathology observed in the hospital regimen reflected a need for early dental intervention. However, dental treatment prior to instituting immunosuppressive therapy posed a problem in the unit as many patients were referred with active neoplastic disease and needed immediate medical treatment. This explains the high number of patients admitted to protocols A and B with gingivitis and caries.

In earlier studies, oral complications have been reported in 40 to 93% of patients with haematological malignancies treated with chemo- or radiotherapy (Sonis et al , 1978; Sonis and Kunz, 1988; Dahllöf et al, 1989; Fayle and Curzon, 1991; Rutkauskus and Davis, 1993). The higher percentages of oral complications in the range of 80 to 90% were recorded in paediatric patients (Holmes, 1991; Fayle et al, 1994). This may be due to the increased susceptibility of this patient group to the cytotoxic effects of chemotherapy (Fayle and Curzon, 1991). It should also be noted that patients being treated for haematological malignancies are at greater risk for oral problems than patients with other forms of malignancies (Sonis and Kunz, 1988). In this study, 75% of patients developed oral problems with the hospital regimen, 65% in protocol A, followed by 48.3% in protocol B. These frequencies are consistent with those of other studies (Sonis and Kunz, 1988; Dahllöf et al, 1989; Fayle and Curzon, 1991; Rutkauskus and Davis, 1993).

An analysis of the distribution of individual oral problems demonstrates, with the exception of ulceration and hairy tongue, a reduction in every oral problem with the implementation of protocols A and B. Mucositis remained the most common oral problem. The percentage of bone

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marrow transplant patients developing mucositis in our study corresponds with that found in the literature (Woo et al, 1993). The effects of chlorhexidine and benzydamine hydrochloride on the severity of mucositis (i.e. number of mucositis days and pain experienced) were beyond the scope of this study. The reduction in mucositis with the use of protocols A and B was found to be mainly in the chemotherapy patient group. This may be explained by the fact that fewer patients in protocols A and B were exposed to high dose chemotherapy. It is known that certain chemotherapy agents are more likely to cause mucositis than others. These include: methotrexate, cytarabine, cyclophosphamide, duanorubicin, doxorubicin and 5-fluorouracil (Carl, 1993). Another factor that needs to be taken into consideration is that individual drug tolerance (drug toxicity) varies between patients. Therefore, individual patients are not likely to react in the same way to each identical course of therapy. This reduction in mucositis may also support the findings by Borowski and coworkers (1994) which showed that oral mucositis may be prevented or reduced by improved or intensive oral care. Improved oral care results in a reduction in inflammation and secondary infection which may also be attributed to the associated beneficial effects of chlorhexidine and benzydamine hydrochloride in this study.

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Candidiasis was the second most frequent problem observed. However, the frequency dropped appreciably from 26.7% in the hospital regimen, to 21.7% and 18.3% in protocols A and B, respectively. Great variability exists in the incidence of candidiasis reported in the literature; this is likely to be due to differences in prophylaxis, antifungal therapies and the patient population. Other studies report an incidence of 15% in paediatric patients (Dahllöf et al, 1989) and 31% in an adult population (Wahlin and Matsson, 1988).

The number of patients who developed gingivitis in the hospital regimen group, was significantly

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higher (20%) when compared to protocols A and B. This may be due to the inconsistent way in which patients used the mouthrinses and the number of mouthrinses prescribed. This frequency, however, was reduced by more than 10% with the implementation of protocols A and B. Interestingly, the results in protocols A and B were exactly the same. The beneficial effect of chlorhexidine on gingivitis in immunocompromised patients is well established in the literature (Ferretti et al, 1987; Meurman et al, 1991). The addition of benzydamine hydrochloride in protocol B did not account for any further reduction in gingivitis. The implementation of pre-treatment scaling and prophylaxis, as suggested by De Beule and coworkers (1991), may reduce the incidence of gingivitis even further.

Due to the antiinflammatory and antimicrobial properties of benzydamine hydrochloride, one would expect a reduction in the frequency of ulceration with its use. However, ulceration was observed with greater frequency in protocol B. These results are difficult to compare to other similar studies as mucositis was mostly included in the criteria used for the assessment of ulceration. No specific guidelines exist regarding the assessment of these oral complications in immuncocompromised patients, and researchers have used different assessment guides.

The principal viral pathogen in immunocompromised patients belongs to the herpes simplex group. Reactivation of herpes simplex may occur in 50 to 90% of patients with antibodies to the virus prior to immunosuppressive therapy (Dahllöf et al, 1989; Epstein et al, 1991). Herpes simplex lesions in the immunocompromised patient are atypical in appearance and the papular and vesicular stages are rarely seen (Schubert, 1991). It causes severe oral lesions which are painful and impairs oral nutrition and are sometimes life-threatening in this group of severely immunocompromised patients. Oral and throat lesions may also be less obvious and are therefore

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less routinely cultured in contrast to lesions of the lip and in this way some herpes simplex infections may not be identified. Schubert (1991) recommends viral culturing of all oral lesions in the immunocompromised patient population for an accurate diagnosis of herpes simplex infection. Although culturing every oral lesion is the ideal, this may not be cost-effective in a hospital setting, depending on the laboratory method employed.

