ORAL HEALTH STATUS IN CHILDREN UNDERGOING TREATMENT FOR NEUTROPENIA

by

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A thesis submitted in conformity with the requirement for the Degree of Masters of Science
Graduate Department of Dentistry
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ABSTRACT

Thesis Title: Oral Health Status in Children Undergoing Treatment for Neutropenia

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Historically, case reports and studies that have reported oral manifestations of neutropenia have documented pain, advanced periodontal disease, premature loss of teeth, ulcerations and/or poor oral hygiene upon initial presentation. The purpose of this cross-sectional study was to assess the oral health of children with neutropenia under the active care of the haematology department at The Hospital for Sick Children and compare the results to that of a healthy control group. Children between the ages of 6 to 18 with neutropenia attending the Marrow Failure and Myelodysplasia Program at The Hospital for Sick Children and healthy control patients that attended the Children’s Clinic, Faculty of Dentistry, University of Toronto were asked to participate in the study. The study consisted of a patient questionnaire, and a dental and radiographic examination. Student’s t-test, Chi-squared test, Fisher’s Exact tests, odds ratios and 95% confidence intervals were calculated to assess for any significant differences. Fifteen patients with neutropenia and 26 healthy controls participated in this study. Patients with neutropenia reported an increased incidence of mouth sores and bleeding gums while brushing. After the dental examination, there were no statistical differences in the presence of ulcerations, gingival recession, tooth mobility, gingival inflammation or plaque and calculus levels. The dmft/t and DMFT/T scores were lower for the group with neutropenia, but only the dmft/t score was significant. This data suggests that patients with neutropenia that are being treated by a haematologist do not experience any more severe oral problems than healthy dental patients.
Acknowledgements

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PREFACE

Thesis Format

This M.Sc. thesis is presented in a ‘publishable style’. Chapter 3 is a manuscript submitted to the peer-reviewed journal, *Pediatric Dentistry*, describing the current project’s findings.

The appendices section contains the assent forms, consent forms, patient questionnaires and dentist questionnaires used to gather information from neutropenic patients from the Hospital for Sick Children and healthy patients from the Faculty of Dentistry, University of Toronto.

Project Presentations

Oral presentation. 3M-ESPE Graduate Student Presentations, Canadian Academy of Paediatric Dentistry, September 2009

Oral presentation. Graduate Student Presentations, Ontario Society of Paediatric Dentists, November 2009

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Poster presentation. Dentsply Research Poster Competition, American Academy of Pediatric Dentistry, May 2010
CHAPTER 1

LITERATURE REVIEW
I. Function of the Immune System

The immune system has been designed to play an integral role in wound healing as well as preventing and eliminating infections. The immune system has two major components: the innate immune system and the adaptive immune system. The innate system, present at birth, recognizes pathogens and tissue damage and mounts an immediate response, but does not impart any long lasting recognition/immunity to the host (Silverthorn 2007). The granulocytic cells involved in the innate immune system are the neutrophils, eosinophils, basophils, mast cells and the monocyte/macrophages. The adaptive immune system is activated by the innate immune system to stimulate either T-lymphocytes to kill the target cell directly (cell-mediated immunity) or stimulate B-lymphocytes to produce antibodies (humoral immunity) to attack the target cell (Silverthorn 2007). When first encountering a pathogen the adaptive immune system takes days to mount a response, but is able to identify each pathogen that has invaded the host and mount a faster response to kill the pathogen upon repeated exposures (Silverthorn 2007). Below is the list of the major cells involved in the human immune system.

1.1 Neutrophils

The neutrophil (polymorphonuclear leukocyte) is the most abundant white blood cell in humans, accounting for 50 – 70% of the total white blood cells (Yang and Hill 1993, Skubitz 2004, Silverthorn 2007). Neutrophils are the first line of defense and function to phagocytose pathogens killing them (Silverthorn 2007). Neutrophils are located in three compartments: the bone marrow, tissues and vascular compartment that consist of the circulating/large blood vessel pool and marginating/small blood vessel pool (Yang and Hill 1993, Skubitz 2004). The bone marrow contains 20 times the circulating concentration of
neutrophils and releases approximately $10^{11}$ neutrophils daily (Bainton 1971, Segal and Holland 2000). 70% of the neutrophils in the marginating pool are located in the liver, lungs and spleen (Peters et al. 1985). Neutrophil development occurs over approximately 2 weeks mainly in the bone marrow with the development of the mitotic pool consisting of myeloblasts, promyelocytes and myelocytes and the maturation pool consisting of meta-myelocytes, band neutrophils and segmented neutrophils (Yang and Hill 1993, Skubitz 2004). Once released from the bone marrow, the half-life for a neutrophil is 6 – 9 hours in the vascular compartment and 1 – 4 days in the tissues (Dancey et al. 1976).

1.2 Eosinophils

Eosinophils account for 1 – 3% of the total white blood cells and are involved in allergic reactions and the fight against parasitic infections (Yang and Hill 1993, Skubitz 2004, Silverthorn 2007). Eosinophil maturation takes between 3 – 6 days (Yang and Hill 1993). The half life of eosinophils is 8 – 12 hours in the vasculature, but they can survive in the tissues for 7 – 10 days (Yang and Hill 1993, Silverthorn 2007). The nucleus contains 2 lobes and the cytoplasm is filled with bright red staining granules (Ackerman and Bellios 1955). The granules contain eosinophil peroxidise, eosinophil cationic protein, eosinophil major basic protein and a eosinophil-derived neurotoxin (Ackerman et al. 1983).

1.3 Basophils

Basophils are rarely found in the bloodstream and little is known about their development except that these cells are fully mature before leaving the bone marrow (Yang and Hill 1993, Skubitz 2004, Silverthorn 2007). Basophils are involved in allergic reactions, IgG-mediated anaphylaxis, immune regulation and increasing humoral immunity responses
Basophils are identified by a high affinity Fc receptor for IgE and large, coarse, purplish-black basophilic granules that obscure the nucleus (Silverthorn 2007). These granules contain peroxidise, heparin, histamine, kallikrein and platelet-activating factor (Hastie et al. 1977).

1.4 Monocytes-macrophages

Monocytes-macrophages account for 1 – 6% of all white blood cells and function as phagocytes and antigen-presenting cells (Silverthorn 2007). Monoblasts are formed in the bone marrow and progress to the promonocytes and finally into monocytes over a period of 6 days (Johnson Jr 1988, Yang and Hill 1993). Once released into the bloodstream, monocytes have a half-life of 1 – 3 days (Johnson Jr 1988). Upon entering the tissues, monocytes are transformed into tissue macrophages and can survive for months to years (Johnson Jr 1988).

1.5 Lymphocytes, Plasma Cells and Natural Killer Cells

B-lymphocytes, T-lymphocytes and natural killer cells that which constitute 20 –35% of the total white blood cells (Silverthorn 2007). B-lymphocytes mature in the bone marrow and transform into plasma cells producing antibodies that attack pathogens (Silverthorn 2007). T-lymphocytes develop in the thymus gland to directly kill virus-infected cells (cytotoxic T-lymphocytes) and also serve to regulate other immune cells (helper T-lymphocytes) (Silverthorn 2007). These natural killer cells, whose function is to attack virus-infected cells and tumour cells develop in secondary lymphoid tissues (Caligiuri 2008).
II. Neutrophil Development

A pluripotent stem cell is capable of self-replication while giving rise to the development of all blood cells in the human body (Baehner and Miller 1995). The pluripotent stem cell will differentiate to the colony-forming unit mixed myeloid, erythroid and monocytic-macrophage (CFU-GEMM) followed next by the colony-forming unit granulocyte monocyte (CFU-GM) (Baehner and Miller 1995). Differentiation to the various cell types is done through exposure to stem cell factors and colony stimulating factors (CSF) (Lisiewicz and Bick 1993, Segal and Holland 2000). Interleukin-3 (IL-3)/(multi-CSF) stimulates the early hematopoietic cells of the erythroid, neutrophil, eosinophil, macrophage, mast cell and megakaryocyte (Bot et al. 1988). Granulocyte macrophage colony-stimulating factor (GM-CSF) stimulates the growth and differentiation of the neutrophils, eosinophils and macrophage precursor cells (Lisiewicz and Bick 1993). GM-CSF also enhances oxidative metabolism, increases superoxide formation, increases the release of lysozyme and increases the chemotactic factors on the cell surface of neutrophils (Burgess et al. 1987, Sullivan et al. 1987, Weisbart et al. 1987). Granulocyte colony-stimulating factor (G-CSF) stimulates neutrophil production, decreases spontaneous neutrophil apoptosis and activates mature neutrophil function by enhancing superoxide release and increasing the surface chemotactic receptors (Metcalf and Nicola 1983, Yuo et al. 1989, Lisiewicz and Bick 1993).

Neutrophil development occurs in the bone marrow and maturation takes approximately 2 weeks (Skubitz 2004). The first week is spent in the proliferative phase in which myeloblasts, promyelocytes and myelocytes are capable of cell division, confirmed through their uptake of titrated thymidine ($^3$H-TdR) in the bone marrow (Bond et al. 1959, Skubitz 2004). The second week is spent in maturation/further differentiation phase where meta-myelocytes, band
neutrophils and mature segmented neutrophils are incapable of cell division (Baehner and Miller 1995, Skubitz 2004).

2.1 Myeloblast
The myeloblast is the earliest recognizable myeloid precursors identified by its large nucleus relative to the volume of cytoplasm, 2 – 5 nucleoli and absence of granules in the cytoplasm (Lisiewicz and Bick 1993, Skubitz 2004). The myeloblast is capable of cell division and less than 5% of myeloid cells are myeloblasts (Lisiewicz and Bick 1993, Baehner and Miller 1995, Skubitz 2004).

2.2 Promyelocyte
The promyelocyte is larger than the myeloblast, has a round or oval nucleus, the nuclear chromatin is diffusely distributed and nucleoli are present but become less prominent as the cell develops (Skubitz 2004). Primary/azurophilic granules (see below) first appear at this stage, formed from the lateral terminations of the lamellae on the inner aspect of the Golgi apparatus (Bainton et al. 1971). Primary granules are only replicated at this stage and are the most concentrated here; their concentration subsequently decreases as these granules are parcelled out into daughter myelocytes (Baehner and Miller 1995, Skubitz 2004).

2.3 Myelocyte
The myelocyte has an eccentric and round or oval nucleus, with small nucleoli that are not visible (Lisiewicz and Bick 1993, Skubitz 2004). Secondary-specific granules (see below) are formed during this stage from the lateral terminations of the outer aspect of the Golgi
apparatus (Bainton et al. 1971). Primary and secondary granules are present with a ratio of 1:3 respectively (Bainton et al. 1971, Baehner and Miller 1995, Skubitz 2004).

2.4 Meta-myelocyte

The meta-myelocyte has a horseshoe-shaped nucleus and a dense nuclear chromatin without any discernable nucleoli (Lisiewicz and Bick 1993, Skubitz 2004). Primary, secondary and tertiary/gelatinase granules are present in the cytoplasm (Skubitz 2004). Beyond this stage, cell division is no longer possible (Lisiewicz and Bick 1993, Skubitz 2004).

2.5 Band Neutrophil

This stage consists of an elongated nucleus with signs of segmentation connected by filamentous strands of heterochromatin and condensation of nuclear chromatin (Lisiewicz and Bick 1993, Stubitz 2004). Band neutrophils have less phagocytic activity in the bone marrow than in the peripheral blood (Altman and Stossel 1974). Bands represent 3% of the differential leukocyte count in healthy subjects (Lisiewicz and Bick 1993).

2.6 Mature Segmented Neutrophil

The nucleus is separated into varying number (1 – 5) of segments connected by thin filaments of chromatin (Lisiewicz and Bick 1993, Skubitz 2004). The mechanism and purpose of the nuclear segmentation are currently unknown (Skubitz 2004). The nucleus of the mature segmented neutrophil stains a deep, purplish color containing coarse, condensed chromatin (Skubitz 2004). The cytoplasm is faint pink and contains fine, specific granules with a ground glass appearance (Skubitz 2004).
III. Neutrophil Granules

Neutrophils contain three types of granules: primary, secondary and tertiary granules. Primary granules are only formed during the promyelocyte stage (Skubitz 2004). The function of primary granules is to mediate O$_2$-independent killing, potentiate O$_2$-dependent killing and modulate tissue inflammation (Yang and Hill 1993). These granules fuse with phagocytic vesicles to release myeloperoxidase, lysozyme, defensins, elastase, cathepsin G, proteinase 3, esterase N, bactericidal permeability-increasing protein, α$_1$-antitrypsin, α-mannosidase, azurocidin, α-fucosidase, cathepsin B, cathepsin D, β-glycerophosphatase, β-glucuronidase, β-galactosidase, β-glucosaminidase, acid mucopolysaccharide heparin binding protein, N-acetyl-β-glucosaminidase, sialidase and ubiquitin protein (Borregaard and Cowland 1997, Skubitz 2004).

Secondary granules formed during the myelocyte stage help to mediate O$_2$-independent killing and regulating inflammatory reactions by releasing their contents into the extracellular space (Yang and Hill 1993, Skubitz 2004). The contents of these granules include apolactoferrin, lysozyme, β$_2$-microglobulin, collagenase, gelatinase, histaminase, heparinise, pro-u PA, vitamin B$_{12}$-binding protein, sialidase, protein kinase C inhibitor, hCAP-18, SGP28 and neutrophil gelatinase-associated lipocalin (Borregaard and Cowland 1997).

Tertiary granules are formed during the meta-myelocyte stage and contain gelatinase, acetyltransferase and lysozyme (Borregaard and Cowland 1997, Skubitz 2004). They play a role in promoting adhesion and regulating respiratory burst and motility (Yang and Hill 1993).
IV. Functional Biology of the Neutrophil

Neutrophils are the first line of defense when a pathogen is present and/or tissue damage occurs.

4.1 Neutrophil Function

The function of neutrophils can be described as:

1. Detection of chemotactic factor
2. Rolling along the vascular endothelium
3. Adherence to the endothelial lining
4. Migration/chemotaxis toward chemotactic factors
5. Phagocytosis
6. Intracellular killing

4.1.1 Detection of Chemotactic Factor

Neutrophils have been known to respond to a variety of chemotactic factors that bind to receptors on the cell surface coupled to guanine nucleotide binding proteins (Gerard and Gerard 1991). Initial recruitment of neutrophils involves the complement fragment, C5a, while interleukin-8 (IL-8) will recruit neutrophils for the next 6 – 48 hours (Skubitz 2004). Other chemotactic factors include histamine, interleukin-1 (IL-1), G-CSF, tumor necrosis factor-α (TNF-α), N-formyl-methionyl-leucyl-phenylalanine (FMLP), leukotriene B₄, platelet activating factor and bacterial products (Skubitz 2004).

4.1.2 Rolling Along the Vascular Endothelium

Initial rolling along the endothelium is accomplished by L-selectins (CD62L, LAM-1, LECAM-1) expressed on the neutrophil cell surface binding to fucosylated structures (e.g. Lewix X and sialyl-Lewix X) on the endothelial surface (Gallatin et al. 1983, Berg

4.1.3 Adherence to the Endothelial Lining

Integrin structures are found on the cell surface of neutrophils composed of heterodimers of α- and β-subunits each with different structural motifs (Carlos and Harlan 1994). There are three different α-subunits (CD11a, CD11b and CD11c) that bind to a common β-subunit (CD18) producing leukocyte factor antigen-1 (LFA-1; CD11a/CD18), macrophage antigen-1 (Mac-1; CD11b/CD18) and leukocyte integrin p-150,95 (CD11c/CD18) (Carlos and Harlan 1994, Kishimoto and Rothlein 1994, Skubitz 2004). These integrin structures are constitutively expressed on the cell surface but exposure to chemotactic factors will cause upregulation of these integrin molecules (Carlos and Harlan 1994). Binding of the neutrophil to the endothelial cell is accomplished through endothelial surface intracellular adhesion molecules 1, 2 and 3 (ICAM-1, ICAM-2 and ICAM-3) (Kishimoto and Rothlein 1994). Once bound, the neutrophil must pass through the endothelium through a process called diapedesis by binding to the endothelial cell platelet-endothelial cell adhesion molecule-1 (PECAM-1) concentrated at endothelial cell junctions (Muller et al. 1993, Vaporciyan et al. 1993).

4.1.4 Migration/Chemotaxis Toward Chemotactic Factors

Chemotaxis, the directional movement of a cell along a concentration gradient, occurs in neutrophils through the formation of pseudopods (Stossel 1993). Neutrophils contain actin microfilaments at the periphery of the cell that form a meshwork connected to the
cell membrane and microtubules that radiate from the centrioles to make the neutrophil a highly motile cell (Hoffstein and Weissmann 1978). Neutrophil movement occurs in a biphasic manner with the first phase being the protrusion of pseudopodia, rich in actin filaments and lacking intracellular organelles towards the chemotactic factors (Stossel 1993). The second phase being the translocation of the nucleus (Stossel 1993). Actin polymerization and depolymerisation along with actin binding protein, myosin and gelsolin are critical to the formation of pseudopods and movement (Yang and Hill 1993, Skubitz 2004).

4.1.5 Phagocytosis

Phagocytosis involves opsonins such as IgM, IgG1, IgG3 and complement fragments C3b and C3bi binding to the invading pathogens, to provide a marker for the neutrophil attachment (Dinauer 1998). Fc receptors (CD1, CD32, CD64 and CD89) and complement receptors (CR1 and CR3) on the neutrophil cell surface recognize the opsonins and form a phagocytic vacuole that encloses the pathogen (Boggs 1975, Dinauer 1998). Pathogens inside the neutrophil are in structures called phagosomes (Skubitz 2004).

4.1.6 Intracellular Killing

Bacterial killing can be divided into two approaches: O2-independent and O2-dependent killing (Skubitz 2004). The O2-independent killing involves fusion of primary, secondary and tertiary granules with the phagosome with subsequent degranulation (Skubitz 2004). Fusion of these granules causes a decrease in pH allowing optimal functioning of enzymes through the granule contents or translocation of H+ ions into the
phagosome (Skubitz 2004). Defensins are small microbicidal peptides that will form voltage-dependent ion channels to kill pathogens (Ganz 1985). Lysozyme hydrolyzes the bacterial cell wall, while lactoferrin binds to iron preventing bacterial growth (Arnold et al. 1977, Skubitz 2004).

O$_2^-$-dependent killing relies upon a respiratory burst through the production of free-radical oxygen products to kill the bacteria, as seen on figure 1 (Yang and Hill 1991). Transmembrane bound gp91-phox and p22phox assembles with cytosolic components p40phox, p47phox and p67phox to form the activated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex which acts as the catalyst to produce superoxide (O$_2^-$) and NADP$^+$ (Cross and Jones 1991, Yang and Hill 1991, Quinn and Gauss 2004). O$_2^-$ is rapidly converted to hydrogen peroxide (H$_2$O$_2$) by superoxide dismutase (Yang and Hill 1991). Myeloperoxidase then converts H$_2$O$_2$ and a chloride ion (Cl$^-$) to form a hypochlorite ion (OCl$^-$) (Yang and Hill 1991). Detoxification of the superoxide radical occurs by glucose-6-phosphate dehydrogenase (G6PD) providing an electron for the reduction of NADP$^+$ to NADPH, catalase acting upon H$_2$O$_2$ producing H$_2$O and O$_2$ and lastly glutathione reductase converting glutathione (GSSG) and H$_2$O$_2$ to a reduced form of glutathione (GSH) and H$_2$O (Yang and Hill 1991).
**Figure 1.** The production of oxygen radicals from the respiratory burst pathway. From Yang KD, Hill HR. *J Pediatr.* 1991; 119: 343-354.
4.2 Neutrophil Extracellular Traps

Neutrophils are also capable of releasing their contents to generate neutrophil extracellular traps (NET) to disarm and kill gram-negative and gram-positive bacteria (Brinkmann et al. 2004). NETs are composed of deoxyribonucleic acid (DNA), proteins from primary, secondary and tertiary granules such as neutrophil elastase, lactoferrin and gelatinase respectively (Brinkmann et al. 2004). NETs provide a physical barrier that prevents the spread of bacteria, while the addition the high concentration of antimicrobial substances in the NETs degrade bacterial virulence factors and kill the bacteria (Brinkmann et al. 2004).

V. Neutrophils in the Oral Cavity

The oral cavity is particularly rich in microorganisms with over 700 bacterial species and bacterial counts in the range of $10^8$ to $10^{11}$ organisms/ml of saliva (Simos et al. 2004, Aas et al. 2005). Neutrophils play an important protective role in preventing the ingress of pathogenic microorganisms. They are found throughout the mouth and saliva entering primarily through the gingival sulcus (Sharry and Krasse 1960, Schiött and Löe 1970). Neutrophils produce NETs to trap bacteria in the gingival sulcus to prevent further ingress into the gingival tissues aiding in the defense against periodontitis (Vitkov et al. 2009, Vitkov et al. 2010). Oral neutrophils counts increase in the presence of poor oral hygiene, gingivitis and inflammation (Schiött and Löe 1970, Woolweaver et al. 1972). Studies evaluating oral neutrophil levels have correlated these values with onset and resolution of neutropenia (see below) and oral pathosis in patients undergoing bone marrow transplantation (BMT) (Wright et al. 1986, Akpek et al. 2003, Cheretakis et al. 2005).
Proper activity/function of the neutrophil is essential to maintaining a healthy oral cavity. Defects in neutrophil function and low neutrophil counts have been associated with periodontal disease (see below).

VI. Classification of Neutropenia

Normal neutrophil values are defined for a given population as the mean ± 2 standard deviations from the mean. An absolute neutrophil count (ANC) of 1,500 cells/mm$^3$, calculated by multiplying the white blood cell count by the percentage of mature segmented neutrophils plus band stage neutrophils noted on the differential cell count is considered the lower limit for normal neutrophil levels; however there is some slight variation depending on the ethnicity of the patient (Watts 2004). Neutropenia is a significant reduction in the absolute number of circulating neutrophils, the severity can be classified as (Dinauer 1998):

- Mild: 1,000 – <1,500 cells/mm$^3$
- Moderate: 500 – <1,000 cells/mm$^3$
- Severe: < 500 cells/mm$^3$

Neutropenia can be caused by immune disorders, congenital non-immune disorders or acquired non-immune disorders due to disturbances in the production, shift in neutrophils from the circulating to marginated (tissue pools) and/or increased peripheral utilization or destruction (Dinauer 1998). Neutropenia patients can present with a wide array of signs & symptoms depending on the cause, severity and duration of neutropenia (Dinauer 1998). A slight fever may be the only sign of an infection in patients with neutropenia as they may not present with tumour (swelling), calor (heat) and pus (Sickles et al. 1975, Watts 2004). Signs of neutropenia that can
be found in the mouth are: stomatitis, gingivitis, periodontitis, opportunistic infections and ulcerations/mouth sores (Watts 2004). Furthermore, skin abscesses, furunculosis, poor wound healing, recurrent infections in the perirectal and genital areas, urinary tract infections, recurrent otitis media and upper respiratory tract infections can also be associated with neutropenia (Watts 2004). Patients with severe neutropenia are at-risk of developing infections which may prove to be life threatening (Dinauer 1998). Endogenous bacterial flora, Staphylococcus aureus from the skin and gram-negative organisms from the gastrointestinal and genitourinary tract are the most common pathogens that produce these infections (Watts 2004).

6.1 Immune

6.1.1 Alloimmune Neonatal Neutropenia

Fetal neutrophils gaining access to the maternal circulatory system stimulate maternal IgG antibodies which then cross the placenta targeting fetal neutrophils, resulting in a condition known as alloimmune neonatal neutropenia (Boxer et al. 1972, Baehner and Miller 1995). The alloimmune antibodies targeting the neutrophil-specific NA antigen system (NA1, NA2, NB1, ND1 and NE1) can last for up to 6 months in the infant, while the neutropenia can last from 2 – 17 weeks after birth (Levine and Madyastha 1986, Dinauer 1998). Infants can present with recurrent fevers, pneumonia, skin abscesses, pyoderma, omphalitis, otitis media, meningitis and septicaemia (Baehner and Miller 1995, Dinauer 1998). Bone marrow samples show myeloid hyperplasia with depletion of mature neutrophils (Dinauer 1998). A diagnosis is made by determining the presence of neutrophil antibodies specific for the infant’s antigenic cell type in the serum in the mother and identifying the reactive antigen expressed by the father’s neutrophils but not by the mothers (Baehner and Miller 1995, Watts 2004).

6.1.2 Primary Autoimmune Neutropenia of Infancy and Childhood/Chronic Benign Neutropenia

Autoimmune neutropenia of infancy and childhood/chronic benign neutropenia follows a relatively benign course. It has an prevalence of approximately 1 in 100,000 children, occurring primarily in children below the age of three with no family history of neutropenia (Lyall et al. 1992, Dinauer 1998). Several antineutrophil antibodies have been developed but have low sensitivity and specificity (Lalezari et al. 1986). There is no known mechanism that triggers the autoantibody production or correlation between the strength of the antibodies and severity of clinical manifestations (Dinauer 1998). The bone marrow in these patients are normal to hypercellular with a reduction in mature neutrophils or bands (Johnson and Buchanan 1991, Neglia et al. 1993). The neutropenia can persist for an average of 20 months, followed by spontaneous remission in most patients (Lalezari et al. 1986).

Most patients present with skin infections, cellulitis, otitis media, gastroenteritis and/or upper respiratory tract infections; however in some situations serious infections resulting in septicaemia, pneumonia and meningitis can occur (Lalezari et al. 1986, Watts 2004). Clinical findings in the oral cavity include ulcerations, hyperplastic edematous gingiva with desquamation, gingival inflammation, recession, periodontitis, furcation radiolucency,

Supportive care is normally indicated with the administration of antibiotics in the presence of infections. In addition, G-CSF, immunoglobulins, anti-Rh(D) immunoglobulin and corticosteroids have been used in severe infections (Bussel et al. 1983, Bussel et al. 1988, Komiyama et al. 1988, Mascarin and Ventura 1993, Dinauer 1998).

6.1.3 Felty’s Syndrome

Felty’s syndrome was first described in 1924 as chronic neutropenia associated with rheumatoid arthritis and splenomegaly (Felty 1924). Patients may present with nodules, ulcers, hyperpigmentation of the lower extremities, vasculitis, neuropathy, pulmonary fibrosis, hepatomegaly and Sjögren’s syndrome (Starkebaum 2002). Laboratory values show high levels of rheumatoid factor, elevated C1q binding (immune complexes), hypergammaglobulinemia and antinuclear antibodies (Starkebaum 2002). It is believed that the neutropenia is a result of antibodies to neutrophil antigens binding to the neutrophils causing functional disturbances, increased adherence to endothelial cells and apoptosis (Hashimoto et al. 1982, Davis et al. 1987).

Management of Felty’s syndrome has been accomplished through the use of lithium carbonate, gold, immunoglobulins, corticosteroid, cyclophosphamide methotrexate, splenectomy, splenic radiation, splenic artery embolization, and G-CSF (Laszlo et al. 1978, Dillon et al. 1986, Canvin et al. 1991, Calverley et al. 1992).
6.1.4 Autoimmune Lymphoproliferative Syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is a genetically heterogenous disorder inherited due to a defect in lymphocyte apoptosis and increased circulating T-lymphocyte receptor (TcR)\(\alpha\beta^+\) CD4+ CD8− or double negative T-lymphocytes (DNTs) (Canale and Smith 1967, Fisher et al. 1995). Autosomal dominant and autosomal recessive forms exist resulting in lymphadenopathy, splenomegaly and autoimmune cytopenia (Canale and Smith 1967, Fisher et al. 1995, Rieux-Laucat et al. 1995). The majority of cases result from a mutation in the tumor necrosis factor receptor superfamily (TNFRSF), located on chromosome 10q24.1, encoding for Fas (CD95 or TNFRSF6), involved with cell apoptosis (Inazawa et al. 1992, Behrmann et al. 1994, Cheng et al. 1995, Fischer et al. 1995. Rieux-Laucat et al. 1995). Other mutations in the intermediates in the Fas signalling pathway have been discovered leading to a classification based upon genetic analysis (Inazawa et al. 1992, Behrmann et al. 1994, Cheng et al. 1995, Fischer et al. 1995, Rieux-Laucat et al. 1995). ALPS Ia is classified as a mutation of the Fas gene, ALPSIb is classified as a mutation in the Fas ligand, APLS II is classified as a mutation in Caspase 8 or 10 and ALPS III is classified when there is no known genetic cause (Wu et al. 1996, Dianzani et al. 1997, Sneller et al. 1997, Wang et al. 1999, Chun et al. 2002).


Management of these patients is accomplished through corticosteroids, immunosuppressants, splenectomy, blood transfusions, G-CSF and BMT (Benkerrou et al.
6.2 Congenital

6.2.1 Cyclic Neutropenia

Cyclic neutropenia (CN), first described in 1910 by Leale, is related to the periodic oscillation of bone marrow production and release of neutrophils; normally between 19 to 21 days (range 14 to 36 days) where neutrophil counts can drop below 200 cells/mm$^3$, followed by a return to normal levels above 1,500 cells/mm$^3$. (Leale 1910, Morley et al 1967, Lange 1983, Baehner and Miller 1995, Dinauer 1998). During periods of normal neutrophil counts, patients are asymptomatic (Baehner and Miller 1995, Dinauer 1998). Reticulocytes, eosinophils, monocytes and platelet numbers will also fluctuate with the neutrophil levels (Morley and Stohlman Jr 1970).

CN is an autosomal dominant disorder with full penetrance but varying expressivity caused by a defect in neutrophil elastase, encoded by the ELA2 gene, located on chromosome 19p13.3 (Horwitz et al. 1999). Neutrophil elastase is a serine protease, synthesized during the differentiation of promyelocytes and packaged in cytoplasmic granules, which are released extracellularly at sites of inflammation (Horwitz et al. 1999). It is believed that the defective neutrophil elastase elicits an unfolded protein response leading to apoptosis through increased transcription of chaperone-encoding endoplasmic reticulum-associated protein degradation and proapoptotic genes (Kollner et al. 2006, Grenda et al. 2007).

Most cases run a benign course with patients presenting before the age of 1 with a decrease in symptoms as they age (Baehner and Miller 1995, Dinauer 1998). Symptoms such as fever, malaise, lymphadenitis, arthritis, skin infections and otitis media are a reflection of


6.2.2 Severe Congenital Neutropenia

The first case of severe congenital neutropenia (SCN) was identified by Kostmann in 1956 in infants younger than 6 months with a ANC less that 200 cells/mm$^3$ from an isolated Swedish community (Kostmann 1956). SCN is a heterogenous disease with autosomal recessive, autosomal dominant, sporadic and X-linked forms presenting as severe neutropenia with maturation arrest of bone marrow progenitor cells at the promyelocyte/myelocyte stage (Berliner 2008, Ward and Dale 2009).

A defect in neutrophil elastase, the $ELA2$ gene on chromosome 19p13, has been found with the autosomal dominant and sporadic forms of SCN (Howard et al. 1999, Ancliff et al. 2000).
2001, Bellanné-Chantelot et al. 2004). There is no association between a particular mutation of the ELA2 gene and expression of either CN or SCN (Dale et al. 2000). Mutations in HCLS-associated protein X-1 (HAX1) on chromosome 1q21.3, a mitochondrial anti-apoptotic protein leading to a loss of mitochondrial membrane potential and apoptosis of neutrophils have been linked with autosomal recessive SCN (Klein et al. 2007, Germeshausen et al. 2008). Neurodevelopmental delay has also been linked to mutations with HAX1 (Germeshausen et al. 2008, Carlsson et al. 2008). Two mutations of the granulocyte colony-stimulating factor receptor (G-CSFR), encoded by the GSFR3R gene, located on chromosome 1p35 – 34.3, have been identified (Inazawa et al. 1991, Ward et al. 1999a, Germeshausen et al. 2007, Ward 2007). The first type is an acquired mutation that produces C-terminally truncated hyper-responsive forms of the receptor (G-CSFR<sup>hyper</sup>) resulting in enhanced proliferation at the cost of maturation (Gits et al. 2006, Liu et al. 2008). Patients with the G-CSFR<sup>hyper</sup> mutation are more susceptible to developing myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML) (Ward et al. 1999b, Germeshausen et al. 2007). The second G-CSFR mutation leads to a hypo-responsive G-CSFR (G-CSFR<sup>hypo</sup>) where patients do not respond to the administration of G-CSF (Ward et al. 1999a).

X-linked forms of SCN have been identified in patients with mutations of the Wiskott-Aldrich syndrome protein (WASp), located on chromosome Xp11.23 – p11.22, expressed only in haematopoietic stem cells involved actin polymerization, cell signalling, cell-cell interaction and cell motility (Devriendt 2001, Moulding et al. 2007). Mutations in WASp lead to unregulated actin polymerization, defects in mitosis, and increased apoptosis (Devriendt et al. 2001, Ancliff et al. 2006, Moulding et al. 2007). The X-linked form of SCN due to the WASp defect should not be confused with the Wiskott-Aldrich syndrome,
whose features include eczema, thrombocytopenia and immunodeficiency (Peacocke and Siminovitch 1987).

Mutations of growth factor-independent protein 1 (GFI1) located on chromosome 1p22, a zinc finger protein functioning as a transcription repressor, have been reported in cases of autosomal dominant SCN (Bell et al. 1995, Person et al. 2003). A defect in glucose-6-phosphatase catalytic subunit 3 (G6PC3) has been proposed to cause the autosomal recessive form of SCN along with thrombocytopenia, cardiac and urogenital abnormalities (Boztug et al. 2009). G6PC3, found on chromosome 17q21.31, acts to breakdown glucose-6-phosphate to glucose and phosphate on the endoplasmic reticulum, (Martin et al. 2002).


G-CSF is now the main treatment approach in these patients to increase neutrophil counts (Bonilla et al. 1998, Dale et al. 2006). A 15 year follow-up study examining the long-term risk of developing MDS/AML showed patients receiving a dose less than 8 \( \mu \text{g/kg/d} \) are at a 15% chance of developing MDS/AML versus 34% chance when taking more than 8
µg/kg/d (Rosenberg et al. 2010). Patients who have developed MDS/AML can only be managed by BMT (Rosenberg et al. 2006).

6.2.3 Fanconi Anemia

Fanconi anemia (FA), first described by Dr. Fanconi in 1927, is a rare autosomal and X-linked recessive condition caused by a cytogenetic instability in which somatic cells are hypersensitive to bifunctional alkylating agents (Fanconi 1927, Sasaku and Tonomura 1973). Studies have shown 11 gene complementation group mutations that can lead to FA: FANCA (16q24.3), FANCB (Xp22.31), FANCC (9q22.3), FANCD1 (13q12.3), FANCD2 (3p25.3), FANCE (6p21.3), FANCF (11p15), FANCG (9p13), FANCJ (21q22.11), FANCL (2p16.1) and FANCM (14q21.3) (Meetei et al. 2003, Meetei et al. 2004, Levitus et al. 2005, Levran et al. 2005). The normal function of these proteins is to protect against genotoxic stress by forming complexes with each other and suppression of apoptotic signalling pathways (Garcia-Higuera et al. 1999, Garcia-Higuera et al. 2001, Medhurst et al. 2001, Pang et al. 2000, Pang et al. 2001, Pang et al. 2002). The diagnosis is confirmed with a mitomycin C (MMC) or diepoxybutane (DEB) chromosomal breakage test of T-lymphocytes looking for metaphase spreads of chromosomal breaks and radial chromosomes (Auerbach et al. 1981).

FA can present with physical abnormalities such as growth retardation, microcephaly, café-au-lait spots, renal abnormalities and abnormal thumbs (Hagerman and Williams 1993). They can present with bone marrow failure with an increased risk of developing MDS/AML or squamous cell carcinoma (Kutler et al. 2003). Intra-orally, they can present with gingivitis, clinical attachment loss, advanced periodontitis, ulcerations, microdontia,

Treatment for bone marrow failure is through BMT (Boyer et al. 2003). Patients who have received BMT must be monitored for the development of solid tumours and chronic graft-versus-host disease (GVHD) (Boyer et al. 2003). Special consideration must to be given during the administration of chemotherapeutic agents and/or radiation as they can have extreme morbidity and a high iatrogenic mortality rate (Alter 2002).

6.2.4 Shwachman-Diamond Syndrome

Shwachman Diamond Syndrome (SDS) is an autosomal recessive disorder caused by a defect of the Shwachman-Bodian-Diamond (SBDS) gene at chromosome 7q11 which encodes for a ribosome maturation protein (Shwachman et al. 1964, Boocock et al. 2003). The SBDS gene causes a decrease CD34+ cells in the bone marrow, suggesting that the defect occurs at an early haematological-lymphocytic stem cell level and increased expression of the Fas glycoprotein leading to premature apoptosis of the progenitor neutrophil in the bone marrow even with the administration of G-CSF (Shwachman et al. 1964, Dror and Freedman 1999, Dror and Freedman 2001, Dror et al. 2001, Stepanovic et al. 2004, Yamaguchi et al. 2007).

Patients with SDS can present with neutropenia or pancytopenia, recurrent infections, steatorrhea, pancreatic insufficiency as a result of exocrine acini destruction and replacement with fatty tissue, anemia, mild thrombocytopenia, kyphosis, scoliosis, vertebral collapse, shortened ribs, syndactyly, clinodactyly, supernumerary thumbs, abnormal development at the metaphyseal growth plates, metaphyseal chondrodysplasia,
osteoporosis, osteomalacia related to impaired vitamin D & K absorption, costochondral thickening, neurological, learning and behavioural difficulties (Shwachman et al. 1964, Bodian et al. 1964, Burke et al. 1967, Pringle et al. 1968). Patients with SDS are at an increased risk of developing MDS/AML (Woods et al. 1981). Oral manifestations reported include mucositis, periodontal infections, increased caries risk and tooth enamel defects such as hypomaturation, hypocalcification and hypoplasia (Ho et al. 2007). Therapeutic care includes dietary modification which includes a high calorie diet with enzyme supplements and supplemental fat soluble vitamins (Hall et al. 2006). Neutropenia can be treated with G-CSF, however it is only used during life threatening situations and does carry a risk of accelerating the transformation into MDS/AML (Hall et al. 2006). Anemia and thrombocytopenia can be treated with blood and platelet transfusions respectively (Hall et al. 2006). BMT is considered for those patients who develop severe bone marrow failure or MDS/AML transformation (Donadieu et al. 2005).

6.2.5 Barth Syndrome

Barth syndrome was first described in 1983 by Barth et al. as an X-linked recessive mutation found at chromosome Xq28, encoding for tafazzin, a protein involved with remodelling of cardiolipin (Barth et al. 1983, Bolhuis et al. 1991, Vaz et al. 2003). A defective cardiolipin has been implicated changing the curvature of the mitochondrial inner membrane and destabilizing the mitochondrial electron transfer chain (Vreken et al. 2000, Vaz et al. 2003). There is considerable variability in terms of onset, severity and progression of disease in these patients (van Raam and Kuijpers 2009). Males can present with neutropenia, cardiomyopathy (biventricular dilatation or left-ventricular non-compaction), skeletal myopathy and/or 3-methylglutaconic aciduria (Barth et al. 1983,
Ichida et al. 2001, van Raam and Kuijpers 2009). Intra-orally, there has been only 1 reported case of a child presenting with recurrent oral ulcerations (Marziliano et al. 2007). Neutrophils isolated from patients with Barth syndrome showed normal functional activity compared with healthy individuals, but an increased binding of annexin-V was noted indicating increased apoptosis of these neutrophils (Kuijpers et al. 2004). Management is dependent on the presenting symptoms of each patient. In cases of severe neutropenia, patients are managed with G-CSF to prevent neutrophil apoptosis (Kuijpers et al. 2004, Yen et al. 2008). Cardiac transplantation is occasionally necessary to treat the cardiomyopathy (Kuijpers et al. 2004, Mangat et al. 2007, Yen et al. 2008).

6.2.6 Cohen Syndrome

Cohen syndrome was first described by Cohen et al. in 1973 with a prevalence estimated at 1:105,000 children (Cohen et al. 1973, Kivite-Kallio et al. 1999). Cohen syndrome is an autosomal recessive mutation of the COH1/VPS13B gene, found on chromosome 8q22, believed to play a role in intracellular vesicle mediated protein sorting (Kolehmainen et al. 2003, Velayos-Baeza et al. 2004, Balikova et al. 2009). A wide range of features have been reported for patient with Cohen syndrome from neutropenia, varying degrees of mental retardation, autistic like behaviour, enlarged corpus callosum, obesity, hypotonia, joint laxity, narrow tapered hands and feet, progressive myopia, retinochoroidal dystrophy, maxillary hypoplasia, mild micrognathia, short philtrum, open mouth and downslanting palpebral fissues (Kivite-Kallio and Norio 2001, Chandler et al. 2003, Howlin et al. 2005). Patients can have intra oral manifestations including recurrent ulcerations, gingivitis, periodontitis, alveolar bone loss, hypomineralization and prominent incisors (Cohen et al. 2001, van Raam and Kuijpers 2009).

Patient management may involve G-CSF administration and an ophthalmologic evaluation to assess visual acuity and pigmentary retinopathy (Kivitie-Kallio et al. 1997).