In this study, herpes lesions were observed in 11.7% of patients in the hospital regimen group. This frequency reduced to 3.3% in protocol B which is equivalent to that observed by Sonis and Kunz (1988). The reduction in herpes simplex infection in this study is interesting, but unexplained, as acyclovir was given prophylactically to all three groups of patients. Other workers reported a much higher incidence, 14% (Fayle and Curzon, 1991) and 19% (Dahllöf et al, 1989) in paediatric patients. No acyclovir prophylaxis was given to patients in the aforementioned studies. Prophylaxis of herpes simplex infection has become routine in herpes simplex seropositive immunocompromised patients (Epstein et al, 1991). Most infections represent reactivation of the latent virus and the virus may spread by contact with infected lesions or secretions. Epstein and coworkers (1991) cited a study where 7% of a group of immunocompromised patients were found to be acyclovir-resistant. Herpes simplex resistance to acyclovir is now more frequently observed in patients with leukaemia, tissue and organ transplants and HIV disease (Epstein et al, 1991).

Montgomery and coworkers (1986) demonstrated many discrepancies in the criteria used to diagnose HSV infection in both the medical and dental literature. Due to the aforementioned factor and the atypical nature of HSV infection in the immunocompromised patient, one may expect great variability in the prevalence of HSV infection reported in these patients. We

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postulate that the improved oral care might also account for the reduction in herpes lesions perhaps by associated benefit to the oral mucosa rendering it less susceptible to viral infection.

Dysgeusia was experienced in 82% and 4% of the bone marrow transplant and chemotherapy patient groups, respectively. Alterations in specific taste modalities (e.g. sweet, sour, etc) was not investigated. The dysgeusia experienced by patients who received bone marrow transplants, did not return to normal before their discharge from the unit. According to Mattsson and coworkers (1992), normalization of taste thresholds is usually achieved 3 - 6 months following transplantation. Interestingly, a few patients complained of a metallic taste in the mouth following chemotherapy. Significant discomfort was not experienced by patients who complained of dry mouth. Temporary relief was obtained by taking frequent sips of water. Patients were also encouraged to sip citrus-containing beverages and suck citrus-flavoured hard sweets to stimulate salivary flow. A 5% and 2% reduction in dysgeusia and dry mouth, respectively, was found with the institution of protocols A and B when compared to the hospital regimen ($p > 0.05$). The frequent use of amphotericin B and benzocaine lozenges in protocols A and B may account for the reduction in dry mouth experienced. However, the reduction in taste alterations with the changed protocols, remains unexplained.

The findings of this study indicate that immunosuppressive chemotherapy- and radiotherapy-associated oral complications, particularly in the chemotherapy patient group, can be significantly reduced with the use of chlorhexidine and benzydamine mouthrinses in structured oral care protocols. Although beneficial effects of benzydamine hydrochloride on pain associated with mucositis was reported (Epstein and Stevenson-Moore, 1986), the effect of this oral rinse on the oral complications in patients receiving chemo- and radiotherapy reported here has not been

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previously documented.

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CONCLUSION

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Some damage to the oral tissues is inevitable during antineoplastic therapy. Meticulous oral hygiene cannot prevent treatment-induced inhibition of cellular replication. The medical, dental and nursing literature is all in agreement that oral complications can be minimized by appropriate oral care which may limit secondary infection and further mucosal damage; it may also reduce the incidence of systemic infection. Effective care may further alleviate general discomfort and improve communication. It may also promote food intake thus improving nutritional status.

Following the literature review and results of this study, the following conclusions and recommendations are made:

- All patients should receive a thorough oral examination before antineoplastic therapy. Patients with existing oral disease should also be treated or appropriately referred.

- Improved oral care and a structured routine reduces oral complications associated with chemo- and radiotherapy.

- Benzydamine hydrochloride should be used as a prophylactic mouthrinse for immunocompromised patients.

- An oral health care worker should be part of the oncology team to facilitate pre-treatment examination and management. The oral health care worker should also provide care and teach patients the importance of adequate oral hygiene throughout their antineoplastic therapy.

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- Further studies are needed to develop and assess various protocols for the prevention of oral complications in chemo-and radiotherapy patients.

It must be recognized that for oral care to be effective, all members of the team (nurse, physician and oral health care worker) should value the importance of oral health to the quality of life for the patient. They should also be attentive to promoting oral health, identifying problems early, and managing problems successfully.

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APPENDIX

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APPENDIX 1

LABEL

A. IDNR:

B. Age:

C. Gender:

D. Haematological diagnosis

1. Acute Leukaemia ☐
2. Chronic Leukaemia ☐
3. Aplastic Anaemia ☐
4. Multiple Myeloma ☐
5. Non-Hodgkins Lymphoma ☐
6. Other ☐

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E. If other specify

.....

F. Treatment Received

1. Chemotherapy ☐
2. Bone Marrow Transplant ☐
3. Observation ☐

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4. Other ☐

G. If other, specify:

.....