6.2.7 Dyskeratosis Congenita

Dyskeratosis congenita was first described by Zinsser in 1906 is a multisystem disorder due to defective telomere maintenance through the action of telomerase (Walne and Dokal 2009). Telomerase, which is present only in germ cells, stem cells and their immediate progeny, helps to maintain telomere lengths (Blasco 2007, Walne and Dokal 2009). An X-linked recessive form has been attributed to the DKCI gene, located at chromosome Xq28, encoding for dyskeratin which is associated with telomerase RNA (Conner et al. 1986, Heiss et al. 1998). An autosomal dominant form has been linked to a mutation in the telomerase reverse transcriptase (TERT) gene, located on chromosome 5p15.33 and in the telomerase RNA component (TERC) gene, located on chromosome 3q21 – 28 (Vulliamy et al. 2001, Armanios et al. 2005). An autosomal recessive form has been identified with the NOP10 gene, found on chromosome 15q14 and NOLA2 gene, found on chromosome 5q35.3 causing reduced telomere length and TERC levels (Walne et al. 2007, Vulliamy et al. 2008). A mutation in the TINF2 gene, located on chromosome 14q11.2, encoding for TIN2, which plays a role in shelterin, a protein complex that determines the structure of the telomeric terminus has been implicated with dyskeratosis congenita (Savage et al. 2008).

The classic triad of symptoms are oral leukoplakia, abnormal skin pigmentation and nail dystrophy that manifest themselves by 10 years of age (Dokal 2000, Walne and Dokal 2009). Patients can also present with other features such as bone marrow failure, defects in

Management of bone marrow failure is accomplished through the use of oxymethalone, G-CSF and BMT (Erduran et al. 2003, Walne and Dokal 2009).

6.2.8 Reticular Dysgenesis

Reticular dysgenesis is one of the most severe forms of combined immunodeficiency caused by an autosomal recessive mutation in the mitochondrial energy metabolism enzyme, adenylate kinase 2 located on chromosome 1p34.3 – 1p36.11 (Vaal and Seynhaeve 1959, Lagresle-Peyrou et al. 2009, Pannicke et al. 2009). Adenylate kinase 2 regulates cellular adenine nucleotides by converting adenosine diphosphate into adenosine monophosphate and adenosine triphosphate (Noma 2005). Bone marrow samples reveal myeloid differentiation blocked at the promyelocyte stage, whereas erythropoiesis and thrombopoiesis are intact (Pannicke et al. 2009). Patients with reticular dysgenesis can present with severe neutropenia leading to life threatening infections in the first days of life, absent lymphocytes, bilateral sensorineural deafness and hypoplasia of the thymus and other lymphoid tissues (Roper et al. 1985, Small et al. 1999, Lagresle-Peyrou et al. 2009). Management of reticular dysgenesis is accomplished through the administration of non-absorbable antibiotics to suppress their intestinal microflora, immunoglobulin therapy and ultimately BMT (Levinsky and Tiedeman 1983, Bertrand et al. 2002). Patients with
reticular dysgenesis are resistant to the growth promoting effects of G-CSF (Bujan et al. 1992).

6.2.9 Griscelli Syndrome Type 2

Griscelli syndrome type 2 (GS2), first described by Griscelli et al. in 1978 is an autosomal recessive mutation of the RAB27A gene, located on chromosome 15q21, encoding for Rab27a; a member for the small GTPase family of protein regulating the exocytosis of secretory lysosomes, melanosomes in melanocytes and lytic granules in T-lymphocytes (Griscelli et al. 1978, Pastural et al. 1997, Ménasché et al. 2000). Patients with GS2 can be confused with Chédiak-Higashi syndrome (CHS) or Hermansky-Pudlak syndrome, type 2 (HP2) with all groups presenting with neutropenia, recurrent pyogenic infections, partial albinism involving their hair, eyebrows and eyelashes; however, GS2 patients can be distinguished from CHS histologically by the lack of leukocyte cytoplasmic giant-granules and from HP2 by the normal bleeding time (Griscelli et al. 1978, Rossi et al. 2008). Patients with CG2 are at an increased risk of developing hemophagocytic lymphohistiocytosis (HLH) leading to uncontrolled CD8+ T-lymphocyte and macrophage activation and infiltration into multiple tissues (de Saint Basile and Fischer 2003, Ménasché et al. 2005). Neutrophils from these patients have a reduced killing capacity due to an inability of the primary granules to release myeloperoxidase (Munafò et al. 2007). Management of these patients is accomplished only through BMT (Aricò et al. 2002, Rossi et al. 2009).
6.2.10 Hermansky-Pudlak Syndrome Type 2

HP2 first identified by Hermansky and Pudlak in 1959 is an autosomal recessive mutation \( AP3BI \) gene located on chromosome 5q14.1, encoding for the \( \beta3A \) subunit of the adaptor protein-3 complex (AP-3) (Hermansky and Pudlak 1959, Dell’Angelica et al. 1997, Dell’Angelica et al. 1999, Jung et al. 2006). The AP-3 complex is involved in vesicular trafficking of transmembrane proteins leading to the formation of melasomal, platelet dense bodies and lysosomal compartments (Dell’Angelica et al. 1999). Patients with HP2 can present with oculocutaneous albinism, photophobia, strabismus, nystagmus, neutropenia, prolonged bleeding time due to defects in platelet aggregation, lung fibrosis, inflammatory colitis and HLH (Shotelersuk et al. 2000, Huizing and Gahl 2002, Huizing et al. 2002). The defect in AP-3 results in abnormal trafficking of neutrophil elastase to primary granules (Benson et al. 2003). Patients with HP2 show an incomplete maturation arrest of the myeloid lineage at the promyelocyte and myelocyte stage while those cells that did mature beyond that stage showed moderate granulocyte dysplasia (Enders et al. 2006). Platelet levels, partial thrombin and partial thromboplastin times are within normal limits, however bleeding time is prolonged in these patients (Huizing and Gahl 2002). These patients can present with aggressive periodontitis, alveolar bone loss and dental caries (Jung et al. 2006).

G-CSF is used for management of the neutropenia while TISSEEL® and concomitant antifibrinolytics are used for the management of prolonged bleeding (Enders et al. 2006, Feliciano et al. 2006).
6.2.11 Cartilage-Hair Hypoplasia

Cartilage-hair hypoplasia is an autosomal recessive mutation of the ribonuclease mitochondrial RNA processing (RMRP) gene, located on chromosome 9p13, first described in the Old Order Amish population group in 1965 and later identified in the Finnish population group (McKusick et al. 1965, Mäkitie and Kaitila 1993, Ridanpää et al. 2001). The RMRP gene is involved with ribosome assembly and cell-cycle regulation by encoding for the untranslated RNA subunit of the ribonucleoprotein endoribonuclease (Ridanpää et al. 2001). Over sixty different RMRP gene mutations have been identified within the promoter and transcribed sequence (Thiel et al. 2007). Mutations in the promoter region reduce the efficacy of interaction between RNA polymerase III and the RMRP gene reducing transcription efficiency, while mutations in the transcribed sequence cause instability and rapid decay of the mRNA (Hermanns et al. 2005, Nakashima et al. 2007).

Patients present with characteristic physical features such as short stature, metaphyseal chondrodysplasia and light-coloured hypoplastic hair (Mäkitie et al. 1992). Other symptoms can present such as macrocytic anemia, neutropenia, recurrent bacterial and viral (varicella) infections, limited elbow extension, ligamentous laxity, predisposition to malignancies, HLH, Hirschprung disease, impairment of cellular and humoral immunity (Lux et al. 1970, Mäkitie et al. 1998, 2000 and 2002).

There is no management for the chondrodysplasia in these patients, but there are strategies for management of their immunodeficiency (Berthet et al. 1996). A patient with T-lymphocyte immunodeficiency should be given inactivated varicella vaccine rather than attenuated varicella to reduce the risk of reactivation, prophylactic acyclovir and considered for BMT in cases of severe T-lymphocyte immunodeficiency (Hardy et al.
Patients with B-lymphocyte immunodeficiency may be given immunoglobulins (Matesic and Hagan 2007). Patient with neutropenia are managed with long-term administration of G-CSF (Ammann et al. 2004).

6.2.12 p14 Deficiency

p14 deficiency has been a recently discovered form of neutropenia caused by an autosomal recessive condition due to a point mutation in the 3-untranslated region of p14, found at chromosome 1q22 (Bohn et al. 2007). p14 is an adaptor molecule controlling the mitogen-activated protein kinase signalling to late endosomes, regulating endosomal traffic and cellular proliferation (Wunderlich et al. 2001, Bohn et al. 2007). p14 has also been shown to have some control over the G-CSF receptor-dependent signal transduction, but the exact cause of neutropenia has yet to be determined (Bohn et al. 2007). Patients can present with severe neutropenia, ineffective degradation of ingested bacteria by neutrophils, short stature, oculocutaneous hypopigmentation, coarse facial features, recurrent bronchopulmonary infections and B-lymphocyte and cytotoxic T-lymphocyte immunodeficiency (Bohn et al. 2007). To date, no oral manifestations of p14 deficiency have been described. BMT from an HLA-identical sibling was attempted in a patient with p14 deficiency, but trigged increased expression of TNF-α and lethal GVHD (Bohn et al. 2008).
6.2.13 CD40 Ligand Deficiency

CD40 ligand deficiency, also known as X-linked hypogammaglobulinemia with hyper IgM or hyper IgM syndrome is an X-linked recessive condition mapped to chromosome Xq26.2, encoding the CD40 ligand (Rosen et al. 1962, Padayachee et al. 1992, Allen et al. 1993). The CD40 ligand is a 261 amino acid transmembrane protein constantly expressed on B-lymphocytes and on activated CD4+ T-lymphocytes (Armitage et al. 1992, Aruffo et al. 1993). Activated CD4+ T-lymphocytes are essential for the isotype switching by B-lymphocytes (Noelle et al. 1992, Coffman et al. 1993).

Patients with CD40 ligand deficiency are susceptible to neutropenia, Pneumocystis carinii related pneumonia (PCP), chronic diarrhea due to Cryptosporidium parvum infections, sclerosing cholangitis, meningoencephalitis, lymphoma, liver cirrhosis leading to liver and biliary tract tumors (Hayward et al. 1997, Levy et al. 1997). Oral manifestations that have been reported include gingivitis and ulcerations (Levy et al. 1997). Management of these patients is accomplished through the administration of immunoglobulins, cotrimoxazole prophylaxis to prevent PCP, careful monitoring of liver function and G-CSF (Wang et al. 1994, Levy et al. 1997).

6.2.14 Purine Nuceloside Phosphorylase Deficiency

Increased levels of deoxyguanosine triphosphate in the mitochondria inhibits mitochondrial DNA repair, increases DNA damage, apoptosis of T-lymphocytes and leads to marrow dysfunction (Mitchell et al. 1978, Dror et al. 2004, Delicou et al. 2007). Patients with PNP deficiency can present in the first few years of life with marrow dysplasia, neutropenia, haemolytic anemia, immune thrombocytopenic purpura, arthritis, pericarditis, systemic lupus erythematosus, mental retardation, cerebral palsy, spastic paresis, tonus abnormalities and lymphoma can develop later on in life (Giblett et al. 1975, Nowak-Wegrzyn et al. 2001, Tabarki et al. 2003, Dror et al. 2004). Hypouricemia and reduced uric acid levels in urine are suggestive of PNP deficiency (Cohen et al. 1976). Management of these patients involve red blood cell transfusions, immunosuppressive agents and BMT (Dror et al. 2004, Delicou et al. 2007).

6.2.15 X-linked Agammaglobulinemia

X-linked agammaglobulinemia, first described by Bruton in 1952 is caused by a mutation of the Bruton agammaglobulinemia tyrosine kinase (btk), located at chromosome Xq21.3 – Xq22 (Bruton 1952, Mensink et al. 1987, Tsukada et al. 1993, Smith et al. 1994). Btk is a non-receptor tyrosine kinase, part of the Tec family of kinases, which is expressed in all haematopoietic lineages except T-lymphocytes and is required for proper maturation of B-lymphocyte precursors in the bone marrow (Tsukada et al. 1993, Smith et al. 1994). Patients present with neutropenia, low numbers of B-lymphocytes, absent plasma cells resulting in the inability to produce antibodies, recurrent bacterial infections, sinusitis, bronchitis, otitis media and pneumonia (Smith et al. 1994, Väliaho et al. 2006). Management of these patients involves the administration of antibiotics and immunoglobulins (Smith et al. 1994, Väliaho et al. 2006).
6.3 Acquired

6.3.1 Infection

Viral infections are the most common cause for neutropenia, developing during within the first two days of illness in conjunction with the peak viremic phase and can last for three to seven days (Dinauer 1998, Watts 2004). Viruses that can cause neutropenia are hepatitis A, hepatitis B, respiratory syncytial virus, influenza A influenza B, measles, rubella and varicella (Dinauer 1998). Due to their short length of duration they rarely lead to severe problems; however some viruses such as hepatitis B, Epstein-Barr and the human immunodeficiency virus (HIV) can damage myeloid precursor cells impairing production/replacement of neutrophils leading to severe complications (Watts 2004). Bacterial infections such as typhoid, paratyphoid, brucellosis, tularaemia, tuberculosis and sepsis can lead to suppression of myeloid production, depletion of neutrophil marrow stores and/or increased neutrophil destruction. (Baehner and Miller 1995, Dinauer 1998, Watts 2004). Rickettsial infections from rickettsial pox, typhus fever, Rocky Mountain spotted fever can cause neutropenia in the first week of infection (Baehner and Miller 1995). Protozoan infections such as malaria and leishmaniasis have been reported to cause neutropenia (Baehner and Miller 1995, Watts 2004).

6.3.2 Nutritional Deficiencies

Starvation, anorexia can lead to pancytopenia while deficiencies in copper, folate or vitamin $\text{B}_{12}$ can impair granulopoiesis and lead to hypersegmented neutrophils (more than 5 lobes) (Baehner and Miller 1995, Watts 2004).
6.3.3 Medication-induced

Idiosyncratic reactions to medications although irregular, are the second most common cause of neutropenia (Watts 2004). There is no manner to determine which medications will cause neutropenia in any given patient due to its high unpredictability. Medications linked to neutropenia include heavy metals, analgesics, anti-inflammatory agents, phenothiazines, antipsychotics, antidepressants, anticonvulsants, antithyroid drugs, cardiovascular drugs, antihistamine, antimicrobials, antimalarials and antivirals (Cline 1993, Baehner and Miller 1995, Watts 2004). There are three mechanisms by which the medications can induce neutropenia (Baehner and Miller 1995, Watts 2004):

1. Dose-dependent inhibition of granulopoiesis
2. Direct toxic effects on granulocyte precursors or the marrow microenvironment
3. Immune-mediated destruction of granulocytes or granulocyte precursors due to either medications acting as haptens to induce antibodies, complement fixation and neutrophil destruction

The duration of the medication-induced neutropenia is variable with immune-mediated medication-induced neutropenia occurring rapidly (hours to 1 – 2 days) versus a delayed onset (weeks) for medications that produce direct toxic effects on the granulocyte precursors (Piscotta 1973, Dinauer 1998, Watts 2004).

6.3.4 Chemotherapy-induced

Cytoxic drugs such as alkylating agents, antimetabolites, vinca alkaloids and antitumor antibiotics are used in cancer therapy to disrupt the replication of bone marrow cells resulting in pancytopenia (Baehner and Miller 1995). High-dose chemotherapy causes
severe neutropenia for greater than 10 – 15 days, while standard dose chemotherapy results in mild to severe neutropenia for less than 5 days (Boogaerts 1995).

6.3.5 Irradiation Exposure

Dose-dependent irradiation exposure causes destruction of haemtopoietic stem cells in the management of malignancies and in preparation for BMT (Cline 1993, Baehner and Miller 1995). Haematopoietic precursor cells are highly sensitive to irradiation, with a dose of 0.25Gy causing the death of lymphocytes (Miller and O’Reilly 1995). Irradiation has been shown to cause increased release of lactate dehydrogenase, increased release of lysozyme, increased collagen biosynthesis, decreased protein kinase C and decreased release of M-CSF (Greenberger 1991).

6.4 Aplastic anemia

Aplastic anemia (AA) is a rare heterogenous disorder of haematopoesis characterized by hypocellular bone marrow, reduction in erythroid, myeloid, megakaryocyte elements and peripheral pancytopenia (Ehrlich 1888, Miller and O’Reilly 1995, Davies and Guinan 2007). The diagnosis of aplastic anemia is given when at least two of the following are present (International Agranulocytosis and Aplastic Anemia Study Group, 1987):

- Haemoglobin count <100 g/mm³
- Neutrophil count <1,500 cells/mm³
- Platelet count <50,000 cells/mm³

AA can arise as a result of exposure to medications, chemicals, viral infections and in pregnancy; however most cases are caused by immune mediated complexes (Miller and O’Reilly 1995, Choudhry et al. 2002, Young et al. 2006). T-bet, a transcription factor that
binds the interferon-γ is upregulated and regulatory T-lymphocytes that inactive auto-reactive T-lymphocytes are decreased in patients with aplastic anemia (Solomou et al. 2006, Solomou et al. 2007). It is believed that cytotoxic T-lymphocytes expressing T-lymphocyte-helper type 1 release interferon-γ, killing haematopoietic progenitor cells (Hoffman et al. 1977, Zoumbos et al. 1985, Young et al. 2006, Davies and Guinan 2007).


Management of AA is accomplished through the administration of antithymocyte globulin, cyclosporine, cyclophosphamide, androgens and BMT (Rispon-Myerstein et al. 1968, Young et al. 2006, Marsh et al. 2009). Transfusion of red blood cells should be given to maintain a safe haemoglobin level above 80 g/mm$^3$ as well monitoring for serum ferritin level to prevent iron overload (Marsh et al. 2009). Platelet transfusions should be considered when the counts are below 10,000 cells/mm$^3$ and/or uncontrolled bleeding occurs (Marsh et al. 2009). Prophylactic antibiotics should be considered in those with severe neutropenia and leukocyte transfusions and/or G-CSF is considered in the presence of a life-threatening infection (Marsh et al. 2009).
VII. Functional Defects in Neutrophils

The recruitment of functional neutrophils to the site of an infection is a complex, dynamic process. Disorders in neutrophil morphology, adhesion, motility, phagocytosis or killing ability can lead to unusual infections that recur despite antibiotic therapy (Watts and Howard 1993). Patients with functional deficits or a hyper-exaggerated response can present intra-orally with aggressive periodontitis with premature loss of their primary and/or permanent dentition (Ciancola et al. 1977, Clark et al. 1977, Lavine et al. 1979, Watts and Howard 1993, Kantarci et al. 2003, Karima et al. 2005, Matthews et al. 2007).

The following is a brief list of the systemic disease entities that have been correlated with altered neutrophil function.

7.1 Papillon-Lefèvre Syndrome

First reported by Papillon and Lefèvre in 1924, Papillon-Lefèvre syndrome (PLS) is a rare autosomal recessive condition caused by a point mutation cathepsin C, encoded on chromosome 11q14-21 (Papillon and Lefèvre 1924, Laass et al. 1997, Toomes et al. 1999). Cathepsin C, expressed in neutrophils, macrophages and epithelial cells is believed to act as an activator for neutrophil elastase and other serine proteases (Adkinson et al. 2002). Patients with PLS present with palmoplantar hyperkeratosis, ectopic calcification of the falx cerebri and choroid plexus, gingival inflammation, rapid periodontal bone loss with premature loss of the primary and permanent dentition (Haneke 1979, Brimstein et al. 1990, Dhanrajani 2009). However once the teeth are lost, the gingiva is no longer inflamed (Haneke 1979, Brimstein et al. 1990, Dhanrajani 2009). Histopathology of PLS demonstrates severe inflammatory infiltration consisting mainly of plasma cells in the
subepithelial connective tissue with few collagen fibres (Preus 1988). Bacterial species identified from plaque samples of PLS patients include *Bacteroides gingivalis*, *Capnocytophagas* spp. and spirochetes, however *Actinobacillus actinomycetecomitans* was the most abundant pathogen cultured (Umeda *et al*. 1990).

Medical management of the hyperkeratosis involves the administration of topical steroids, salicylic acid and retinoids (Dhanrajani 2009). Ullbro *et al*. have proposed dental management strategies for patients with PLS, as seen on Table 1 (Ullbro *et al*. 2003). Abdulwassie *et al*. has shown successful oral rehabilitation with the use of dental implants (Abdulwassie *et al*. 1996).