H. Course of Chemotherapy

1. 1st ☐
2. 2nd ☐
3. 3rd ☐
4. 4th ☐
5. 5th ☐
6. 6th ☐

I. Type of chemotherapy

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1. CTRIV ☐
2. CEM ☐
3. H-D Cyclo ☐
4. Other ☐

CTRIV - Etoposide, duanorubicin and cytosine arabinoside

CEM - Cytosine arabinoside, methotrexate and epipodophyllotoxin

H-D Cyclo - High dose cyclophosphamide

Other - High dose cytosine arabinoside and VAAP (vincristine, asparaginase, adriamycin and prednisone)

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J. **If other, specify**:

.....

K. **Oral management protocol**

1. Hospital ☐
2. A ☐
3. B ☐

L. **Pretreatment Oral Examination**

1. Angular cheilitis ☐
2. Ulceration ☐
3. Gingivitis ☐
4. Caries, visible ☐
5. Candidiasis ☐
6. Other ☐
7. None of the above ☐

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M. **Lesion observed during therapy**

1. Herpetic lesions ☐
2. Angular cheilitis ☐
3. Ulceration ☐
4. Mucositis ☐
5. Gingivitis ☐
6. Hairy tongue ☐
7. Candidiasis ☐

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8. Other ☐

9. None of the above ☐

N. If other, specify:

.....

O. Lab tests

1. Mouth swabs taken for Candida? ☐

2. Mouth swabs taken for HSV? ☐

P. Symptoms Experienced

1. Dysgeusia ☐

2. Dry Mouth ☐

3. Dental Pain ☐

4. Burning Mouth ☐

5. Other ☐

6. None of the above ☐

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ARTICLE

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An efficacious oral health care protocol for immunocompromised patients

A twice-weekly oral and perioral examination was provided to 120 patients receiving antineoplastic therapy. Sixty patients were monitored while following the traditional hospital oral care protocol (chlorhexidine, hydrogen peroxide, sodium bicarbonate, thymol glycol, benzocaine mouthrinse, and nystatin). The mouth care protocol was then changed (experimental protocol = chlorhexidine, benzocaine lozenges, amphotericin B lozenges), and patients were monitored until the sample size matched that of the hospital mouth care regime. There was a statistically significant reduction in oral complications upon introduction and maintenance of the experimental protocol.

Patients with hematological disorders undergoing cytotoxic, chemotherapeutic and/or radiation therapy show an increased predisposition to oral complications. These therapies disrupt the oral mucosal barrier, leading to mucosal ulcerations, hemorrhage, mucositis, viral, bacterial, and fungal infections, and salivary gland dysfunction.[1,2] These oral problems may complicate therapy, prolong hospitalization, and cause extreme discomfort to the patient, reducing the quality of life. Disruption of tissue integrity in the oral cavity may also act as a port of entry for systemic infections.[3] Oral health care measures are of vital importance in preventing such infections.[4-7] The purposes of this study were to (1) evaluate oral complications related to antineoplastic therapy, (2) assess problems related to oral care, and (3) formulate an effective mouth management protocol for these patients.

Hypothesis

The hypothesis of this study was that patients with hematological malignancies using the experimental oral care protocol would have a lower incidence of treatment-related oral complications than would patients with hematological malignancies using the hospital oral care regime.

Methods

Study population

Between September, 1992, and October, 1994, 120 patients with hematological malignancies were treated as inpatients in the Haematology Protected Unit at Groote Schuur Hospital, Cape Town, South Africa. Their treatment included chemotherapy or bone marrow transplantation. Bone marrow transplant recipients received a combination of chemo- and radiotherapy. All patients received prophylactic acyclovir 200 mg 5 times daily or 5 mg/kg every 8 hours intravenously. Oral acyclovir therapy was continued for 90 days. From the first day of admittance, patients were kept in an isolation room until their discharge. Visitors wore gowns and boots. Patients of all ages and both sexes were monitored. Patients who had succumbed to the disease and not completed their antineoplastic therapy were excluded.

Data collection

An examination form was devised to summarize and record data for each patient. All eligible patients were interviewed and given an oral and perioral examination before receiving antineoplastic treatment. Visual examination was done by means of a dental mirror and probe using the hospital auditory torch provided by the ear, nose, and throat specialists. The patients' oral status was assessed twice weekly by a single skilled examiner (dentist) during therapy until their discharge. All complaints were documented, and oral lesions

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noted. Diagnoses for oral candidiasis and herpes simplex infection were confirmed by cultures obtained from mouth and throat swabs. Oral microbial cultures were done only when an oral infection was suspected.

Criteria for assessment

Herpes simplex (HSV) infection: Reactivation of HSV was considered when typical HSV mucosal or lip lesions were observed or when HSV was demonstrated in swabs taken from blister walls.

Candida infection: Colonization alone with *Candida albicans* was not considered as infection. Clinical signs including those for erythematous candidiasis had to be present, such as bleeding and the formation of distinct microbiologically proven colonies on mucous membranes.

Oral ulceration: All types of mucosal ulcers that were not considered as being caused by HSV infection were included in this group. These ulcers were likely caused by trauma, cytotoxic therapy, or infection.

Mucositis: Diagnosed by the presence of mucosal erythema, ulcerations, and/or pseudomembranes associated with pain following chemo- or radiotherapy.