**Deciduous dentition**

- Oral hygiene instruction and prophylaxis every third month
- Teeth with advanced periodontal disease: extraction
- All teeth should be extracted at least 6 months before eruption of the first permanent tooth; antibiotics should be given for 2 weeks after extraction. Recommended antibiotics: amoxicillin + clavulanic acid (20-40mg/kg/d) in divided doses every 8 hours

**Permanent dentition**

- Oral hygiene instruction and prophylaxis every third month
- Mouth rinses twice daily with chlorhexidine gluconate 0.2%
- Teeth with moderate periodontal disease (bone loss <30% of the root length, probing pocket depths <5mm):
  - Dental scaling
  - Prophylaxis once every month
  - Antibiotic treatment for 4 weeks; recommended antibiotics: amoxicillin (20-50 mg/kg/d) + metronidazole (15-35 mg/kg/d) in divided doses every 8 hours
- Teeth with advanced periodontal disease (bone loss >30% of the root length, probing pocket depth >6mm): extraction
7.2 Leukocyte Adhesion Deficiency, Type 1

Leukocyte adhesion deficiency, type 1 (LAD-1) is due to an autosomal recessive defect of CD18, β-subunit of β2 integrins, located on chromosome 21q22 (Suomalainen et al. 1986, Dana et al. 1987). As a result of the defective β2 integrin, neutrophils are unable to adhere to the endothelial cell wall, migrate into the site of the infection and those that do make it to the site of infection have difficulty with phagocytosis (Dinauer 1998). Patients with LAD can present with delayed separation of the umbilical cord, recurrent bacterial infections without the formation of any pus depending on the expression of CD18 (Crowley et al. 1980, Dinauer 1998). Intra-oral manifestations reported with LAD-1 include ulcerations, gingival inflammation, premature tooth loss of the primary and permanent dentition (Waldrop et al. 1987, Cox and Weathers 2008).

Management of LAD-1 is accomplished through the use of BMT (Dinauer 1998, Cox and Weathers 2008).

7.3 Leukocyte Adhesion Deficiency, Type 2

Leukocyte adhesion deficiency, type 2 (LAD-2)/congenital disorder of glycosylation, type IIc (CDG2C) is a very rare autosomal recessive disorder due to defect in the SLC35C1 gene on chromosome 11p11.2 (Lühn et al. 2001). SLC35C1 encodes for a GDP-fucose transporter resulting a defect in fucose metabolism leading to an absence of sialyl-Lewis X glycoproteins, which are essential in leukocyte rolling (Etzioni et al. 1992, Lühn et al. 2001). To date only 8 cases in the literature reporting recurrent infections, facial dysmorphism, short stature, mental retardation, neutrophilia and a Bombay blood group
phenotype due to the absence of the H antigen, which requires fucose (Etzioni et al. 1992, Yakubenia and Wild 2006). No oral manifestation of LAD-2 have been reported. Management of LAD-2 is accomplished through the administration of oral fucose which resulted in improved psychomotor capabilities, decreased the frequency of infections and returned neutrophil counts to normal (Marquardt et al. 1999).

7.4 Leukocyte Adhesion Deficiency, Type 3

Leukocyte adhesion deficiency, type 3 (LAD-3) is an autosomal recessive disorder of the FERMT3 gene located on chromosome 11q12 (Svensson et al. 2009). FERMT3 encodes for kindlin-3 which is an intracellular protein that activates the β-integrins on neutrophils and platelets (Svensson et al. 2009). As a result of the disrupted β-integrins, neutrophils are unable to adhere to the endothelial surface (Svensson et al. 2009). Patients with LAD-3 present with recurrent infections, glanzman’s thombasthenia and neutrophilia (Alon and Etioni 2003, Mory et al. 2008, Svensson et al. 2009).

Management of LAD-3 is accomplished through the use of BMT (Malinin et al. 2009).

7.5 Hyperimmunoglobulin E Syndrome

Hyperimmunoglobulin E syndrome (HIES), first described in 1966 by Davis et al. is an autosomal dominant disorder of the STAT3 gene on chromosome 17q21, as a result the T-lymphocytes are unable to differentiate into interleukin-17 producing T-helper lymphocytes (David et al. 1966, Minegishi et al. 2007, Milner et al. 2008).

Patients with HIES present with a history of recurrent pneumonia, ‘cold’ skin abscesses, elevated immunoglobulin E levels and eosinophilia (Davis et al. 1966, Watts and Howard
The term ‘cold’ abscesses are used as these infections lack the usual signs of an infection such as warmth, erythema and tenderness (Davis et al. 1966). Common pathogens for the infections include bacteria *S. aureus*, *Apergillus* species and fungi *Candida* species (Watts and Howard 1993). A neutrophil chemotaxis defect has been identified in patients with HIES, however this varies in severity among patients and within a single patient over time (Hill et al. 1974, van Scoy et al. 1975, Watts and Howard 1993). The etiology for the chemotaxis defect has been attributed to either the monocytes producing a leukocyte chemotaxis inhibitor or a decreased release of interferon gamma from lymphocytes (Donabedian and Gallin 1982, Borges et al. 2000). Administration of interferon gamma has shown success in restoring the chemotaxis defect (Jeppson et al. 1991). Oral manifestations include ulcerations, gingivitis and over-retained primary teeth rather than premature loss as one would expect with a neutrophil defect (Grimbacher et al. 1999).

Management of patients with HIES include the use of antibiotics, antifungals and surgical debridement (Watts and Howard 1993, Dinauer 1998).

### 7.6 Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is due to a defect in enzyme NADPH oxidase resulting in the inability to produce oxygen free radicals to kill phagocytosed microorganisms (Berendes et al. 1957, Bridges et al. 1959, Dinauer 1998). Two thirds of cases of CGD are due a X-linked recessive mutation of the of the *CYBB* gene on chromosome Xp21.1 encoding for gp91-phox, while the remaining one third is due to an autosomal recessive mutation of the *NCF1* gene on chromosome 7q11 encoding for p47phox, the *NCF2* gene on chromosome 1q25 encoding for p67phox and the *CYBA* gene
on chromosome 16q24 encoding for p22phox (Clarke et al. 1989, Francke et al. 1990, Roos et al. 1996, Segal et al. 2000, Winkelstein et al. 2000, Kannengiesser et al. 2008). Diagnosis of CGD is confirmed through the nitroblue tetrazolium test, where normal neutrophils will produce a dark blue pigment while abnormal neutrophils will remain yellow (Segal et al. 2000, Towbin and Chavas 2010).


Treatment involves prophylactic administration of cotrimoxazole and itraconazole with surgical drainage of abscesses (Watts and Howard 1993, Mouy et al. 1994, Dinauer 1998). Interferon gamma has been used to reduce the rate of infection in these patients (Weening et al. 1995).

VIII. Combined Neutropenia and Functional Defects in Neutrophil

8.1 Glycogen Storage Disease Type 1b

Glycogen storage diseases comprise of a group of metabolic disorders resulting in abnormalities with synthesis and degradation of glycogen (Gilbert-Barness and Barness 2000). Glycogen storage disease Type 1b (GSD1b) an autosomal recessive disorder caused by a defect in the glucose-6-phosphate translocase (G6PT) an enzyme encoded on
chromosome 11q23 preventing glucose-6-phosphate from being transported across the endoplasmic reticulum of hepatocytes (Lange et al. 1978, Stoelting and Dierdorf 1993, Annabi et al. 1998, Gilbert-Barness and Barness 2000, Pierre et al. 2008). As a result, the hepatocytes accumulate glycogen as they are unable to metabolize glycogen into glucose (Gilbert-Barness and Barness 2000). Diagnosis is based upon clinical presentation and reduced levels of glucose-6-phosphate and elevated glycogen levels in fresh, unfrozen liver tissue samples (Gilbert-Barness and Barness 2000). Features of GSD1b include hypoglycemia that can precipitate seizures or coma, ketoacidosis, lactic acidosis, hyperlipidemia, gout, hepatomegaly, hepatic adenoma, growth retardation, delayed puberty, bleeding complications due to platelet dysfunction, enlarged kidneys, renal damage, osteoporosis, polycystic ovaries, neutropenia, neutrophil dysfunction and increased susceptibility to infections (Ambruso et al. 1985, Wolfsdorf et al. 1999, Gilbert-Barness and Barness 2000, Visser et al. 2000, Rake et al. 2002, Melis et al. 2005). Neutrophils from patients with GSD1b have shown increased apoptosis through binding to annexin-V (Kuijpers et al. 2003). Oral manifestations of GSD1b include rapidly progressing periodontal disease, delayed development of the dentition, dental caries, abscess, candidiasis and recurrent episodes of stomatitis (Loevy et al. 1983, Barrett et al. 1990, Dougherty and Gataletto 1995, Salapata et al. 1995, Katz et al. 1997).

Management of GSD1b involve dietary management with frequent feeding, high carbohydrate diet and pharmacotherapy to reduce hypoglycemia (Katz et al. 1997, Pierre et al. 2008). Administration of vitamin E and G-CSF is used to improve neutrophil levels and function and in some situations BMT have been performed (Calderwood et al. 2001, Kannourakis 2002, Melis et al. 2005, Pierre et al. 2008, Melis et al. 2009).
8.2 Chédiak-Higashi syndrome

CHS is a rare, autosomal recessive inherited disorder with less than 500 cases reported over the past twenty years (Kaplan et al. 2008). The mutant gene CHS/Beige, was first identified in a mouse model, followed by identification in the human gene CHS/LYST, located at chromosome 1q42.1 – q42.2 (Barbosa et al. 1996, Barrat et al. 1996, Nagle et al. 1996, Perou et al. 1996). The function of the CHS/LYST protein has yet to be fully determined, but is believed to regulate vesicle trafficking (Kaplan et al. 2008).

Patients with CHS present with a wide array of clinical manifestations such as severe immunodeficiency, bleeding problems, frequent bacterial infections, variable oculocutaneous albinism, photosensitivity, progressive neurologic dysfunction (weakness, ataxia, sensory deficits) and a lymphoproliferative disorder called the ‘accelerated phase’ that results in a lymphocytic infiltration of the major organs of the body (Padgett et al. 1968, Sung et al. 1969, Buchanan and Handin 1976, BenEzra et al. 1980, de Boer et al. 1981, Valenzuela and Morningstar 1981, Introne et al. 1999, Ward et al. 2002, Kaplan et al. 2008). A diagnostic feature of this disorder is the presence of enlarged vesicles of lysosome origin affecting neutrophils, lysosomes, melanosomes, platelet dense granules and cytolytic granules (Kaplan et al. 2009). The primary and secondary granules found in neutrophils fuse together forming large intracellular inclusions that decrease neutrophil migration and intracellular killing ability leading to the frequent bacterial infections (White and Clawson 1980). Patients with CHS can present intra-orally with periodontitis, gingival bleeding, recession, periodontal pockets >10mm, extensive bone resorption, tooth mobility and enamel dysplasia (Delcourt-Debruyne et al. 2000, Shibutani et al. 2000, Bailleul-Forestier et al. 2008).
Management involves daily prophylactic antibiotic administration to minimize the chance of developing an infection, while BMT is used to resolve the bleeding and immunologic complications (Tardieu et al. 2005, Kaplan et al. 2008). There is no cure for the progressive neurological degeneration that occurs with this syndrome; ultimately patients will succumb to organ failure brought on by the ‘accelerated phase’ (Tardieu et al. 2005, Kaplan et al. 2008)

8.3 Warts, Hypogammaglobulinemia, Infections and Myelokathexis

Warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome is an autosomal dominant condition related to a C-terminus deletion mutation in the CXC chemokine receptor 4 (CXCR4) gene, located on chromosome 2q21 (Wetzler et al. 1990, Hernandez et al. 2003). Chemokine receptors are involved in sensing gradients leading to cell migration, cytoskeletal reorganization, cell polarization and integrin activation (Balabanian et al. 2005). CXCR4 are present in keratinocytes and when defective in patients with WHIM, can lead to warts caused by the human papillomavirus (HPV) family (Balabanian et al. 2005). These lesions can be found anywhere on the body leading to dysplastic lesions that can progress into carcinoma (Wetzler et al. 1990, Gulino 2003, Kawai and Malech 2009). B-lymphocyte lymphopenia is a common finding leading to hypogammaglobulinemia (Wetzler et al. 1990, Kawai and Malech 2009). Myelokathexis is a rare condition leading to moderate/severe neutropenia and altered neutrophil motility (Zueler 1964). Bone marrow samples from these patients show hyperplastic hypersegmented degenerating granulocytes with delayed release into the vascular compartment (Wetzler et al. 1990, Dinauer 1998, Aprikyan et al. 2000). Neutrophils have
an abnormal morphologic appearance of pyknotic nuclei, nuclear hypersegmentation with very thin filaments connecting the nuclear lobes (Zuelzer 1964, O’Regan et al. 1977).

Clinical features of WHIM are recurrent episodes of pneumonias, sinusitis, cellulitis, urinary tract infections, thrombophlebitis, omphalitis, osteomyelitis, and skin infections (Wetzler et al. 1990). Gingivitis, stomatitis and premature tooth loss have been reported intra-orally (Weston et al. 1991).

Daily antibiotic prophylaxis of trimethoprim-sulfamethoxazole has been suggested for these patients (Wetzler et al. 1990, Kawai and Malech 2009). Immunoglobulins have been given successfully in these patients to reduce the risk of infections (Wetzler et al. 1990, Goddard et al. 1994). Administration of G-CSF, epinephrine or corticosteroids induce a prompt release of neutrophils that may reach normal levels within hours (Hord et al. 1997, Cernelc et al. 2000). Wart prevention should be managed through vaccination against HPV, while any lesions present should be biopsied and removed if pre-malignant or malignant lesions are found (Kawai and Malech 2009).

8.4 Lazy Leukocyte Syndrome

Lazy leukocyte syndrome (LLS), first described by Miller et al. in 1970 is characterized by a combination of neutrophils that show poor random motility and chemotaxis and neutropenia; however bone marrow samples indicate normal neutrophil counts and morphology (Miller et al. 1975, Constantopoulos et al. 1975). Pinkerton et al. postulated that the pathogenesis of LLS is a defect in the actomyosin-like microtubular protein in the neutrophil membrane resulting in defective migration of neutrophils to tissue and site of inflammation (Pinkerton et al. 1978, Patrone et al. 1979).
Patients can present clinically with recurrent stomatitis, infections (i.e. otitis media, tonsillitis) and low-grade fevers (Miller et al. 1970, Constantopoulos et al. 1975, Yoda et al. 1980). Patients with LLS have been reported to have ulcerations, gingivitis, periodontitis and tooth loss (Miller et al. 1970, Arnold and Hoffman 1979, Goldman et al. 1984, Aggarwal et al. 1985).

Management of these patients is mainly supportive with the use of antibiotics and antifungals (Constantolopous et al. 1975)

**IX. Medical Management of Patients with Neutropenia**

The management of neutropenia depends on the underlying cause, severity of the neutropenia and each patient’s history of infections/hospital admissions. Supportive care with good whole body and oral hygiene, avoiding trauma to the oral and peri-rectal area, immunizations, cleaning all cuts and abrasions to the skin, antibiotics and/or antifungal agents are the main treatment modality. In more severe situations the use of steroids, G-CSF, IVIG, leukocyte transfusions and/or BMT are considered.

**9.1 Antibiotics**

Historically, the most common antibiotics given for prophylaxis were the penicillin’s and trimethoprim-sulfamethoxazole (Welte and Dale 1996). Fluoroquinolones have become the antibiotic of choice for prophylaxis in chemotherapy-induced myelosuppression due to it’s ability to reduce the number of infectious episodes and mortality (Pascoe and Steven 2009, Wingard and Elmongy 2009). Concerns with antibiotic prophylaxis include microorganisms
developing antimicrobial resistance, allergic reactions and gastrointestinal complaints (Welte and Dale 1996). Ultimately, the decision for or against antibiotic prophylaxis rests with the physician based upon patient specific factors.

A patient with neutropenia who is febrile should be given a broad spectrum antibiotic after blood cultures are obtained (Dinauer 1998). If the cultures show no growth, antibiotics should be given for at least three days after the patient is afebrile, however if the patient continues to be febrile antibiotics should be continued (Dinauer 1998).

9.2 Antifungals

Invasive fungal diseases can cause significant morbidity and mortality in patients with neutropenia. Administration of antifungal agents should be considered as a prophylaxis as it has been shown to reduce the rate of invasive fungal disease when neutropenic patients have a persistent fever and are receiving antibiotics (Dinauer 1998, Goldberg et al. 2008, Almyroudis and Segal 2009). Amphotericin B has traditionally been used but concerns about its toxicity have resulted in fluconazole, echinocandins and/or posaconazole being used instead (Dinauer 1998, Almyroudis and Segal 2009).

9.3 Steroids

Corticosteroids are used when the cause of neutropenia is determined to be an autoimmune response destroying the neutrophil precursor cells and mature neutrophils (Dinauer 1998, Worth et al. 2006).

Androgens (testosterone, nortestosterone, oxymethalone) encourage the release of neutrophils from the bone marrow but does not promote neutrophil development. (Udupa and Reissman 1974, Udupa and Reissman 1975, Beran et al. 1982, Kim et al. 2005, Hosseinimehr et al.
Androgens stimulate mainly erythroid progenitor cells and improve their survival, while having minimal effect on other haematopoetic progenitor cells (Kim et al. 2005). Side effects of continuous steroid use are liver toxicity, increased risk of an infection and developing diabetes mellitus (Walne and Dokal 2009).

9.4 Immunoglobulins

Immunoglobulins have been used in the treatment of patients with primary immune deficiencies, inflammatory disease, autoimmune diseases and acute infections (Kivity et al. 2010). Immunoglobulins are obtained from the purified pooled plasma of over a thousand donors containing >95% unmodified immunoglobulin G, trace amounts of immunoglobulin A or immunoglobulin M (Kivity et al. 2010). The suspected mechanism of immunoglobulins is through the blockage of Fc receptors in the reticuloendothelial system (Fehr et al. 1982, Hanada et al. 1988, Dwyer and Buckley 1992). Side effects from the administration of immunoglobulins include headaches, nausea, vomiting, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnea, back pain, diarrhea, blood pressure changes, tachycardia, anaphylaxis, renal failure, deep vein thrombosis, asptic meningitis, autoimmune haemolytic anemia, skin reactions and arthritis (Branagan et al. 1996, Sherer et al. 2001, Wittstock et al. 2003, Dalakas 2004, Orbach et al. 2005).

9.5 Granulocyte Colony-Stimulating Factor

G-CSF is normally produced by the human body in low levels (range <30 – 163 pg/ml), but during periods of stress the production of G-CSF can increase dramatically (range <30 – 3,199 pg/ml) (Watari et al. 1989, Kawakami et al. 1990). Patients with neutropenia taking G-CSF are now able to maintain near normal levels of neutrophils, reducing the duration and


Side effects of G-CSF that have been reported include arthritis, bone pain, splenomegaly, hepatomegaly, thrombocytopenia, osteopenia, osteoporosis, vasculitis and glomerulonephritis (Freedman et al. 2000, Cottle et al. 2002, Starkebaum 2002). Patients with SCN, SDS and refractory neutropenia patients receiving G-CSF have an increased risk of developing MDS/AML over time (Freedman and Alter 2002, Hall et al. 2006, Rosenberg et al. 2006).

9.6 Granulocyte Transfusions

Neutropenic patients with documented sepsis that do not respond to the above mentioned treatment modalities should be considered for granulocyte transfusions (Strauss 1993, Huestis and Glasser 1994, Peters et al. 1999). Historically, the problem with this procedure was the low clinical yield of leukocytes obtained; however recent improvements in
collection techniques have allowed for renewed interest in this technique. Donors are administered G-CSF and/or corticosteroids before collection to produce high yields of granulocytes 2 – 10 times and to prolong the half-life of the transfused granulocytes (Bensinger et al. 1993, Leavey et al. 2000, Price et al. 2000). Leukocytes are collected by continuous flow centrifugation with the addition of starch and a citrated anticoagulant to increase efficiency and acceleration of red cell sedimentation (van de Wetering et al. 2007). The granulocyte concentrations should be stored at room temperature (20 – 24°C) and transfused as soon as possible, no later than 24 hours after collection (Peters 2009).

Disadvantages of granulocyte transfusions are the cost, short survival time of granulocytes requires frequent infusions, possible transmission of viral infections and potential GVHD (Watts 2004).

9.7 Bone Marrow Transplantation

In the treatment of neutropenia, BMT is often the last resort physicians will use after all other treatment strategies have been proven to be ineffective or the development of MDS/AML has occurred (Elhasid and Rowe 2010). Allogenic BMT requires recipients to be matched with donors for human leukocyte antigen (HLA) alleles and antigens (Petersdorf 2008). Matched sibling donors can be found in about 20 – 30% of cases, so the majority rely on unrelated donors (Young et al. 2006, Petersdorf 2008). If a perfect match cannot be found and the decision has been made to proceed with BMT, the recipient is at an increased risk of developing GVHD (Petersdorf 2008).

In preparation for BMT, the recipients bone marrow is destroyed through the use of radiation therapy and/or chemotherapy, however improved success has been noted with the use of only chemotherapy (Young et al. 2006). Donated stem cells are then transplanted to
the recipient to allow for production of new red blood cells, white blood cells and platelets. During their treatment, patients do not have an immune system and are very susceptible to infections, so they are kept in isolation, given G-CSF, antibiotics and antifungals (Madero et al. 1999). Engraftment (successful BMT) can be seen with resolution of mucositis, fever and an increase in the absolute neutrophil count (Ali et al. 2002).

X. Dental Management of Patients with Neutropenia

Patients with neutropenia have been shown to present with pain from dental caries, aggressive periodontal disease, ulcerations and opportunistic infections due to the constant presence of bacteria in the oral cavity. Bacteria cultured intra-orally from patients with neutropenia and periodontal disease show no difference to healthy patients with periodontal disease (Vaughan et al. 1990, Kamma et al. 1998). Vaughan et al. examined the gingiva of a patient with chronic neutropenia and found a thin pocket epithelium with intercellular spacing in which neutrophils and plasma cells were present followed by a non-continuous epithelium-connective junction at the basement membrane (Vaughan et al. 1990). They also noted that the connective tissue showed collagen lysis predominantly filled with neutrophils and plasma cells (Vaughan et al. 1989).

The main goal in dental care for the patient with neutropenia is to have the patient practice excellent daily oral hygiene to prevent the development of any oral disease. The purpose of recall appointments is to reinforce good oral hygiene practices, monitor for the development of oral diseases, intercept and treat any developing oral diseases before the treatment becomes extensive. Patients with neutropenia have been seen as frequently as 7 visits per month, but the

A few case reports have discussed providing antibiotic coverage to patients with neutropenia prior to dental treatment, but there is no set definition as to what type, when and how long these patients should receive antibiotics unlike the criteria set for by the American Heart Association for patients with cardiac defects (Scully et al. 1982, da Fonseca and Fontes 2000, Wilson et al. 2007). Studies have shown that dental procedures, toothbrushing and even eating can introduce a transitory bacteremia (Schlein et al. 1991, Roberts et al. 1997, Forner et al. 2006). Ultimately, dentists should consult with the patient’s haematologist to determine if antibiotic coverage is required for dental treatment and for how long. Systemic antibiotics such as amoxicillin, augmentin, metronidazole, tetracycline and localized delivery of minocycline have been used in conjunction with scaling and debridement to facilitate resolution of the periodontal infection (Kamma et al. 1998, Vaughan et al. 1990, Goultschin et al. 2000, Okada et al. 2000, Nakai et al. 2003, Oyaizu et al. 2005).

Ulcerations have been managed with a variety of strategies such as a bland diet, kapectate, benadryl, triamcinolone, lignocaine mouth rinse and cotrimoxazole (Scully and Gilmour 1986, Vaughan et al. 1990, Kirstilä et al. 1993, Dougherty and Galaletto 1995, Salapata et al. 1995).

Oral hygiene for a patient with neutropenia can be difficult if the patient has ulcerations or aggressive periodontal disease. The use of an ultra-soft toothbrush and toothette’s have been recommended to be used during these periods (Valdez and Patton 1990, Oyaizu et al. 2005). Patients have been given chlorhexidine rinses, iodine rinses and fluoride rinses to use at home to manage the periodontal disease and dental caries (Rylander and Ericsson 1981, Spencer and Fleming 1985, Valdez and Patton 1990, Vaughan et al. 1990, Kirstilä et al. 1993, Kamma et al. 1998).
CHAPTER 2

RESEARCH QUESTION
PURPOSE OF RESEARCH


2006). An oral health-related quality of life survey of children with neutropenia compared with healthy controls demonstrated that children with neutropenia had an overall worse rating of the health of their teeth and mouth (Cheretakis et al. 2007). Theoretically, the administration of G-CSF to increase the neutrophil counts in these patients should render these patients indistinguishable from normal patients. The purpose of this survey study was to determine the prevalence of periodontal disease, dental caries and ulcerations in patients with neutropenia.
CHAPTER 3

ORAL HEALTH STATUS IN CHILDREN UNDERGOING TREATMENT FOR NEUTROPENIA

This chapter has been submitted to *Pediatric Dentistry*

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The patient questionnaire and clinical assessment forms can be seen on appendices A – L. A complete breakdown of the patient questionnaire responses and clinical examination results based upon severity of neutropenia can be seen on appendices M and N respectively. Post-hoc power calculations can be seen on appendix O.
ORAL HEALTH STATUS IN CHILDREN UNDERGOING TREATMENT FOR NEUTROPENIA

ABSTRACT

Purpose: The purpose of this cross-sectional study was to assess and compare the oral health of children with neutropenia, who are under the active care of a haematologist in a designated marrow failure and myelodysplasia program, to the oral health status of a healthy control group.

Methods: Children aged 6–18 with neutropenia attending the Marrow Failure and Myelodysplasia Program at The Hospital for Sick Children and controls attending the Children’s Clinic, Faculty of Dentistry, University of Toronto were asked to participate in the study consisting of a patient questionnaire followed by a dental and radiographic examination.

Results: Fifteen patients with neutropenia (mean age 12.14±4.04 years) and 26 healthy controls (mean age 11.61±3.82 years) participated in this study. Patients with neutropenia reported significantly increased mouth sores ($p<0.008$) and bleeding gums while brushing ($p<0.001$). The dmft/t score was significantly lower for the neutropenia group ($p<0.009$). The clinical examination also showed that there were no statistically significant differences with respect to ulcerations, gingival recession, tooth mobility, gingival inflammation, periodontal bone loss, DMFT/T scores, plaque and calculus levels.

Conclusions: These data demonstrate that pediatric patients who have been treated successfully for neutropenia do not present with an increased risk of oral diseases.

Keywords: children, neutropenia, oral health, ulceration, gingivitis, periodontal bone loss, dmft, DMFT

(Abstract word count 199)
INTRODUCTION

Neutrophils are critical components of the innate immune system and are responsible for maintaining both general and oral health in the face of the constant challenges created by invasive microorganisms including viruses, fungi and bacteria. Neutrophils are the first cells to respond to an infection or tissue damage and phagocytose the invading microorganisms through the formation of free oxygen radicals, enzymes (e.g. myeloperoxidase, lysozyme, lactoferrin and gelatinase) and extracellularly through the formation of neutrophil extracellular traps that act to trap and kill the bacteria with the above mentioned enzymes (Dinauer 1998, Watts 2004, Brinkmann et al. 2005). Remarkably, the oral cavity is particularly rich in microorganisms with bacterial counts in the range of $10^8$ to $10^{11}$ organisms/ml of saliva (Simos et al. 2004). It is noteworthy that the gingival tissues, as part of the overall integumentary system represent the only area in the body where there is actual penetration of structures (e.g. teeth) through the integument, thereby creating in effect the potential for ready ingress of bacterial microorganisms (Ten Cate 1998). Clearly then this area of the body is unique given not only the bacterial challenge but also the fact that potentially pathogenic organisms have a readily available pathway into the body. Fortunately, in addition to the seal created between the teeth and the gingival tissues, there exists the innate immune system that plays a generally protective, role in preventing the ingress of putative pathogenic microorganisms. The principal cell of the innate immune system is, as mentioned above, the neutrophil. Given the protective role played by neutrophils, defective/hyperactive function of the neutrophil or a paucity of these cells, known as neutropenia (see below) could be a significant risk factor in the development of aggressive periodontitis and other oral diseases (Armitage 1999). Historically, case reports and studies that have focused on the oral manifestations of neutropenia have reported they are at risk for the development of oral problems including: poor oral hygiene, plaque, calculus, dental caries, pain,
severe gingivitis, spontaneous gingival bleeding, tooth mobility, aggressive periodontitis with advanced bone loss and ulcerations of the soft tissues (Dougherty and Gataletto 1995, Delcourt-Debruyne et al. 2000, Goultschin et al. 2000, Hakki et al. 2005). As a consequence, various preventive and treatment strategies have been developed to manage oral disease for patients with neutropenia including therapies such as: chlorhexidine rinses, iodine rinses, minocycline ointments, systemic antibiotics, monthly hygiene appointments, splinting of mobile teeth, open flap debridement, selective extractions of teeth with poor/hopeless prognosis (Dougherty and Gataletto 1995, Delcourt-Debruyne et al. 2000, Goultschin et al. 2000, Defraia and Marinelli 2001, Hakki et al. 2005). In some cases where periodontal disease is advanced all teeth have been extracted (Defraia and Marinelli 2001). This suggests that patients with neutropenia suffer from aggressive periodontal disease and require intensive preventive and active treatment strategies.

Neutropenia is defined as a significant reduction in the absolute number of circulating neutrophils (ANC); the severity can be classified as mild (1,000 – <1,500 cells/mm³), moderate (500 – <1,000 cells/mm³) or severe (< 500 cells/mm³) (Dinauer 1998). Neutropenia can be caused by intrinsic defects in myeloid cells or progenitors (e.g. cyclic neutropenia, severe congenital neutropenia, Shwachman-Diamond syndrome or Fanconi anemia) or more commonly through an extrinsic factor (e.g. infections, medications, chemicals or nutritional deficiencies) (Dinauer 1998). Patients suffering from neutropenia can present with a wide array of signs and symptoms depending on the cause, severity and duration of their neutropenia (Dinauer 1998). Patients with neutropenia are at an increased risk of infections that may only present as a slight fever instead of the classical signs of swelling, heat and/or pus (Watts 2004). Patients with neutropenia may present with: skin abscesses, stomatitis, furunculosis and poor wound healing; recurrent infections in the perirectal and genital areas; urinary tract infections; recurrent otitis
media and upper respiratory tract infections (Dinauer 1998, Watts 2004). Patients with severe neutropenia are at-risk of developing infections involving the lungs, gastrointestinal tract, septicemia and other life threatening infections (Watts 2004). As alluded to above, management of patients with neutropenia involved the use of antibiotics, antifungals, steroids, granulocyte transfusions and immunoglobulins (Dinauer 1998). In the 1980’s, granulocyte colony-stimulating factor (G-CSF) was introduced which increased the number of circulating neutrophils in otherwise neutropenic patients by stimulating the proliferation, differentiation and maturation of neutrophil precursor cells (Dale et al. 1993). This has reduced the frequency and severity of infections, improved prognosis, quality of life and treatment outcome of patients with neutropenia (Dale et al. 1993, Jones et al. 1993). As well, there have been case reports in the literature indicating that G-CSF in combination with periodontal treatment can prevent the development of aggressive periodontitis, reduce the frequency of oral ulcerations and improve the oral health of patients with neutropenia (Quinn et al. 1993, Hastürk et al. 1998, Goultschin et al. 2000, Nakai et al. 2003, Carlsson et al. 2006). However, despite treatment with G-CSF patients could still be at risk for the development of oral infectious/inflammatory diseases. One patient treated at the Mount Sinai Hospital in Toronto had neutropenia that was being managed by the use of G-CSF. Yet, she continued to suffer from such severe periodontitis that eventually all of her teeth had to be extracted despite a normal neutrophil count. In addition to this case there are other data that suggest that despite G-CSF-mediated reconstitution of normal peripheral neutrophil counts, oral diseases remained significant (Carlsson et al. 2006). In relation to this, an oral health-related quality of life survey was carried out in children with neutropenia as well as healthy controls (Cheretakis et al. 2007). The findings showed that children with neutropenia rated the health of their teeth and mouth significantly poorer than the control group. Significantly more children with neutropenia reported severe oral symptoms, functional limitations and
problems with both emotional and social well-being. The data showed 18.6% of these children did not have regular dental care. Given the variance of findings relating to the oral health status of children with neutropenia, an observational cross-sectional study was performed to determine the prevalence of oral disease in patients with neutropenia.

MATERIALS AND METHODS

This observational cross-sectional study was conducted between September 2008 and June 2010 and consisted of a patient questionnaire followed up with a dental and radiographic examination.

Study Subjects

Participants in the study included children aged 6 to 18 with any etiology of chronic congenital/idiopathic form of neutropenia attending the Marrow Failure and Myelodysplasia Program (MFMP) at The Hospital for Sick Children (Sickkids). Healthy control children aged 6 to 18 attending the Children’s Clinic at the Faculty of Dentistry, University of Toronto (U of T), for a new patient examination or recall appointment were asked to participate in this study to serve as haematologically healthy age and sex matched controls. The study was approved by the U of T and Sickkids Research Ethics Board, written consent and assent was obtained from all participants.

Patient Questionnaire

The patient questionnaire consisted of 4 parts: general patient information, medication history, oral health assessment and dental history. The general patient information included demographic information such as age and sex. The severity of neutropenia for each patient was calculated by
obtaining the average ANC for 6 months prior to participating in the study. Medication history was designed to assess if the patient had at one point during their treatment received G-CSF, steroids, immunoglobulins or other medications to treat the neutropenia. The oral health assessment obtained information about oral health from the patients’ perspective regarding mouth sores, use of antibiotics, bleeding during brushing and pain. Dental history information such as frequency of regular dental care, prevention strategies, and treatment were asked.

**Dental and Radiographic Examination**

Dental examinations were conducted by one individual (MP). The examiner specifically documented any soft tissue disease, presence of ulcerations (active or healing), gingival health using the Löe-Silness gingival index (0 – absence of inflammation, 1 – mild inflammation with slight change in colour and little change in texture, 2 – moderate inflammation with moderate glazing, redness, edema, hypertrophy and bleeding on pressure, 3 – severe inflammation with marked redness, hypertrophy, tendency for spontaneous bleeding and ulceration), plaque and calculus levels (0 – no plaque or calculus, 1 – mild plaque ± calculus with tooth appearing clean but plaque removed from gingival third, 2 – moderate plaque ± calculus with deposits visible to naked eye, 3 – heavy plaque ± calculus with material filling the niche between the gingival margin and tooth surface), pathological tooth mobility > 1 mm in a buccal-lingual direction, teeth with dysplastic features, congenitally missing, recession, extracted and signs of premature or delayed exfoliation of primary and permanent teeth (Löe and Silness 1963). Dental caries and restoration history were measured using dmft-DMFT (decayed, missing or filled teeth; lowercase letters for primary teeth, uppercase for permanent teeth) scores. Congenitally missing or exfoliated primary teeth did not contribute to the dmft or DMFT score. The dmft and DMFT scores change as a patient ages with exfoliation of primary teeth and eruption of permanent teeth.
Raw dmft and DMFT scores were divided respectively by total number of primary and permanent teeth present in the oral cavity providing dmft/t and DMFT/T scores (Ho et al. 2007).

No periodontal probing depth values were obtained as the administration of antibiotics for the dental examination was deemed to be an exclusion factor regarding participation of patients with neutropenia, while those patients diagnosed with aplastic anemia were often suffering from thrombocytopenia.

Radiographic examination was performed using the ‘as low as reasonably achievable’ (ALARA) principle. For the neutropenia group, if no dental radiographs were taken within the past 6 months, new ones were obtained by one individual (MP). If radiographs were taken within the last 6 months, consent was obtained to acquire copies of the most recent radiographs from their dentist. In 2 instances the patients did not co-operate and radiographs were not taken. Healthy control patients, as part of their new patient appointment or recall schedule had radiographs taken by undergraduate dental students and these were used in lieu of taking new radiographs. Radiographs were assessed by one individual (MP) for level of periodontal bone height, periapical/furcation patholosis, dental caries, restorations, missing teeth and if possible presence/absence of succedaneous teeth.

**Data Analysis**

Data were compiled and analyzed using SPSS® 15.0 for Windows®. Differences between means were assessed using Student’s t-test. Fisher’s Exact tests and Chi-squared tests were used to assess differences in proportions. Mantel-Haenszel Odds Ratios (OR) and 95% confidence intervals (CI) were calculated. Results were considered significant if \( p < 0.05 \).
RESULTS

A total of 41 subjects (24 males, 17 females) participated in this study. There were 15 patients in the neutropenia group (11 males, 4 females) with a mean age of 12.14 ± 4.04 (SD) years. There were 26 patients in the healthy control group (13 males, 13 females) with a mean age of 11.61 ± 3.82(SD) years. The neutropenic group included 8 patients with acquired aplastic anemia, 3 patients with unclassified idiopathic neutropenia, 2 patients with Shwachman-Diamond syndrome, 1 patient with chronic neutropenia and 1 patient with cyclic neutropenia. The mean ANC for the neutropenia group was 1.83 ± 1.96SD x 10^9 cells/ml. Based upon the ANC, the neutropenic group had 6 patients that were considered to have normal a normal ANC, 1 patient with mild neutropenia, 7 patients with moderate neutropenia and 1 patient with severe neutropenia. Fifty three percent of the neutropenic patients responded to the survey/study and at the time of the study were treated with G-CSF or had been treated with this agent in the past. Eight patients with neutropenia were treated with G-CSF, 7 were treated with steroids and 2 were treated immunoglobulins (table 2).

Dental History

None of the patients from either group complained of pain (spontaneous, thermally induced pain such as that associated with drinking cold and/or hot as well as pain with chewing). 5 of the 15 patients with neutropenia compared to 3 of the 26 from the control group had visited a paediatric dentist over the past 2 years. This difference was not statistically significant ($p<0.12$). None of participants from the neutropenia or control group visited a periodontist. There was no significant difference in the frequency of dental visits when comparing the 2 groups of patients. The most frequently reported interval between recall visits for patients who did visit a dentist was 6 months (table 3).
There were significant differences in the incidence of mouth sores/ulcerations such that 8 of the 15 patients with neutropenia reported having mouth ulcers while 3 of the 26 control patients reported mouth sores/ulcerations (OR 8.76, 95% CI 1.82–42.27, $p<0.008$). Eleven of the 15 patients with neutropenia reported bleeding gingival tissues with brushing as compared to 5 of the 26 patients in the control group (OR 11.55, 95% CI 2.57–51.95, $p<0.001$) (table 4).

None of the participants in the neutropenia and control groups had been treated with an antibiotic mouth rinse or any form of supplemental fluoride for the prevention of dental caries. Three of the 15 patients with neutropenia were given antibiotics for treatment of a dental problem while only 1 of the 26 control patients were treated with antibiotics. However, these differences were not statistically significant ($p<0.13$). There were no antibiotics given for any periodontal infection for either the neutropenia or control group. No significant differences were found with respect the reasons for tooth extractions ($p<0.11$). None of the patients from the neutropenia and control group had any form of gum surgery (table 4).

**Soft Tissue Findings**

Upon clinical examination, neither the neutopenic or control group participants presented with soft tissue disease. None of the patients had measurable recession on first permanent molars, or any tooth. None of the patients had active and/or healing ulcerations. There was no significant difference noted in the degree of gingival inflammation, plaque or calculus levels in either group (table 5).