Gingivitis: Only a clinical diagnosis based on the appearance of the gingiva, *e.g.*, erythema, edema and/or bleeding, was made for gingivitis, since probing caused extreme discomfort.

Angular cheilitis: Defined as inflammation or ulceration of the commissures of the lips.

Oral care

Sixty patients were monitored while following the traditional hospital mouth management protocol (Table 1, n = 60). Medications were used at two hourly intervals without any specific sequence. The mouth care regime in the unit was then changed to the experimental protocol, and patients were monitored until the sample size matched that of the traditional oral regime. The experimental regime (Table 1, n = 60) included a structured routine so that maximum benefits could be obtained from all medications. Oral hygiene instructions were given to both groups of patients. Brushing was encouraged in both groups but was discontinued in the presence of mucositis. A Water Pik® was used to remove sloughing in patients with mucositis. In addition, benzocaine mouthrinse and lozenges were prescribed for mucositis occurring in both groups of patients. All patients were followed from the first day of the conditioning regimen until their discharge from the unit. Since treatment regimes varied in the unit, the patients' duration of admission varied. Some patients had several short stays, while others remained inpatients. The latter were in hospital for at least two months. Therefore, precise mean duration of admission could not be determined.

Table 1. Mouth care regimes.

Hospital Oral Care Regime*	Experimental Protocol
Mouthrinses:	Routine
Chlorhexidine	7H30 - Brush teeth
Hydrogen peroxide	8H30 - Amphotericin B loz
Sodium bicarbonate	11H30 - Brush teeth
Thymol glycol	12H30 - Chlorhexidine
Nystatin	16H30 - Amphotericin B loz
	17H00 - Brush teeth
	20H00 - Chlorhexidine

*Benzocaine mouthrinse (hospital regime) and benzocaine lozenges (experimental protocol) were included in above regimes when mucositis is present.
Instructions
Hospital Oral Care Regime: Rinse mouth on a two-hourly basis, rotating the above rinses.
Experimental Protocol: 0.2% Chlorhexidine - Rinse with 10 mL for 30 seconds.

Statistical analysis

All data were captured on a database in the DBASE IV data-capturing pro-

Table 2. Patient characteristics.

Patients in Study	Hospital Regime	Experimental Protocol
Total evaluated patients	60	60
Age		
Mean	31.72	30.47
Range	12-68	4-67
Gender		
Male	41 (68.3%)	35 (58.3%)
Female	19 (31.7%)	25 (41.7%)
Diagnosis		
Acute leukemia	44 (71.0%)	38 (66.7%)
Chronic leukemia	8 (12.9%)	3 (5.3%)
Aplastic leukemia	2 (3.2%)	4 (7.0%)
Multiple myeloma	2 (3.2%)	1 (1.8%)
Non-Hodgkins lymphoma	4 (6.5%)	7 (10.5%)
Other*	1 (1.6%)	5 (8.8%)

*Includes myeloproliferative syndrome, Fanconi's anemia, and promyelocytic leukemia.

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Table 3. Treatment modalities in each group by percentage.

	Hospital Regime (n = 60)	Experimental Protocol (n = 60)
Treatment		
Chemotherapy	41 (68.3%)	37 (61.7%)
Bone Marrow Transplant	13 (21.7%)	15 (25.0%)
Observation	5 (8.3%)	3 (5.0%)
Other[a]	1 (1.7%)	5 (8.3%)
Chemotherapy Type		
Etoposide, daunorubicin and cytosine arabinoside	25 (56.8%)	23 (62.2%)
Cytosine arabinoside, methotrexate, and epipodophyllotoxin	7 (15.9%)	7 (18.9%)
High-dose cyclophosphamide	6 (13.6%)	4 (10.8%)
Other[b]	6 (13.6%)	3 (8.1%)

[a]Includes: ALG (Antilymphocytic Globulin) and Retinoic Acid.
[b]Includes: VAAP (vincristine, asparaginase, adriamycin, and prednisone) and high-dose cytosine arabinoside.

gram. The statistical analysis of the data was carried out on the Epi Info 5 statistical package. P-values of less than 0.05 were regarded as statistically significant.

Results

The sample consisted of 120 patients with hematologic disorders. Table 2 presents the demographic characteristics in the two groups. The patients' ages ranged from 4 to 68 years. A majority of patients suffered from acute leukaemia (71.0% of patients using the hospital mouth care regime and 66.7% using the experimental protocol). Patients entering the unit either received chemotherapy or a bone marrow transplant or came in for observation (Table 3). Various chemotherapy modalities were used. The majority of chemotherapy patients received a combination of etoposide, daunorubicin, and cytosine arabinoside. A Chi-square (χ^2) test of independence was done to determine whether there were any differences in the distribution of subjects by treatment modalities between the two protocol groups. No significant difference between the two protocol groups with respect to the type of medical treatment received was found ($\chi^2 = 3.596$; $p > 0.05$), nor was any difference with respect to specific chemotherapy courses ($\chi^2 = 2.409$; $p > 0.05$).