**Hard Tissue Findings**

One of the 15 patients with neutropenia had pathological tooth mobility while no pathological tooth mobility was found in patients from the control group ($p<0.37$). Similarly, there were no
differences in the periodontal bone levels assessed in the radiographs when both groups were compared ($p<0.13$). A sample of the radiographs from a patient with neutropenia and a control patient can be seen in Figure 1. A statistically significant difference was found with the dmft/t, but unexpectedly, it was actually higher in the control group (0.30±0.31) compared to the patients with neutropenia (0.06±0.11) ($p<0.017$). There was no significant difference in the DMFT/T scores between the 2 groups ($p<0.27$) (table 6).
Table 2. Demographics, diagnosis and medical intervention, neutropenia vs. controls

<table>
<thead>
<tr>
<th></th>
<th>Neutropenia (N = 15)</th>
<th>Control (N = 26)</th>
<th>t-tests, p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age and standard deviation in years</td>
<td>12.14 ± 4.04</td>
<td>11.61 ± 3.82</td>
<td>0.41, 0.68*</td>
</tr>
<tr>
<td>Male : Female ratio</td>
<td>2.75 : 1</td>
<td>1 : 1</td>
<td>0.14†</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>53.33% (8)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Unclassified idiopathic</td>
<td>20% (3)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td>13.34% (2)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Chronic neutropenia</td>
<td>6.67% (1)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Cyclic neutropenia</td>
<td>6.67% (1)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Mean absolute neutrophil count (x 10^9 cells/ml)</td>
<td>1.83 ± 1.96</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Severity of neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal &gt;1.5 x 10^9 cells/ml</td>
<td>40% (6)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Mild 1.0- &lt; 1.5 x 10^9 cells/ml</td>
<td>6.67% (1)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Moderate 0.5 - &lt;1.0 x 10^9 cells/ml</td>
<td>46.67% (7)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Severe &lt;0.5 x 10^9 cells/ml</td>
<td>6.67% (1)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Current or previous medical intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor</td>
<td>53.33% (8)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>46.67% (7)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>13.34% (2)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

* t-tests obtained using Student’s t-test, equal variances assumed

† p-value obtained from Fisher’s Exact test
Table 3. Dental history: dental providers and frequency of dental appointments, neutropenia vs controls

<table>
<thead>
<tr>
<th></th>
<th>Neutropenia (N = 15)</th>
<th>Control (N = 26)</th>
<th>p-values</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have pain (spontaneous, drinking cold liquids, hot liquids and/or chewing)?</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has ever been to a pediatric dentist?</td>
<td>33.33% (5)</td>
<td>11.54% (3)</td>
<td>0.12*</td>
<td>3.83 (0.76 – 19.22)‡</td>
</tr>
<tr>
<td>Has ever been to a periodontist?</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of dental appointments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every month</td>
<td>20% (3)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 3 months</td>
<td>0% (0)</td>
<td>3.85% (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 6 months</td>
<td>33.34% (5)</td>
<td>57.70% (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 9 months</td>
<td>13.34% (2)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 12 months</td>
<td>13.34% (2)</td>
<td>19.23% (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 24 months</td>
<td>0% (0)</td>
<td>11.54% (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never been to dentist</td>
<td>6.67% (1)</td>
<td>7.70% (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not answered</td>
<td>13.34% (2)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p-values obtained using Fisher’s Exact test
† p-value obtained using Chi-squared test
‡ Mantel-Haenszel odds ratio (OR) and 95% confidence (CI)
**Table 4.** Dental history: oral health assessment prevention and intervention strategies, neutropenia vs. controls

<table>
<thead>
<tr>
<th></th>
<th>Neutropenia (N = 15)</th>
<th>Control (N = 26)</th>
<th>p-values</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Do you get mouth sores?</strong></td>
<td>53.34% (8)</td>
<td>11.54% (3)</td>
<td>0.008*</td>
<td>8.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.82 – 42.27)‡</td>
</tr>
<tr>
<td><strong>Do your gums bleed when brushing?</strong></td>
<td>73.34% (11)</td>
<td>19.23% (5)</td>
<td>0.001*</td>
<td>11.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2.57 – 51.95)‡</td>
</tr>
<tr>
<td><strong>Dental prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic mouth rinse</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoride rinse, tablets, supplements</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dental intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics given for dentally related reason</td>
<td>20% (3)</td>
<td>3.85% (1)</td>
<td>0.13*</td>
<td>6.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.59 – 66.56)‡</td>
</tr>
<tr>
<td>Periodontal infection</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endodontic/periapical infection</td>
<td>6.67% (1)</td>
<td>3.85% (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis prior to extractions</td>
<td>13.34% (2)</td>
<td>0% (0)</td>
<td>0.11*</td>
<td>3.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.82 – 11.78)‡</td>
</tr>
<tr>
<td>Tooth extractions</td>
<td>53.34% (8)</td>
<td>26.93% (7)</td>
<td>0.11*</td>
<td></td>
</tr>
<tr>
<td>Decayed/cavities</td>
<td>13.34% (2)</td>
<td>15.39% (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loose</td>
<td>6.67% (1)</td>
<td>3.85% (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crowding</td>
<td>33.34% (5)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisdom teeth</td>
<td>0% (0)</td>
<td>3.85% (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0% (0)</td>
<td>7.69% (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gum surgery</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p-values obtained using Fisher’s Exact test

† Mantel-Haenszel odds ratio (OR) and 95% confidence (CI)
Table 5. Soft tissue findings from the dental examination, neutropenia vs controls

<table>
<thead>
<tr>
<th></th>
<th>Neutropenia (N = 15)</th>
<th>Control (N = 26)</th>
<th>p-values</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ulcerations present</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recession noted on</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>permanent first molars</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gingival health: level of inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>40% (6)</td>
<td>23.08% (6)</td>
<td>0.08†</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.20 – 4.95)†</td>
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<tr>
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<td></td>
<td>3.17</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.74 – 13.60)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.03 – 4.19)†</td>
</tr>
<tr>
<td>Mild</td>
<td>40% (6)</td>
<td>73.08% (19)</td>
<td>0.15*</td>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>0.09*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Moderate</td>
<td>20% (3)</td>
<td>3.85% (1)</td>
<td>0.58*</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque and calculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No plaque or calculus</td>
<td>20% (3)</td>
<td>3.85% (1)</td>
<td>0.08†</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.04 – 24.55)†</td>
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<td></td>
<td>8.25</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>(0.74 – 91.26)†</td>
</tr>
<tr>
<td>Minimal plaque and</td>
<td>53.34% (8)</td>
<td>84.62% (22)</td>
<td>0.09*</td>
<td></td>
</tr>
<tr>
<td>calculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate plaque and</td>
<td>26.67% (4)</td>
<td>11.54% (3)</td>
<td>1.00*</td>
<td></td>
</tr>
<tr>
<td>calculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy plaque and</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>calculus</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* p-values obtained using Fisher’s Exact test
† p-values obtained using Chi-squared test
‡ Mantel-Haenszel odds ratio (OR) and 95% confidence (CI)
**Table 6.** Hard tissue findings from the dental and radiographic examination, neutropenia vs controls

<table>
<thead>
<tr>
<th></th>
<th>Neutropenia (N = 15)</th>
<th>Control (N = 26)</th>
<th>t-tests, p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic tooth mobility</td>
<td>6.67% (1)</td>
<td>0% (0)</td>
<td>0.37*</td>
</tr>
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<td>Periodontal bone loss</td>
<td>15.39% (2/13)</td>
<td>0% (0)</td>
<td>0.13*</td>
</tr>
<tr>
<td>Primary dentition caries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dmft</td>
<td>0.63 ± 1.19</td>
<td>2.94 ± 3.16</td>
<td>-2.59, 0.017†</td>
</tr>
<tr>
<td>d.f. = 22</td>
<td>0.06 ± 0.11</td>
<td>0.30 ± 0.31</td>
<td>-2.88, 0.009†</td>
</tr>
<tr>
<td>dmft/t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent dentition caries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMFT</td>
<td>2.00 ± 2.96</td>
<td>2.58 ± 3.04</td>
<td>-0.59, 0.56‡</td>
</tr>
<tr>
<td>d.f. = 39</td>
<td>0.08 ± 0.11</td>
<td>0.12 ± 0.13</td>
<td>-1.10, 0.28‡</td>
</tr>
</tbody>
</table>

* p-values obtained using Fisher’s Exact test

† t-tests obtained using Student’s t-test, equal variances not assumed

‡ t-tests obtained using Student’s t-test, equal variances assumed
1a. Bitewing radiograph from a neutropenia patient

1b. Bitewing radiograph from a control patient

**Figure 2.** (a) Bitewing radiographs from a patient with neutropenia showing periodontal bone loss, dental caries noted on the primary mandibular left first and second molars. (b) Bitewing radiograph from a control patient showing no periodontal bone loss and dental restorations on the primary maxillary right first and second molars, primary mandibular left first and second molars, primary mandibular right first and second molars, permanent mandibular left first molar and permanent mandibular right first molar.
DISCUSSION

In this study, we have shown that patients with neutropenia had good oral health. Most were on a 6-month recall appointment schedule with a general dentist and were not part of any particular preventive program. This is contrary to many of the case reports that indicated the need for monthly appointments in conjunction with a comprehensive preventive program (e.g. monthly recalls, good oral hygiene, chlorhexidine rinse, iodine rinse, systemic antibiotics) as a means to prevent the progression of periodontal disease. In fact, of the patients in the neutropenia group, only 1 patient had a tooth extracted due to being loose (it was not infected). The 3 patients with neutropenia who reported monthly dental visits were being seen for orthodontic adjustment appointments. This is even more intriguing since it might have been expected that patients with a putative immune deficiency who are also undergoing orthodontic treatment necessitating the use of plaque-retaining appliances, would be at a higher than normal risk for periodontal disease and/or caries, and yet their attendance was only for management of the orthodontic condition, with no evidence for an increased incidence of inflammatory or infectious disease (Isaac and Tholouli 2008). Overall, the frequency of dental appointments in patients with neutropenia is similar to an earlier study that determined that 37.0% and 33.3% of patients with neutropenia visited their dentist every 6 months and 12 months respectively (Cheretakis et al. 2007).

Patients with neutropenia did report an increased frequency of mouth sores and gingival bleeding while brushing but clinical examination did not show any soft tissue disease or gingival recession. Patients with neutropenia are taught to be vigilant about maintaining good oral hygiene to prevent the development of oral diseases. They may have been more careful to note any incidences of bleeding gums and ulcerations and ‘programmed’ to report incidents of bleeding or ulceration with greater reliability than ‘healthy’ patients. In any case, the results from this questionnaire regarding the frequency of mouth sores (53.34%) and bleeding while
brushing (73.34%) was similar to that reported in a previous study where 65% and 58% of patients with Shwachman-Diamond syndrome reported ulcerations and gingival bleeding respectively (Ho et al. 2007).

Periodontal bone loss was assessed to reflect the cumulative effects of periodontal disease in the absence of performing periodontal probing depths and bleeding upon probing. Based on radiographic examination, differences in periodontal bone height could not be demonstrated when comparing the neutropenia and control group. This finding is similar to findings reported in other studies showing that there was no radiographic evidence of periodontal bone resorption (Tekcicek et al. 2007, Atkinson et al. 2008). Surprisingly, the dmft/t and DMFT/T scores for the neutropenia group were lower than the control group, but the difference was only statistically significant for the primary dentition (e.g. dmft/t). In another study focused on patients with Shwachman-Diamond syndrome, higher dmft and DMFT scores were noted as compared to controls (Ho et al. 2007). Yet in another study, it was shown that there was no significant difference in DMFS scores for patients with dyskeratosis congenita compared to controls (Atkinson et al. 2008). Higher dmft/t and DMFT/T scores found in the control participants collected from the Children’s Clinic, Faculty of Dentistry, University of Toronto (compared to the neutropenic patients) may have been due to an inherent bias and case selection. Many of these patients had been sent to the university because of their extensive caries history and so a further study might be improved by comparing patients with neutropenia with a sample of patients from the general population who are visiting general dentists in the community.

Another issue here could be related to the fact that although all patients in the study group had ‘neutropenia’, the etiological factors underlying their neutropenic states were different. Perhaps then, the presence of neutropenia alone does not convey homogeneity to the group, meaning that further study should focus on patients with a particular type of neutropenia or should be powered
to a level where patients with different types of neutropenia can be studied and compared to one another as well as controls.

Patients in the neutropenia group reported more frequent ulcerations and bleeding gums while brushing, while a one-time clinical examination of these patients could not confirm any such difference. However, if the differences do exist they could have been missed as a consequence of the sample size (which was not calculated on the basis of ulcerations for example) or due to the cyclic nature of the sores/ulcerations. This finding could also imply that the neutrophils produced in such patients are functionally different than those in the controls, but that is highly speculative. The patients in this investigation had not been diagnosed with aggressive periodontitis, had not been seen for monthly hygiene appointments, had not seen a periodontist, were not given special treatment recommendations (e.g. antibiotic mouth rinse, fluoride treatment) or had periodontal surgery. These findings are in complete opposition to data reported by others suggesting that patients with neutropenia (treated or not, presumably) should be placed under aggressive preventive and treatment regimens (Spencer and Fleming 1985, Dougherty and Gataletto 1995, Delcourt-Debruyne et al. 2000, Goultschin et al. 2000, Defraia and Marinelli 2001, Hakki et al. 2005).

Future studies could be done to increase the sample size through multi-centre studies to determine the validity of these results as all of the patients with neutropenia were being seen in the Marrow Failure and Myelodysplasia Program at SickKids. Microbiological testing for specific periodontal pathogens, salivary bacterial counts, periodontal probing and bleeding on probing could be done to aid in periodontal diagnosis. The activity of oral and peripheral neutrophils in the study populations could be assessed in addition to obtaining the ANC.
CONCLUSION

These data demonstrate that while patients being treated for neutropenia do report having frequent oral ulcerations and bleeding gums while brushing, a one-time clinical examination failed to demonstrate any difference in terms of overall oral and gingival health compared to healthy age matched controls. This finding is in contrast to the overall impression obtained from the cases and case series presented in the scientific literature that highlight cases of severe periodontitis in pediatric patients presenting with neutropenia. This is likely due to the fact that the cases presented are almost always newly diagnosed neutropenic patients who are not being successfully treated for their neutropenia. Hence, it would appear that patients who have been treated successfully for neutropenia (using G-CSF and other agents noted above) do not appear to have an increased risk of oral diseases.
CHAPTER FOUR

STUDY LIMITATIONS AND FUTURE DIRECTION
STUDY LIMITATIONS

Limitations of this study include the small sample size for the neutropenia group due to the rarity of the condition and variation in the etiology of neutropenia as each have different manifestations and severity of neutropenia. Many of the congenital forms of neutropenia are autosomal recessive, as such the gender distribution was anticipated to be a 1 : 1 ratio, however, the gender distribution was non-optimized as there was almost a 3 : 1 ratio heavily favouring males for the neutropenia group. There is no mention of unequal gender distribution in the literature to date. Observer bias could have affected the results of the clinical and radiographic evaluation as the principal investigator (MP) was not blinded to the health status of each study participant. A one time examination was completed which may not represent the true oral health status of children with neutropenia. Participants in the neutropenia group were aware in advance of the clinical examination and may have improved their oral hygiene practices prior to their appointment. In retrospect, having the radiographs evaluated by a blinded examiner could have given the results from the periodontal bone height more validity.

FUTURE DIRECTION

Increasing the sample size through a collaboration between multiple healthcare centres to give researchers a better idea of oral health status of children undergoing treatment for neutropenia would be the first priority. Smoking history was included in the patient questionnaire but was not reported as all patients from the neutropenia and control group reported to have never smoked. Future studies should remove smoking history in the child patient questionnaire but leave that in the adult questionnaire as there is a possibility they may have started to smoke. Neutrophil function of each patient in the neutropenia group could be investigated to determine ability to kill
the microbial pathogens rather than relying on the neutrophil counts. Children with neutropenia attending The Hospital for Sick Children dental clinic who have already been given antibiotics for their scaling and cleaning appointment could have other diagnostic tests (e.g. periodontal probing and bleeding upon probing) performed to aid in determining a periodontal diagnosis. During the course of the study, a number of the participants from the neutropenia group were in active orthodontic treatment, while other patients inquired about the possibility of starting orthodontic treatment. Concerns were raised as to the possibility of increased gingival inflammation and irritation of the mucosa due to the brackets and wires which will retain plaque and debris and make daily oral care more difficult. A future study could be comparing the periodontal health of patients with neutropenia to controls while under active orthodontic care.
CHAPTER 5
THESIS SUMMARY
THESIS SUMMARY

Neutropenia due to a variety of congenital or acquired defects are susceptible to infections anywhere in their body. The oral cavity is constantly exposed to bacteria and our knowledge on the oral health status of children with neutropenia are compiled mainly from case reports and series indicating they suffer from aggressive periodontal disease, ulcerations, tooth loss and dental caries. Our study shows that patients under the active care of haematologists do report frequent oral ulcerations and bleeding gums, but a one time clinical examination of these patients showed no difference in their oral and gingival health compared to healthy controls.
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APPENDICES
Appendix A

Assent Form – Hospital for Sick Children
**Title of Research Project**

Oral Disease Prevalence in Neutropenia

**Investigators**

Michael Park (416) 978-6685  
Michael Glogauer (416) 978-6685  
Yigal Dror (416) 813-5630

**Why are we doing this study?**

Infections in the teeth and the mouth often cause pain and make you feel uncomfortable. At this time, doctors and dentists need to know if people with neutropenia get these unpleasant infections more times than most people. In our study, we try to compare how healthy your mouth is compared to your brother/sister who does not have neutropenia. We would be very happy and thankful if you can help us to find the answers.

**What will happen during the study?**

During your visit to the Hematology Clinic at the hospital you will be seen by Dr. Park for a check-up and we may need to take x-rays of your teeth to make sure that your teeth are okay. If you have a dentist that you regularly see that is okay. We would still like to check your mouth and get copies of the last set of teeth x-rays from your dentist if they were taken within the last six months. We would also like to look through your chart here at the hospital to look at what medicines you have taken and the level of white blood cells prior to your dental check-up.

**Are there good things and bad things about the study?**

The good thing about this study is that we can help doctors and dentists learn more about the health of the teeth and mouth in people with neutropenia. Being a part of this study will take up some of your time.

**Who will know about what I did in the study?**

No one will know about what you did in the study. If we feel your health may be in danger, we may have to tell your doctor about your results.

**Can I decide if I want to be in the study?**

Yes. Only you can decide if you want to be in this study. Even after you start, you can change your mind and decide not to finish your part of the study. We are discussing the study with your parents and you should talk to them about it too.

**Assent**

“I was present when _______________________________ read this form and gave his/her verbal assent.”

Name of person who obtained assent  (usually parent)  Signature/Date
Appendix B

Assent Form – University of Toronto
ASSENT FORM

Assent Form Version Date  02.01.2008

• Title of Research Project
Oral Disease Prevalence in Neutropenia

• Investigators
  Michael Park (416) 978-6841
  Michael Glogauer (416) 978-0163
  Yigal Dror (416) 813-5630

• Why are we doing this study?
Infections in the teeth and the mouth often cause pain and make you feel uncomfortable. At this time, doctors and dentists need to know if people with neutropenia (low white blood cells) get these unpleasant infections more times than most people. In our study, we try to compare how healthy your mouth is compared to someone who has neutropenia. We would be very happy and thankful if you can help us to find the answers.

• What will happen during the study?
During your visit to the Faculty of Dentistry, University of Toronto, you will be seen by Dr. Park for a check-up and we may need to take x-rays of your teeth to make sure that your teeth are okay.

• Are there good things and bad things about the study?
The good thing about this study is that we can help doctors and dentists learn more about the health of the teeth and mouth in people with neutropenia.

• Who will know about what I did in the study?
No one will know about what you did in the study.

• Can I decide if I want to be in the study?
Yes. Only you can decide if you want to be in this study. Even after you start, you can change your mind and decide not to finish your part of the study. We are discussing the study with your parents and you should talk to them about it too.

• Questions about the study
If you have any more questions about the study, please feel free to call Dr. Michael Park at (416) 978-6841.
If you have questions about your rights as a research participant, please contact Jill Parsons, Health Sciences Ethics Review Officer, Ethics Review Office, University of Toronto, at telephone (416) 946-5806 or by email: jc.parsons@utoronto.ca.

• Assent
"I was present when ___________________________ read this form and gave his/her verbal assent."

______________________________  ____________________________
Name of person who obtained assent  Signature/Date
(usually parent)

Name: 
Date of Birth: 
Patient #:
Appendix C

Consent Form – Hospital for Sick Children
Title of Research Project:
Oral Disease Prevalence in Neutropenia

Investigators:
Michael Park (416) 978-6685
Michael Glogauer (416) 978-6685
Yigal Dror (416) 813-5630

Purpose of the Research
The most common infectious diseases of man are oral diseases related to teeth. Certain population groups especially those with systemic health conditions are often at significantly higher risk of developing oral disease. However, the burden of oral disease in neutropenia is currently not well understood. The recognition of the oral health providers associated with neutropenia will enable the education of oral healthcare providers, and assist the implementation of preventive treatment regimens and treatment standards for neutropenia patients. This survey will focus on the extent and severity of oral diseases in neutropenia patients as this area has not been studied in any detail.

Description of the Research
During your visit to the Hematology Clinic at the hospital you will be seen by Dr. Park for a check-up. At that time, we may need to take intra oral x-rays to ensure no cavities are present. If your child regularly sees a dentist, the check-up will not interfere with your own dentist's schedule. We would like to contact your dentist and with your permission, obtain copies of the last set of intra oral x-rays, if they were taken within the last six months. Our goal is not to take your child away from their dentist, but to help in ensuring that your child’s oral health needs are being met. If there are any treatment needs, you are more than welcome to go back to your dentist for treatment at their office. If you would like treatment to be done at the dental clinic at the hospital, this can be arranged. Please be aware that dentistry is not an OHIP covered benefit and any treatment (eg. x-rays, cleanings, fillings, extractions, etc…) would have to be paid for, just like in a private dental office.

We would also like to look through your child's medical records to determine what medications you have taken and as well record the white blood cell count and neutrophil count in an attempt to correlate these results to your response in the survey and dental check-up.

If changes are made to the study or new information that might affect your (your child's) willingness to continue to participate in the research becomes available, you will be informed.

Potential Harms Injuries, Discomforts or Inconvenience
There are no known harms associated with participation in this study. A time commitment is required to participate in this research.

Potential Benefits
You (your child) will receive an oral health assessment from participating in this study.
Confidentiality
All information will be strictly private and confidential. Your samples will be number coded at the time of collection and laboratory personnel will be blinded to the patient source. Only the principal researchers involved in this project will have access to the data gathered during the course of this study which will be stored in a locked location and destroyed after the completion of the study. Confidentiality will be respected and no information that discloses the identity of any subject will be released or published without consent unless required by law. For your information, the research consent form will be inserted in the patient health record.

Participation
Participation in research is voluntary. If you choose to participate in this study you can withdraw from the study at any time. You will continue to have access to quality care at HSC. Your participation may contribute to the creation of new diagnostic tests, new medicines or other events that may have commercial value. However, your participation in this study will not entitle you to a share in any future economic benefits.
A copy of the consent form will be provided for you to keep.

Consent
“By signing this form, I agree that:
1) The study has been explained to me. All my questions were answered.
2) The possible harms and discomforts and the possible benefits (if any) of this study have been explained to me.
3) I know about the alternatives to taking part in this study. I understand that I have the right not to participate and the right to stop at any time. The decision about whether or not to participate will not affect my health care at the Hospital for Sick Children.
4) I am free now, and in the future, to ask any questions about the study.
5) I have been told that all information about me will be kept confidential, except where release of information is required by law.
6) I understand that no information that would identify me will be released or printed without asking me first.”