All patients received a baseline examination before their antineoplastic therapy. Oral lesions encountered at baseline examination included herpetic lesions, angular cheilitis, and ulceration (Table 4). No significant difference between the two patient groups was found with respect to the oral complications encountered at baseline examination ($\chi^2 = 1.224$; $p > 0.05$).

Table 4. Frequency of oral complications at baseline examination.

	Hospital Regime n = 60	Experimental Protocol n = 60
Angular Cheilitis	1	0
Ulceration	2	0
Gingivitis	1	5
Candidiasis	1	0
Caries	3	4

The frequencies of oral complications in use of the two treatment protocols are compared in Table 5. All oral complications during therapy were noted as single observations. Although not statistically significant, only 65% of patients developed oral lesions while using the experimental protocol, a 10% reduction when compared with those using the hospital oral care regime. With regard to individual oral conditions, only the differences in gingivitis between the two oral care management schemes approached significance.

Tables 6a and b illustrate the frequencies of oral lesions during the different treatment modalities with the two protocols. The overall reduced frequency of all oral conditions combined in the chemotherapy patient group with the use of the experimental protocol achieved significance ($\chi^2 = 4.327$; $p = 0.037$). As was expected, mucositis was significantly high in the bone marrow transplant patient group, since mucositis is an inevitable side-effect of radiotherapy. Gingivitis was also shown to be significantly high in the chemotherapy patient group using the hospital oral care regime.

Following mucositis, oropharyngeal candidiasis was the most frequent oral problem observed. As mentioned elsewhere, fungal cultures were done only when an oral infection was suspected. Sixty-four percent of swabs taken from suspected lesions were shown to be positive with the hospital mouth care regime, while only 54% of swabs from patients receiving the experimental protocol showed a positive candidal infection. This reduction was not statistically significant ($p = 0.317$). Seventy-three percent of all bone marrow transplant patients (receiving chemo- and radiotherapy) developed mucositis.

Discussion

For oral complications during and after radio- and chemotherapy to be

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minimized or prevented, patients should be carefully examined and assessed before treatment. Early and aggressive dental interventions are essential to reduce the frequency of oral problems associated with antineoplastic therapy. The prevalence of visible caries and other soft tissue pathology at the baseline examination reflects a need for early dental intervention. Dental treatment prior to the institution of immunosuppressive therapy is often impractical, because many patients are referred to the dentist with active neoplastic disease and need immediate medical treatment. This explains the high number of patients admitted to the experimental protocol group with gingivitis and caries.

With the traditional mouth care regime, patients rinsed with a single mouthrinse every two hours without any specific sequence. Brushing was encouraged but was not included in the two-hour mouthcare regime. Compliance was poor, probably due to the absence of a structured routine in the hospital mouth care regime, where patients chose their own medication of preference (*e.g.*, according to taste), several of which were available. We instituted a structured routine to obtain maximum benefits of all medications and mechanical cleansing. This was implemented to prevent a reduced efficacy of chlorhexidine as a result of combining it with other oral medications.[8,9] The changed regime was generally well-accepted by patients, and compliance was noticeably better.

In South Africa, 0.2% chlorhexidine gluconate (Corsodyl®, manufactured by SmithKline Beecham) is widely available and was therefore used in this study. Other workers have used a 0.12% solution.[10,11] The latter authors have shown chlorhexidine gluconate to be effective in removing plaque in the immunocompromised patient. This results from its capacity to remain active in the mouth for at least 4 hours, providing antibacterial action.[12] Dramatic reductions in both the incidence and severity of mucositis and oral Candida infections are also reported when chlorhexidine was used by patients receiving chemotherapy and bone marrow transplantation.[10]

Interestingly enough, this was not seen in other studies.[13,14] In addition, chlorhexidine gel reduces the caries risk of patients treated with radiation.[15] Since patients were required to use several other oral medications, we prescribed a chlorhexidine rinse only twice daily. More frequent rinsing may have increased the risk of potential interaction and inactivation of chlorhexidine and nystatin.[9]

The reduction in herpes simplex infection is interesting but unexplained, since acyclovir was given prophylactically to both groups of patients. We postulate that the improved oral care might also account for the reduction in herpes lesions, perhaps by associated benefit to the oral mucosa, rendering it less susceptible to viral infection.

Herpetic lesions in immunocompromised patients are atypical in appearance and location.[16] The "normal transition" of these lesions from red papules to vesicles to ulcer is rarely seen. The progress of herpetic lesions in immunocompromised patients is described as an accelerated, maturational process, since lesions frequently first appear as ulcerations.[16] Lesions also tend to be more extensive and aggressive, slow- or non-healing, and extremely painful. Extraoral herpes simplex infections often become secondarily infected, and appropriate antibiotics can prevent this.

Fungal infections in the immunocompromised patient mostly involve *Candida albicans* and, once established, can spread to other organ systems *via* deglutition, droplet aspiration, or the hematological route. Early administration of oral antifungal prophylaxis and aggressive treatment of confirmed fungal infection are essential.[17] The clinical management of oral candidiasis consists principally of administering topical antifungal therapy, including nystatin, clotrimazole, and amphotericin B.[18] Prolonged contact between the medication and the infected surface increases the effect. Therefore,

Table 5. Frequency of oral lesions observed during therapy.

	Hospital Regime n = 60	Experimental Protocol n = 60	*p*-value
Pts with lesions	45 (75%)	39 (65.0%)	0.233
Herpetic lesions	7 (11.7%)	5 (8.3%)	0.544
Angular cheilitis	2 (3.3%)	2 (3.3%)	1.000
Ulceration	8 (13.3%)	4 (6.7%)	0.255
Mucositis	22 (36.7%)	20 (33.3%)	0.703
Gingivitis	12 (20.0%)	5 (8.3%)	0.068
Hairy tongue	1 (1.7%)	1 (1.7%)	1.000
Candidiasis	16 (26.7%)	13 (21.7%)	0.524

Table 6(a). Frequencies of patients with oral lesions during different treatment modalities.

	Hospital Oral Care Regime (n = 60)	Experimental Protocol (n = 60)	Total (*p*-value)
Chemotherapy	30	18	63 ($p = 0.037$)*
Bone Marrow Transplant	13	15	42 ($p = 1.000$)
Observation	2	3	6 ($p = 0.112$)

*p-value < 0.05 is statistically significant.

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Table 6(b). Frequencies of oral lesions observed during various treatment therapies.

	Hospital Mouth Care Regime (n = 60)					Protocol A (n = 60)					
	Chemo[a]	BMT[b]	Obs[c]	Total (%)	*p*-value	Chemo[a]	BMT[b]	Obs[c]	Other	Total (%)	*p*-valu
HSV**	5	1	1	11.7	0.921	3	0	1	1	8.3	0.58
AC**	2	0	0	3.3	0.339	0	1	1	0	3.3	0.07
Ulceration	6	1	1	13.3	0.729	2	0	1	1	6.7	0.32
Mucositis	9	13	0	36.7	0.007*	5	14	1	0	33.3	0.00
Gingivitis	11	1	0	20.0	0.049*	4	0	0	1	8.3	0.61
Hairy tongue	1	0	0	1.7	0.502	1	0	0	0	1.7	0.46
Candidiasis	10	5	1	26.7	0.698	9	3	0	1	21.7	0.56

[a]Chemotherapy.
[b]Bone Marrow Transplant.
[c]Observation.
*P-values less than 0.05 are statistically significant.
**HSV - Herpes simplex; AC - Angular cheilitis.

amphotericin B lozenges or nystatin oral suspension frozen in the form of ice cubes can provide prolonged mucosal contact.

Other recommended antifungals include the azole-derivative antimicrobials such as miconazole, ketoconazole, fluconazole, and itraconazole.[18,19] Miconazole has the advantage of being bacteriostatic in addition to having a fungicidal effect—therefore being appropriate for the treatment of angular cheilitis, where a mixed bacterial/fungal flora may be present.[19] Ketoconazole is reported to have excellent absorptive properties because of its capacity to reach therapeutic blood levels when given orally. Therefore, this drug is used widely in the management of chronic mucocutaneous candidiasis, gastrointestinal candidiasis, and candidiasis in immunocompromised patients.[1,19] Ketoconazole, however, has several side-effects, such as endocrine disturbances, hepatitis, and interaction with cyclosporin, which is important in organ transplant patients.[20]

Fluconazole and itraconazole were shown to be effective in controlling candidiasis in immunocompromised patients.[21] Fluconazole was also shown to eliminate oropharyngeal and esophageal candidiasis effectively in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex.[20,21]

The percentage of bone marrow transplant patients (receiving chemo- and radiotherapy) developing mucositis in our study corresponds to that found in the literature.[22] Management is largely symptomatic because, to date, no specific agent has been shown to be effective.[23] Studies conducted to determine the efficacy of chlorhexidine show a reduction in the number of bacterial and fungal pathogens, but they do not demonstrate a reduction in the incidence of ulcerations and mucositis.[13] Therefore, chlorhexidine should be used only as an antiplaque and antigingivitis agent to augment oral hygiene in bone marrow transplant patients.[13] In a double-blind randomized study, fewer and less painful mucositis lesions were found with the prophylactic use of chlorhexidine in bone marrow transplant patients.[24] Most commercial mouthwashes are potentially harmful and should be avoided by individuals with stomatitis or at high risk of developing stomatitis.[25,26] The main arguments against these mouthwashes are related to the irritant stomatitis allegedly caused by thymol, glycol, and methylsalicylates, as well as by alcohol. We therefore excluded thymol glycol tablets, and alcohol-free benzocaine lozenges replaced the alcohol-containing benzocaine mouthrinse. Intensive oral care (including restorative dentistry and tooth and gum brushing three times daily after meals during aplasia) was shown to be effective in decreasing the occurrence of oral mucositis in patients treated with high-dose chemotherapy.[27]

Hydrogen peroxide was eliminated from the experimental protocol because it irritates the mucosa in the presence of stomatitis and because it causes an overgrowth of the papillae of the tongue.[28]

Sodium bicarbonate was also eliminated from the experimental protocol because it causes a burning sensation, has an unpleasant taste, and damages the oral mucosa.[29]

Our findings show a statistically significant reduction in the frequency of oral problems associated with chemotherapy with the use of the experimental protocol, thus supporting our hypothesis.