I hereby consent to participate.

The Person who may be contacted about the research is:
Dr. Michael Park
who may be reached at telephone #
416 978-6685

Name of Patient and Age

Signature (if 16 yrs. or over)

Date
Appendix D

Consent Form – University of Toronto
RESEARCH CONSENT FORM

Consent Form Version Date  02.02.2008

Title of Research Project:
Oral Disease Prevalence in Neutropenia

Investigators:
Michael Park (416) 978-6841
Michael Glogauer (416) 978-0163
Yigal Dror (416) 813-5630

Purpose of the Research
The most common infectious diseases of man are oral diseases related to teeth. Certain population
groups especially those with systemic health conditions are often at significantly higher risk of
developing oral disease. However, the burden of oral disease in neutropenia (low white blood cells) is
currently not well understood. The recognition of the oral health providers associated with
neutropenia will enable the education of oral healthcare providers, and assist the implementation of
preventive treatment regimens and treatment standards for neutropenia patients. This survey will
focus on the extent and severity of oral diseases in neutropenia patients as this area has not been
studied in any detail.

Description of the Research
During your visit to the Faculty of Dentistry, University of Toronto, you will be seen by Dr. Park for a
check-up. At that time, we may need to take intra oral x-rays to ensure no cavities are present.

If changes are made to the study or new information that might affect your (your child’s) willingness to
continue to participate in the research becomes available, you will be informed.

Potential Harms Injuries, Discomforts or Inconvenience
There are no known harms associated with participation in this study.

Potential Benefits
There are no potential benefits to your child for participating in this study.

Confidentiality
All information will be strictly private and confidential. Only the principal researchers involved in this
project will have access to the data gathered during the course of this study which will be stored in a
locked location and stored for 10 years after completion of the study. Confidentiality will be respected
and no information that discloses the identity of any subject will be released or published without
consent unless required by law. For your information, the research consent form will be inserted in
the patient health record.

Participation
Participation in research is voluntary. If you choose to participate in this study you can withdraw from
the study at any time. You will continue to have access to quality care at HSC. Your participation may
contribute to the creation of new diagnostic tests, new medicines or other events that may have
commercial value. However, your participation in this study will not entitle you to a share in any future
economic benefits.
A copy of the consent form will be provided for you to keep.
Questions about the study
If you have any more questions about the study, please feel free to call Dr. Michael Park at (416) 978-6841.
If you have questions about your rights as a research participant, please contact Jill Parsons, Health Sciences Ethics Review Officer, Ethics Review Office, University of Toronto, at telephone (416) 946-5806 or by email: jc.parsons@utoronto.ca.

Consent
"By signing this form, I agree that:
1. The study has been explained to me. All my questions were answered.
2. The possible harms and discomforts and the possible benefits (if any) of this study have been explained to me.
3. I know about the alternatives to taking part in this study. I understand that I have the right not to participate and the right to stop at any time. The decision about whether or not to participate will not affect my health care at the Faculty of Dentistry, University of Toronto.
4. I am free now, and in the future, to ask any questions about the study.
5. I have been told that all information about me will be kept confidential, except where release of information is required by law.
6. I understand that no information that would identify me will be released or printed without asking me first."

I hereby consent to participate.                                    The Person who may be contacted about the research is:

__________________________________________                        Dr. Michael Park
Name of Patient and Age

__________________________________________                        who may be reached at telephone 
Signature (parent)                                                 #

__________________________________________                        416 978-6841
Date
Appendix E

Patient Questionnaire – Hospital for Sick Children

Under 16 years of age
Thanks for agreeing to help us with our study!

We are asking for your participation on behalf of your child in a research study. The purpose of this form is to give you information that will allow you to decide if you would like your child to be a part of this study.

**Purpose & Benefits of the Study**

Health care professionals need to know more about the oral health care problems associated with neutropenia. It is known that neutropenic patients (patients with low levels of the infection fighting blood cells) are prone to bacterial infections, however the nature and severity of the oral infections for this population has not been thoroughly studied. Due to the wide-spread distribution of neutropenic patients, we are using a questionnaire approach which will rely upon you to fill out, a clinical and radiographic (x-ray) will be taken during your visit to the Dentistry clinic at HSC. Using the results of this study we hope to further our understanding of the oral effects of neutropenia and also to look at the effects that this disease has on normal oral function and the resulting effects on the quality of life, examination. Duplicates of the most recent radiographs will be needed (within 6 months) or radiographs

We have enclosed a questionnaire (blue set) for you to fill out. You are expected to return the completed questionnaire during your visit at the Dentistry clinic at HSC. Otherwise, it would be very helpful if you could collect all the completed questionnaires (from both siblings) and send them all in at the same time in the provided envelop. Alternatively, non-neutropenic sibling’s package can be mailed separately and directly to the address below. To achieve the best possible scientific results, the more information we can gather, the better the survey will be. Your participation will be greatly appreciated. However, should you have difficulty providing some of the requested information, please feel free to submit an incomplete package.

- Answer as **honestly** as you can. All answers are **private**; no one you know will see them.
- All questionnaires are to be filled in anonymously and will be coded without any personal identification.
- Read each question **carefully**.
- Put an ✜ in the box for the answer that is best for you.

Please return questionnaires to:

Michael Park D.D.S.  
Faculty of Dentistry, University of Toronto  
Room 221 Fitzgerald Building,  
150 College Street, Toronto, Ontario, M5S 3E2 CANADA  
e-mail: michael.park@utoronto.ca
# CHILD ORAL HEALTH QUESTIONNAIRE

## General Patient Information

<table>
<thead>
<tr>
<th>Name: __________________________ (optional)</th>
<th>Race:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Date: _____/<strong><strong>/</strong></strong> (DD/MM/YY)</td>
<td>☐ Caucasian  ☐ Black  ☐ Asian  ☐ Native Indian  ☐ Hispanic  ☐ Other  Specify: __________________________</td>
</tr>
<tr>
<td>Height: ________ kg</td>
<td></td>
</tr>
<tr>
<td>Weight: ________ cm</td>
<td></td>
</tr>
<tr>
<td>Gender:</td>
<td>☐ Male  ☐ Female</td>
</tr>
<tr>
<td>Number of siblings ________</td>
<td>Has your child been diagnosed with Neutropenia?  ☐ Yes  ☐ No</td>
</tr>
<tr>
<td>Number of siblings who have been diagnosed with Neutropenia ________</td>
<td>If yes, what type is it?  ☐ Severe congenital  ☐ Cyclic  ☐ Idiopathic  ☐ Other  Specify: __________________________</td>
</tr>
</tbody>
</table>

## Diet

<p>| Does your child chew sugarless gum? | Does your child have a dietitian?  ☐ Yes  ☐ No |</p>
<table>
<thead>
<tr>
<th>☐ Yes  ☐ No</th>
<th>On any special diet?  ☐ Yes  ☐ No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your child use sugar substitutes?</td>
<td>If yes, for what reason?  ____________________________________________</td>
</tr>
<tr>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
</tbody>
</table>

---

144
### Medication History

Is your child currently or has he/she ever undergone growth factor therapy?  
☐ Yes  ☐ No  ☐ Don’t know

If so, please list growth colony stimulating factor (G-CSF) with start dates, stop dates and date of last dosage adjustment.

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Past</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others:</td>
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</tr>
</tbody>
</table>

**Other medications:**

- Steroids:  
- Gamma Globulin:  
- Antacids/H2 blockers:  
- Other, Specify:  
- Other, Specify:  
- Other, Specify:  

**Bone Marrow Transplant Date:**  ____/____/____ (DD/MM/YY)

Does your child smoke?  
☐ Yes  ☐ No

If yes, please indicate number of years he/she has smoked and the average number of packs per day?

______ number of years  ______ average packs of cigarettes per day

Does the medical doctor stress the importance of oral health and oral hygiene?  
☐ Yes  ☐ No

### Oral Health Assessment

Does your child get mouth sores?  
☐ Yes  ☐ No

If yes, where?

<table>
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<tr>
<th></th>
<th>&lt; 1× per year</th>
<th>1-2× per year</th>
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</tr>
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<td>☐ Other</td>
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☐ Yes  ☐ No
### Oral Health Assessment (Continued)

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### Dental History

<table>
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Dental History (Continued)

Has the dentist prescribed any of the following that your child use everyday or frequently?

Please specify:

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<th>Product</th>
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<td></td>
</tr>
<tr>
<td>Fluoride tablets/supplements</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please answer the following questions to the best of your ability.

Has a dentist pulled / extracted any of your child's teeth?

Yes  No

If yes, how many?

Reasons (if known):

- Wisdom teeth
- Tooth crowding
- Loose
- Decay / Cavity

Other reasons:

Has your child lost any adult (permanent) teeth?

Yes  No

Are your child's gums inflamed / swollen frequently?

Yes  No

Are any of the adult teeth loose?

Yes  No

Are the gums shrinking?

Yes  No

What types of dental treatment has your child undergone?

- Gum surgery
- Root Canals
- Tooth Extraction (pulling out tooth)
- Teeth Cleaning (polishing during recall visits)
- Scaling (deep tooth cleaning)
- Fillings (including crowns / caps)

Yes  No  Don't know

Has your child seen any of the following dental specialists?

- Periodontist (gum specialist)
- Oral Surgeon (specialist for wisdom teeth extraction & jaw surgery)
- Orthodontist (specialist for alignment of teeth with braces)
- Oral Pathologist (specialist for investigation of oral disease)
- Endodontist (root canal specialist)
- Pediatric dentist (specialist for children and special needs)

Yes  No  Don't know

If so, for what reason?

____________________________________________________________________
Appendix F

Patient Questionnaire – University of Toronto

Under 16 years of age
Thanks for agreeing to help us with our study!

We are asking for your participation on behalf of your child in a research study. The purpose of this form is to give you information that will allow you to decide if you would like your child to be a part of this study.

**Purpose & Benefits of the Study**

It is known that neutropenic patients (patients with low levels of the infection fighting blood cells) are prone to bacterial infections, however the nature and severity of the oral infections for this population has not been thoroughly studied. Your participation is important as we are using your results from this questionnaire to compare them with patients with neutropenia to further our understanding of the oral effects of neutropenia and also to look at the effects that this disease has on normal oral function and the resulting effects on the quality of life.

A clinical and radiographic (x-ray) examination will be taken during your visit to the Faculty of Dentistry, University of Toronto. We have enclosed a questionnaire for you to fill out. To achieve the best possible scientific results, the more information we can gather, the better the survey will be. Your participation will be greatly appreciated. However, should you have difficulty providing some of the requested information, please feel free to submit an incomplete package.

- Answer as honestly as you can. All answers are private; no one you know will see them.
- All questionnaires are to be filled in anonymously and will be coded without any personal identification.
- Read each question carefully.
- Put an ☒ in the box for the answer that is best for you.

Please return questionnaires to:

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**CHILD ORAL HEALTH QUESTIONNAIRE**

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<tr>
<th>General Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>
| Name: ______________________ (optional) | Race:  
| Birth Date: ____/____/____ (DD/MM/YY) | □ Caucasian  
| Height: _______ cm | □ Black  
| Weight: ________ kg | □ Asian  
| Gender:  
| □ Male  
| □ Female | □ Native Indian  
| | □ Hispanic  
| | □ Other  
| Specify: __________________________ | Specify: __________________________ |

| Number of siblings _______  
| Number of siblings who have been diagnosed with Neutropenia _______  
| Has your child been diagnosed with Neutropenia? | □ Yes  
| | □ No  
| If yes, what type is it?  
| □ Severe congenital  
| □ Cyclic  
| □ Idiopathic  
| □ Other  
| Specify: __________________________ |

<table>
<thead>
<tr>
<th>Diet</th>
</tr>
</thead>
</table>
| Does your child chew sugarless gum? | Does your child have a dietitian? | □ Yes  
| □ Yes  
| | □ No  
| Does your child use sugar substitutes? | On any special diet?  
| □ Yes | □ Yes  
| □ No  
| If yes, for what reason? | □ No  
| | __________________________ |
### Medication History

Is your child currently or has he/she ever undergone growth factor therapy?  
☐ Yes  ☐ No  ☐ Don’t know

If so, please list growth colony stimulating factor (G-CSF) with start dates, stop dates and date of last dosage adjustment.

**G-CSF:** ______________________________________________________

**Others:** ______________________________________________________

**Others:** ______________________________________________________

<table>
<thead>
<tr>
<th>Other medications:</th>
<th>None</th>
<th>Past</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Gamma Globulin:</td>
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</tbody>
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**Bone Marrow Transplant**  
☐ Yes Date: _____/_____/____ (DD/MM/YY)  ☐ No

**Does your child smoke?**  
☐ Yes  ☐ No

If yes, please indicate number of years he/she has smoked and the average number of packs per day?

______ number of years  ______ average packs of cigarettes per day

**Does the medical doctor stress the importance of oral health and oral hygiene?**  
☐ Yes  ☐ No

### Oral Health Assessment

**Does your child get mouth sores?**  
☐ Yes  ☐ No

If yes, where?

<table>
<thead>
<tr>
<th>And how often?</th>
<th>&lt; 1× per year</th>
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<td>☐</td>
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</tr>
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<td>☐</td>
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*Please answer the following questions to the best you can.*

Has a dentist pulled / extracted any of your child's teeth? □ Yes □ No

If yes, how many? ____________________________

Reasons (if known)?

- Wisdom teeth
- Tooth crowding
- Loose
- Decay / Cavity
- Other reasons: ____________________________

Has your child lost any adult (permanent) teeth? □ Yes □ No

Are your child's gums inflamed / swollen frequently? □ Yes □ No

Are any of the adult teeth loose? □ Yes □ No

Are the gums shrinking? □ Yes □ No

What types of dental treatment has your child undergone?

- Gum surgery □ Yes □ No □ Don't know
- Root Canals □ Yes □ No □ Don’t know
- Tooth Extraction (pulling out tooth) □ Yes □ No □ Don’t know
- Teeth Cleaning (polishing during recall visits) □ Yes □ No □ Don’t know
- Scaling (deep tooth cleaning) □ Yes □ No □ Don’t know
- Fillings (including crowns / caps) □ Yes □ No □ Don’t know

Has your child seen any of the following dental specialists?

- Periodontist (gum specialist) □ Yes □ No □ Don’t know
- Oral Surgeon (specialist for wisdom teeth extraction & jaw surgery) □ Yes □ No □ Don’t know
- Orthodontist (specialist for alignment of teeth with braces) □ Yes □ No □ Don’t know
- Oral Pathologist (specialist for investigation of oral disease) □ Yes □ No □ Don’t know
- Endodontist (root canal specialist) □ Yes □ No □ Don’t know
- Pediatric dentist (specialist for children and special needs) □ Yes □ No □ Don’t know

If so, for what reason? ____________________________________
Appendix G

Patient Questionnaire – Hospital for Sick Children

Over 16 years of age
Thanks for agreeing to help us with our study!

We are asking for your participation in a research study. The purpose of this form is to give you information that will allow you to decide if you would like to be a part of this study.

**Purpose & Benefits of the Study**

Health care professionals need to know more about the oral health care problems associated with neutropenia. It is known that neutropenic patients (patients with low levels of the infection fighting blood cells) are prone to bacterial infections, however the nature and severity of the oral infections for this population has not been thoroughly studied. Due to the wide-spread distribution of neutropenic patients, we are using a questionnaire approach which will rely upon you to fill out, a clinical and radiographic (x-ray) examination. Duplicates of the most recent radiographs will be needed (within 6 months) or radiographs will be taken during your visit to the Dentistry clinic at HSC. Using the results of this study we hope to further our understanding of the oral effects of neutropenia and also to look at the effects that this disease has on normal oral function and the resulting effects on the quality of life.

We have enclosed a questionnaire (blue set) for you to fill out. You are expected to return your completed questionnaire during your visit at the Dentistry clinic at HSC. Otherwise, it would be very helpful if you could collect the completed questionnaire from your sibling and send it in at the same time as you send in your questionnaire in the provided envelop. Alternatively, your sibling’s package can also be mailed separately and directly to the address below. To achieve the best possible scientific results, the more information we can gather, the better the survey will be. Your participation will be greatly appreciated. However, should you have difficulty providing some of the requested information, please feel free to submit an incomplete package.

- Answer as **honestly** as you can. All answers are **private**; no one you know will see them.
- All questionnaires are to be filled in anonymously and will be coded without any personal identification
- Read each question **carefully**
- Put an ☐ in the box for the answer that is best for you

Please return questionnaires to:

Michael Park D.D.S.
Faculty of Dentistry, University of Toronto
Room 221 Fitzgerald Building,
150 College Street, Toronto,
Ontario, M5S 3E2
CANADA

e-mail: michael.park@utoronto.ca
# ADULT ORAL HEALTH QUESTIONNAIRE

## General Patient Information

<table>
<thead>
<tr>
<th>Name: ____________________________ (optional)</th>
<th>Race:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Date: <em><strong><strong>/</strong></strong></em>/____ (DD/MM/YY)</td>
<td>[ ] Caucasian</td>
</tr>
<tr>
<td>Height: ________ kg</td>
<td>[ ] Black</td>
</tr>
<tr>
<td>Weight: ________ cm</td>
<td>[ ] Asian</td>
</tr>
<tr>
<td>Gender:</td>
<td>[ ] Native Indian</td>
</tr>
<tr>
<td>[ ] Male</td>
<td>[ ] Hispanic</td>
</tr>
<tr>
<td>[ ] Female</td>
<td>[ ] Other</td>
</tr>
<tr>
<td>Specify: ____________________________</td>
<td>[ ] Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Have you been diagnosed with Neutropenia?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of siblings ________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of siblings who have been diagnosed with Neutropenia ________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, what type is it?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Severe congenital</td>
</tr>
<tr>
<td>[ ] Cyclic</td>
</tr>
<tr>
<td>[ ] Idiopathic</td>
</tr>
<tr>
<td>[ ] Other, specify: ________</td>
</tr>
<tr>
<td>[ ] Don’t know</td>
</tr>
</tbody>
</table>

## Diet

<table>
<thead>
<tr>
<th>Do you chew sugarless gum?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do you have a dietitian?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Are you on any special diet?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, for what reason?</th>
</tr>
</thead>
<tbody>
<tr>
<td>____________________________</td>
</tr>
<tr>
<td>____________________________</td>
</tr>
<tr>
<td>____________________________</td>
</tr>
</tbody>
</table>
### Medication History

Are you currently or have you ever undergone growth factor therapy?  
☐ Yes  ☐ No  ☐ Don't know

If so, please list growth colony stimulating factor (G-CSF) with start dates, stop dates and date of last dosage adjustment.

G-CSF: __________________________________________________________
Others: __________________________________________________________
Others: __________________________________________________________

<table>
<thead>
<tr>
<th>Other medications:</th>
<th>None</th>
<th>Past</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Gamma Globulin:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Antacids/H2 blockers:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other, Specify:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other, Specify:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other, Specify:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Bone Marrow Transplant Date:   _____/_____/____ (DD/MM/YY)

Do you smoke?  ☐ Yes  ☐ No

If yes, please indicate number of years you have smoked and the average number of packs per day?

______ number of years  ______ average packs of cigarettes per day

Does your medical doctor stress the importance of oral health and oral hygiene?  ☐ Yes  ☐ No

### Oral Health Assessment

Do you get mouth sores?  ☐ Yes  ☐ No

If yes, where?  
If how often?