While every attempt was made to standardize our sample, limitations of our study included the varying nature of the patients' condition

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(both systemic and oral) and the variability of the treatment regimes. While some success was achieved by changing from the hospital oral care regime to the experimental protocol, future studies are planned to modify both the dose and timing of the oral medications (*e.g.*, benzydamine hydrochloride) administered.

Both patients and staff appreciated the reduction in morbidity associated with oral problems. It is important to improve the quality of life of patients receiving chemo- and/or radiotherapy, particularly because this can affect compliance with required treatment. Additionally, the risk of the oral cavity being a portal of entry for systemic infection is reduced.[3]

This study was supported by the South African Medical Research Council. We thank Professor Peter Jacobs, the staff of wards F4 and E5, and Drs. Mike Du Toit and Errol Holland for their support and assistance throughout the duration of this study.

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Professor Dent et al. *reply:* We are in broad agreement with the points made by Dr Kessel. Yes, the numbers in the trial we reported were small, and certainly lacked the statistical power we would have liked. We felt, however, that it was important to update this trial as it was one of only three (the others were NSABP (B04) and the Cancer Research Campaign (King's/Cambridge) trials) to compare mastectomy with axillary clearance to mastectomy without it, without the confounding factors of any additional therapy. We would not dream of making sweeping generalisations from our trial alone.

None of these trials, or a meta-analysis of all related trials, showed any survival advantage to axillary dissection.[1] Should axillary dissection be undertaken for 'accurate staging' to determine adjuvant therapy, if not improve survival? Well, most patients receive adjuvant therapy anyway, even those who are node-negative.[2,3] The subsets of patients with *in situ* or T1a carcinomas rarely have axillary involvement, so do not need clearance.[4] The only argument that we can see is for local control, and here harms, benefits and costs must be compared. Most agree that prophylactic axillary irradiation and surgery are equivalent. A pragmatic approach would be with conservation surgery either to dissect or irradiate, and with mastectomy not to dissect with DCIS, T1a and in the elderly; outside of these, sample, dissect, watch or irradiate. The results are the same, but the harms, benefits and costs might vary for the individual patient.

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Benzydamine hydrochloride (Andolex) improves oral mucosal health in the immunocompromised patient

To the Editor: Patients with haematological disorders undergoing chemo- and/or radiotherapy show an increased predisposition to systemic and oral complications. These oral problems may complicate therapy, prolong hospitalisation and cause extreme discomfort to the patient, reducing the quality of life. The oral cavity may also act as a port of entry for systemic infections.[1]

The aims of this study were to: (*i*) evaluate oral complications related to antineoplastic therapy; and (*ii*) formulate an effective mouth management protocol for these patients.

Between September 1992 and August 1995, all patients with haematological malignancies who were treated as inpatients in the Haematology Protected Unit at Groote Schuur Hospital, Cape Town, were monitored. Their treatment included chemotherapy or bone marrow transplantation. An examination form was devised to record and summarise data for each patient. All eligible patients were interviewed and given an oral and peri-oral examination before receiving antineoplastic treatment. The patients' oral status was assessed twice weekly by a single skilled examiner (dentist) during therapy until their discharge. Diagnoses of oral candidiasis and herpes simplex infection were confirmed by culture.

Sixty patients were monitored while following the traditional hospital mouth management regimen. The medications included nystatin, chlorhexidine, thymol glycol, hydrogen peroxide and sodium bicarbonate. The hospital regimen was then changed to protocol A (consisting of chlorhexidine and amphotericin B lozenges only) and patients were monitored until the sample size matched that of the traditional oral regimen ($N = 60$).

A further 60 patients were monitored after benzydamine hydrochloride (Andolex; 3M) was added to protocol A (now designated protocol B). Benzydamine hydrochloride is reported to be of benefit in the prevention and management of pain in oral mucositis associated with radiation therapy.[2] It is a non-steroidal drug that reportedly possesses analgesic, anaesthetic, anti-inflammatory and antimicrobial properties.

The majority of the 180 patients monitored suffered from acute leukaemia (72.2%). Other diagnoses include chronic leukaemia, aplastic anaemia, multiple myeloma and non-Hodgkin's lymphoma. Of the patients entering the unit 63.0% received chemotherapy followed by bone marrow transplantation (25.0%). Other therapies included retinoic acid and antilymphocytic globulin (7%). No significant differences between the three groups were found in respect of type of medical treatment ($P > 0.05$).

Oral lesions encountered at baseline examination included herpetic lesions, angular cheilitis and ulceration. No significant differences between the patient groups were found in respect of the oral complications encountered at baseline examination.

We found a statistically significant reduction in all the oral lesions combined with the use of protocols A and B (Table I, $P = 0.007$). Only 65.0% of patients developed oral lesions with the use of protocol A, a 10.0% reduction when compared with the hospital oral care regimen. With the use of protocol B, only 48.3% of patients had some form of oral complication, a 26.7% reduction when compared with the hospital regimen.

Our findings show a statistically significant reduction in the frequency of oral problems associated with antineoplastic therapy with the use of protocols A and B. This improvement may be due to a structured routine and improved oral care. We recommend benzydamine hydrochloride as a prophylactic mouth-rinse for immunocompromised patients.

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Table I. Frequency of oral lesions observed during therapy

	Hospital regimen (*N* = 60)	Protocol A (*N* = 60)	Protocol B (*N* = 60)	*P*-value
Patients with lesions	45 (75%)	39 (65.0%)	29 (48.3%)	0.007*
HSV lesions	7 (11.7%)	5 (8.3%)	2 (3.3%)	0.089
Angular cheilitis	2 (3.3%)	2 (3.3%)	1 (1.7%)	0.576
Ulceration	8 (13.3%)	4 (6.7%)	5 (8.3%)	0.350
Mucositis	22 (36.7%)	20 (33.3%)	19 (31.7%)	0.563
Gingivitis	12 (20.0%)	5 (8.3%)	5 (8.3%)	0.051
Hairy tongue	1 (1.7%)	1 (1.7%)	1 (1.7%)	1.000
Candidiasis	16 (26.7%)	13 (21.7%)	11 (18.3%)	0.273

* $P < 0.05$ is statistically significant.
HSV = herpes simplex virus.

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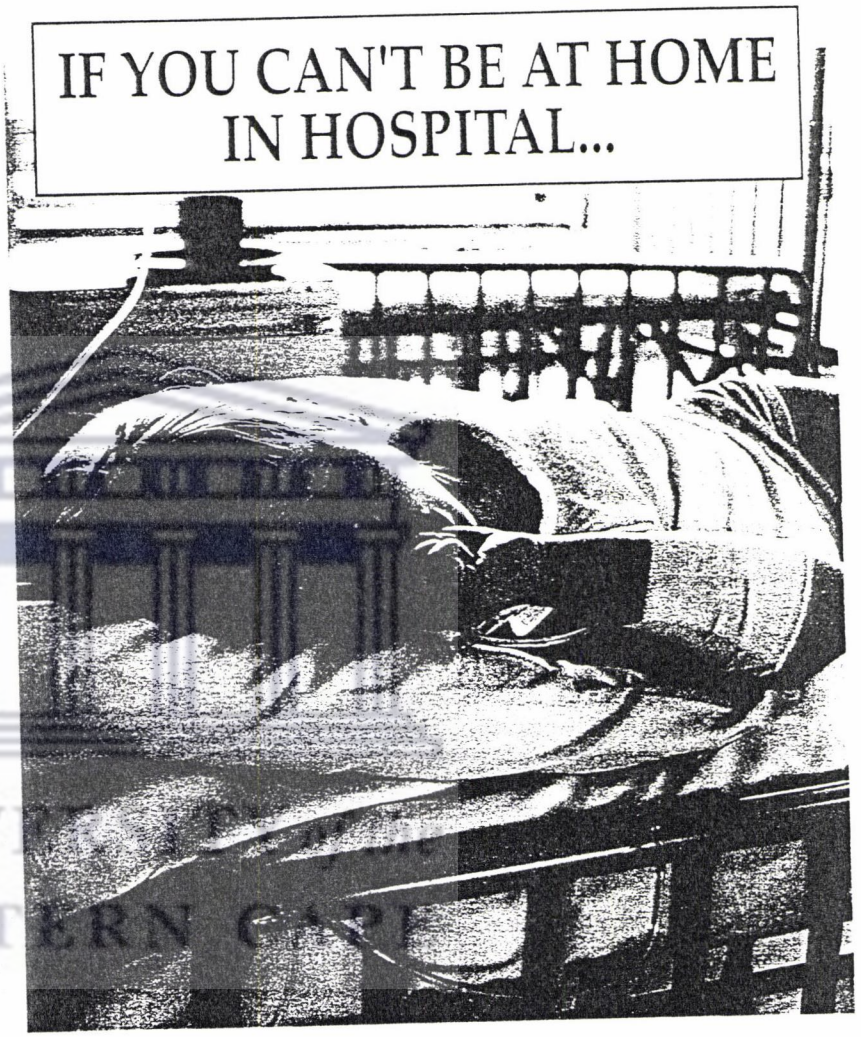
Race-specific education — a proven failure?

To the Editor: I am old enough to have marched in the streets of Cape Town in the 1960s over the issue of academic freedom. I am old enough to remember socialist realism as practised in the Soviet Union. I am also young enough currently to be studying psychiatry at a 'white' university. It is those 'qualifications' that make me reply to M. Nethononda's editorial.[1]

There is only one international scientific truth. This is specific to our stage of industrial development in the world but not to any country or political group. You cannot teach medicine to cure the ills of the rural poor or uplift black people. These are social problems for governments to solve. Of course, if the government cannot afford universities and medical schools it can close them and use the money for the poor.

It is a dereliction of duty for the government to expect university outreach programmes to provide health care. Such programmes can only be used by the university to acquaint their students with health problems in those areas, and must be part of a general teaching curriculum aimed at teaching medical science. Poor students in all countries are disadvantaged in education. Again, it is the business of



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