<table>
<thead>
<tr>
<th></th>
<th>&lt; 1× per year</th>
<th>1-2× per year</th>
<th>3-4× per year</th>
<th>&gt; 4× per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gums</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Cheeks</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Lips</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
### Oral Health Assessment (Continued)

**Do you get dental (tooth related) infections that require antibiotics?**
- Yes □ No □

**If yes, how many times per year (approximate average)?**
- Less than once per year □
- 1 – 2× per year □
- 3 – 4× per year □
- Greater than 4× per year □

**Do your gums bleed when you brush your teeth?**
- Yes □ No □

**If yes, how frequent on average do you notice bleeding when brushing?**
- More than 3 days per week □
- 2 – 3 days per week □
- Less than twice per week □

**Do your teeth have pain under the following conditions?**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes □ No □</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously</td>
<td></td>
</tr>
<tr>
<td>Chewing</td>
<td></td>
</tr>
<tr>
<td>Drinking cold liquids</td>
<td></td>
</tr>
<tr>
<td>Drinking hot liquids</td>
<td></td>
</tr>
</tbody>
</table>

**Dental History**

**Do you have a dentist?**
- Yes □ No □

**Was your last dental visit within the past 12 months?**
- Yes □ No □

**Approximately how often do you have dental visits over the past 2 years?**
- Every 3 months □
- Every 6 months □
- Every 12 months □
- Every 24 months □
- Every ______ months □
- Never □

**Do you have dental insurance?**
- Yes □ No □

**Is the cost of dental care a factor in the frequency of your dental care visits?**
- Yes □ No □

**If you do not have dental insurance, would you go for recall dental visits as frequently?**
- Yes □ No □

**Has your dentist prescribed any of the following that you use everyday or frequently?**

<table>
<thead>
<tr>
<th>Prescribed Item</th>
<th>Yes □ No □</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special toothpaste</td>
<td></td>
</tr>
<tr>
<td>Special antibiotic mouth-rinse</td>
<td></td>
</tr>
<tr>
<td>Fluoride rinse</td>
<td></td>
</tr>
<tr>
<td>Fluoride tablets/supplements</td>
<td></td>
</tr>
</tbody>
</table>

Please specify:

- Special toothpaste: ____________________________
- Special antibiotic mouth-rinse: ____________________________
- Fluoride rinse: ____________________________
- Fluoride tablets/supplements: ____________________________
## Dental History
*(Please answer the following questions the best you can)*

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has a dentist pulled / extracted any of your teeth?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, how many?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasons (if known)?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Wisdom teeth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tooth crowding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Loose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Decay / Cavity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other reasons:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you lost any adult (permanent) teeth?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are your gums inflamed / swollen frequently?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are any of your adult teeth loose?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are your gums shrinking?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What types of dental treatment have you undergone?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Gum surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Root Canals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tooth Extraction <em>(pulling out tooth)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Teeth Cleaning <em>(polishing during recall visits)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Scaling <em>(deep tooth cleaning)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fillings <em>(including crowns / caps)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you seen any of the following dental specialists?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Periodontist <em>(gum specialist)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oral Surgeon <em>(specialist for wisdom teeth extraction &amp; jaw surgery)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Orthodontist <em>(specialist for alignment of teeth with braces)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oral Pathologist <em>(specialist for investigation of oral disease)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Endodontist <em>(root canal specialist)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pediatric dentist <em>(specialist for children and special needs)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If so, for what reason?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix H

Patient Questionnaire – University of Toronto

Over 16 years of age
Thanks for agreeing to help us with our study!

We are asking for your participation on behalf of your child in a research study. The purpose of this form is to give you information that will allow you to decide if you would like your child to be a part of this study.

Purpose & Benefits of the Study
It is known that neutropenic patients (patients with low levels of the infection fighting blood cells) are prone to bacterial infections, however the nature and severity of the oral infections for this population has not been thoroughly studied. Your participation is important as we are using your results from this questionnaire to compare them with patients with neutropenia to further our understanding of the oral effects of neutropenia and also to look at the effects that this disease has on normal oral function and the resulting effects on the quality of life.

A clinical and radiographic (x-ray) examination will be taken during your visit to the Faculty of Dentistry, University of Toronto. We have enclosed a questionnaire for you to fill out. To achieve the best possible scientific results, the more information we can gather, the better the survey will be. Your participation will be greatly appreciated. However, should you have difficulty providing some of the requested information, please feel free to submit an incomplete package.

- Answer as honestly as you can. All answers are private; no one you know will see them.
- All questionnaires are to be filled in anonymously and will be coded without any personal identification.
- Read each question carefully.
- Put an ☑ in the box for the answer that is best for you.

Please return questionnaires to:

Michael Park D.D.S.
Faculty of Dentistry, University of Toronto
Room 221 Fitzgerald Building,
150 College Street, Toronto,
Ontario, M5S 3E2 CANADA
e-mail: michael.park@utoronto.ca
<table>
<thead>
<tr>
<th>General Patient Information</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name: _______________________(optional)</td>
<td>Do you have a dietitian?  □ Yes □ No</td>
</tr>
<tr>
<td>Birth Date: <strong><strong>/</strong></strong>/___ (DD/MM/YY)</td>
<td>Are you on any special diet?  □ Yes □ No</td>
</tr>
<tr>
<td>Height: ________ kg</td>
<td>If yes, for what reason?</td>
</tr>
<tr>
<td>Weight: ________ cm</td>
<td></td>
</tr>
<tr>
<td>Gender: □ Male □ Female</td>
<td>_____________________________________________</td>
</tr>
<tr>
<td>Race: □ Caucasian □ Black □ Asian □ Native Indian □ Hispanic □ Other □ Other, specify: _______ □ Don’t know</td>
<td></td>
</tr>
<tr>
<td>Have you been diagnosed with Neutropenia? □ Yes □ No</td>
<td></td>
</tr>
<tr>
<td>Number of siblings _________</td>
<td>Do you chew sugarless gum? □ Yes □ No</td>
</tr>
<tr>
<td>Number of siblings who have been diagnosed with Neutropenia _________</td>
<td></td>
</tr>
<tr>
<td>If yes, what type is it? □ Severe congenital □ Cyclic □ Idiopathic □ Other, specify: _______ □ Don’t know</td>
<td></td>
</tr>
</tbody>
</table>
### Medication History

Are you currently or have you ever undergone growth factor therapy?  
☐ Yes  ☐ No  ☐ Don’t know

If so, please list growth colony stimulating factor (G-CSF) with start dates, stop dates and date of last dosage adjustment.

G-CSF:  

Others:  

Others:  

<table>
<thead>
<tr>
<th>Other medications:</th>
<th>None</th>
<th>Past</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Gamma Globulin:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Antacids/H2 blockers:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other, Specify:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other, Specify:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other, Specify:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Bone Marrow Transplant Date:  ____/____/___ (DD/MM/YY)

Do you smoke?  ☐ Yes  ☐ No

If yes, please indicate number of years you have smoked and the average number of packs per day?

_____ number of years  _____ average packs of cigarettes per day

Does your medical doctor stress the importance of oral health and oral hygiene?  ☐ Yes  ☐ No

### Oral Health Assessment

Do you get mouth sores?  ☐ Yes  ☐ No

If yes, where?

<table>
<thead>
<tr>
<th>And how often?</th>
<th>&lt; 1× per year</th>
<th>1-2× per year</th>
<th>3-4× per year</th>
<th>&gt; 4× per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Gums</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐ Cheeks</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐ Lips</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐ Other</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
### Oral Health Assessment (Continued)

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you get dental (tooth related) infections that require antibiotics?</td>
<td></td>
<td>Yes/No</td>
</tr>
<tr>
<td>If yes, how many times per year (approximate average)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Less than once per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1 – 2× per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 3 – 4× per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Greater than 4× per year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do your gums bleed when you brush your teeth?</td>
<td></td>
<td>Yes/No</td>
</tr>
<tr>
<td>If yes, how frequent on average do you notice bleeding when brushing?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- More than 3 days per week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 2 – 3 days per week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Less than twice per week</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do your teeth have pain under the following conditions?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneously</td>
<td>Yes/No</td>
<td></td>
</tr>
<tr>
<td>Chewing</td>
<td>Yes/No</td>
<td></td>
</tr>
<tr>
<td>Drinking cold liquids</td>
<td>Yes/No</td>
<td></td>
</tr>
<tr>
<td>Drinking hot liquids</td>
<td>Yes/No</td>
<td></td>
</tr>
</tbody>
</table>

### Dental History

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have a dentist?</td>
<td></td>
<td>Yes/No</td>
</tr>
<tr>
<td>Was your last dental visit within the past 12 months?</td>
<td></td>
<td>Yes/No</td>
</tr>
<tr>
<td>Approximately how often do you have dental visits over the past 2 years?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Every 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Every 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Every 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Every 24 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Every ______ months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have dental insurance?</td>
<td></td>
<td>Yes/No</td>
</tr>
<tr>
<td>Is the cost of dental care a factor in the frequency of your dental care visits?</td>
<td>Yes/No</td>
<td></td>
</tr>
<tr>
<td>If you do not have dental insurance, would you go for recall dental visits as frequently?</td>
<td>Yes/No</td>
<td></td>
</tr>
</tbody>
</table>

| Question                                                                 | Options                         | Yes/No   |
| Has your dentist prescribed any of the following that you use everyday or frequently? | Please specify:               |          |
| Special toothpaste                                                       |                                 | Yes/No   |
| Special antibiotic mouth-rinse                                           |                                 | Yes/No   |
| Fluoride rinse                                                           |                                 | Yes/No   |
| Fluoride tablets/supplements                                            |                                 | Yes/No   |
# Dental History
*(Please answer the following questions the best you can)*

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
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</thead>
<tbody>
<tr>
<td>Has a dentist pulled / extracted any of your teeth?</td>
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<tr>
<td>If yes, how many?</td>
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<tr>
<td>Reasons (if known)?</td>
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<tr>
<td>Wisdom teeth</td>
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<tr>
<td>Tooth crowding</td>
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<tr>
<td>Loose</td>
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<tr>
<td>Decay / Cavity</td>
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<tr>
<td>Other reasons:</td>
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<tr>
<td>Have you lost any adult (permanent) teeth?</td>
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<tr>
<td>Are your gums inflamed / swollen frequently?</td>
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<tr>
<td>Are any of your adult teeth loose?</td>
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<tr>
<td>Are your gums shrinking?</td>
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<tr>
<td>What types of dental treatment have you undergone?</td>
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<tr>
<td>Gum surgery</td>
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<tr>
<td>Root Canals</td>
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<tr>
<td>Tooth Extraction <em>(pulling out tooth)</em></td>
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<tr>
<td>Teeth Cleaning <em>(polishing during recall visits)</em></td>
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<tr>
<td>Scaling <em>(deep tooth cleaning)</em></td>
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<tr>
<td>Fillings <em>(including crowns / caps)</em></td>
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<tr>
<td>Have you seen any of the following dental specialists?</td>
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<tr>
<td>Periodontist <em>(gum specialist)</em></td>
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<tr>
<td>Oral Surgeon <em>(specialist for wisdom teeth extraction &amp; jaw surgery)</em></td>
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<tr>
<td>Orthodontist <em>(specialist for alignment of teeth with braces)</em></td>
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<tr>
<td>Oral Pathologist <em>(specialist for investigation of oral disease)</em></td>
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<tr>
<td>Endodontist <em>(root canal specialist)</em></td>
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<tr>
<td>Pediatric dentist <em>(specialist for children and special needs)</em></td>
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</table>

If so, for what reason?

__________________________________________________________

__________________________________________________________
Appendix I

Dentist Questionnaire – Hospital for Sick Children

Under 16 years of age
DENTIST QUESTIONNAIRE  
(Primary / Mixed Dentition)

Comments can be added adjacent to the question, on the reverse side of the page or on an added page.

The F.D.I. tooth numbering system will be used.

- Tooth 18 is the third molar (wisdom tooth) and 11 is the central incisor in the upper right quadrant.
- Tooth 28 is the third molar (wisdom tooth) and 21 is the central incisor in the upper left quadrant.
- Tooth 38 is the third molar (wisdom tooth) and 31 is the central incisor in the lower left quadrant.
- Tooth 48 is the third molar (wisdom tooth) and 41 is the central incisor in the lower right quadrant.

Are you a dental specialist?  
☐ Yes  ☐ No

If yes, please indicate below your specialty:  
☐ Periodontist  ☐ Pediatric dentist  ☐ Other, please specify: _______________________

Patient’s Name: _______________________

Does the patient have Neutropenia?  
☐ Yes  ☐ No

Which of the patient’s teeth are missing?  (Circle tooth number)

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</tbody>
</table>

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48  47  46  45  44  43  42  41
21  22  23  24  25  26  27  28
31  32  33  34  35  36  37  38

Were any teeth congenitally missing?  
☐ Yes  ☐ No  ☐ Unknown
If yes, please identify them: ____________________________________________

Were there any retained primary teeth?  
☐ Yes  ☐ No  ☐ Unknown
If yes, please identify them: ____________________________________________

Were any of the primary teeth prematurely lost?  
☐ Yes  ☐ No  ☐ Unknown
If yes, please identify them: ____________________________________________

Were any of the permanent teeth delayed in their eruption?  
☐ Yes  ☐ No  ☐ Unknown
If yes, please identify them: ____________________________________________
Review of case studies reveals that the first molars of neutropenic patients are often the most severely affected by periodontal disease. We are asking for a brief evaluation of the periodontal status of these teeth in your patient. Please fill out the following section even if your patient does not suffer from neutropenia.

<table>
<thead>
<tr>
<th>Tooth Number</th>
<th>Are any periodontal probing depths greater than 4 mm associated with any of the first molars?</th>
<th>Is there any recession noted on the first molars?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Right First Molar (16)</td>
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<td>☐</td>
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<td>Upper Left First Molar (26)</td>
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<td>Lower Left First Molar (36)</td>
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<td>☐</td>
</tr>
<tr>
<td>Lower Right First Molar (46)</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

If you have noted any other teeth with significant attachment loss during your previous examinations of the patient please list them below (with the probing depths and/or the attachment loss):

If so what was/were the reason(s)?

☐ Periodontal Infection
☐ Endodontic/Periapical Infection
☐ Other, please specify:

To your knowledge has the patient been prescribed antibiotics for any dental related reasons?

☐ Yes
☐ No

To your knowledge, is the patient resistant to any antibiotics?

Please classify the patient’s gingival health by describing the level of inflammation and its localization:

☐ None
☐ Localized
☐ Mild
☐ Generalized
☐ Moderate
☐ Severe

Please describe the nature of bleeding on probing:

☐ None
☐ Mild
☐ Moderate
☐ Severe

Please describe the patient’s oral hygiene based on plaque and calculus levels:

☐ No Plaque ± no Calculus
☐ Minimal Plaque ± Calculus
☐ Moderate Plaque ± Calculus
☐ Heavy Plaque ± Calculus

Does your patient present or complain of oral ulcerations?

☐ Yes
☐ No

If so, please describe number, frequency, location and history:

____________________________________________________________________

____________________________________________________________________
Which of the patient’s teeth are mobile / loose?

Mobility is graded using the following Classification

- ☺ No mobility
- ◐ Tooth moves greater than 1 mm in a buccal-lingual direction

Please circle all teeth that are graded as 1.

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48  47  46  45  44  43  42  41  31  32  33  34  35  36  37  38

If forwarding radiographs disregard the following questions.

Do the patient’s most current dental radiographs reveal any periodontal bone loss? ☐ Yes ☐ No

Does the bone loss exceed the 50% support level on any tooth? ☐ Yes ☐ No

If yes, please circle the ones involved below:

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</table>

18  17  16  15  14  13  12  11  21  22  23  24  25  26  27  28

48  47  46  45  44  43  42  41  31  32  33  34  35  36  37  38

Does the bone loss exceed the one-third support level on any tooth? ☐ Yes ☐ No

If yes, please circle the ones involved below:

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18  17  16  15  14  13  12  11  21  22  23  24  25  26  27  28

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Appendix J

Dentist Questionnaire – University of Toronto

Under 16 years of age
DENTIST QUESTIONNAIRE
(Primary/Mixed Dentition)

Comments can be added adjacent to the question, on the reverse side of the page or on an added page.

The F.D.I. tooth numbering system will be used.
- Tooth 18 is the third molar (wisdom tooth) and 11 is the central incisor in the upper right quadrant.
- Tooth 28 is the third molar (wisdom tooth) and 21 is the central incisor in the upper left quadrant.
- Tooth 38 is the third molar (wisdom tooth) and 31 is the central incisor in the lower left quadrant.
- Tooth 48 is the third molar (wisdom tooth) and 41 is the central incisor in the lower right quadrant.

Are you a dental specialist?
☐ Yes
☐ No

If yes, please indicate below your specialty:
☐ Periodontist
☐ Pediatric dentist
☐ Other, please specify: ______________________

Patient’s Name: _____________________________________________________________

Does the patient have Neutropenia?
☐ Yes ☐ No

Which of the patient’s teeth are missing? (Circle tooth number)

<table>
<thead>
<tr>
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</tbody>
</table>

Were any teeth congenitally missing?
☐ Yes
☐ No
☐ Unknown
If yes, please identify them:
____________________________________
____________________________________

Were any of the primary teeth prematurely lost?
☐ Yes
☐ No
☐ Unknown
If yes, please identify them:
____________________________________
____________________________________

Were any of the permanent teeth delayed in their eruption?
☐ Yes
☐ No
☐ Unknown
If yes, please identify them:
____________________________________
____________________________________

Are there any retained primary teeth?
☐ Yes
☐ No
☐ Unknown
If yes, please identify them:
____________________________________
____________________________________
Review of case studies reveals that the first molars of neutropenic patients are often the most severely affected by periodontal disease. We are asking for a brief evaluation of the periodontal status of these teeth in your patient. (Please fill out the following section even if your patient does not suffer from neutropenia)

| Please draw a line through the tooth number for any missing tooth & circle ones that are unerupted. |
| Are any periodontal probing depths greater than 4 mm associated with any of the first molars (place a check in the adjacent box for a probing depth greater than 4 mm)? If so what are the values (write on adjacent line)? |
| Is there any recession noted on the first molars (place a check in the adjacent box for any recession measured from the cemento-enamel junction to the crest of the gingival tissue)? If so what are the values (write on adjacent line)? |
| ☐ Upper Right First Molar (16) _______ |
| ☐ Upper Left First Molar (26) _______ |
| ☐ Lower Left First Molar (36) _______ |
| ☐ Lower Right First Molar (46) _______ |
| ☐ Upper Right First Molar (16) _______ |
| ☐ Upper Left First Molar (26) _______ |
| ☐ Lower Left First Molar (36) _______ |
| ☐ Lower Right First Molar (46) _______ |

If you have noted any other teeth with significant attachment loss during your previous examinations of the patient please list them below (with the probing depths and/or the attachment loss)

______________________________________________________________________
______________________________________________________________________

To your knowledge has the patient been prescribed antibiotics for any dental related reasons?
☐ Yes
☐ No
To your knowledge, is the patient resistant to any antibiotics?

If so what was/were the reason(s)?
☐ Periodontal Infection
☐ Endodontic/Periapical Infection
☐ Other, please specify:


Please classify the patient’s gingival health by describing the level of inflammation and its localization:
☐ None
☐ Localized
☐ Mild
☐ Generalized
☐ Moderate
☐ Severe

Please describe the nature of bleeding on probing:
☐ None
☐ Mild
☐ Moderate
☐ Severe

Please describe the patient’s oral hygiene based on plaque and calculus levels:
☐ No Plaque ± no Calculus
☐ Minimal Plaque ± Calculus
☐ Moderate Plaque ± Calculus
☐ Heavy Plaque ± Calculus

Does your patient present or complain of oral ulcerations?
☐ Yes
☐ No
If so, please describe number, frequency, location and history

______________________________________________________________________
______________________________________________________________________
Which of the patient’s teeth are mobile / loose?

Mobility is graded using the following Classification
- No mobility
- Tooth moves greater than 1 mm in a buccal-lingual direction

Please circle all teeth that are graded as 1.

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</table>

If forwarding radiographs disregard the following questions.

Do the patient’s most current dental radiographs reveal any periodontal bone loss?  
- Yes  
- No

Does the bone loss exceed the 50% support level on any tooth?  
If yes, please circle the ones involved below:

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Does the bone loss exceed the one-third support level on any tooth?  
If yes, please circle the ones involved below:

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Appendix K

Dentist Questionnaire – Hospital for Sick Children

Over 16 years of age
DENTIST QUESTIONNAIRE
(Adult, Permanent Dentition)

Comments can be added adjacent to the question, on the reverse side of the page or on an added page.

The F.D.I. tooth numbering system will be used.
- Tooth 18 is the third molar (wisdom tooth) and 11 is the central incisor in the upper right quadrant.
- Tooth 28 is the third molar (wisdom tooth) and 21 is the central incisor in the upper left quadrant.
- Tooth 38 is the third molar (wisdom tooth) and 31 is the central incisor in the lower left quadrant.
- Tooth 48 is the third molar (wisdom tooth) and 41 is the central incisor in the lower right quadrant.

<table>
<thead>
<tr>
<th>Are you a dental specialist?</th>
<th>If yes, please indicate below your specialty:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes</td>
<td>□ Periodontist</td>
</tr>
<tr>
<td>□ No</td>
<td>□ Pediatric dentist</td>
</tr>
<tr>
<td></td>
<td>□ Other, please specify: _________________</td>
</tr>
</tbody>
</table>

Patient’s Name: ____________________________

Does the patient have Neutropenia?
□ Yes □ No

Which of the patient’s permanent teeth are missing? (Circle tooth number)

<table>
<thead>
<tr>
<th>18</th>
<th>17</th>
<th>16</th>
<th>15</th>
<th>14</th>
<th>13</th>
<th>12</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>47</td>
<td>46</td>
<td>45</td>
<td>44</td>
<td>43</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>21</td>
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<td>28</td>
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<td>31</td>
<td>32</td>
<td>33</td>
<td>34</td>
<td>35</td>
<td>36</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

Were any teeth congenitally missing?
□ Yes
□ No
□ Unknown
If yes, please identify them:

------------------

Are there any retained primary teeth?
□ Yes
□ No
□ Unknown
If yes, please identify them:

------------------

Were any of the teeth prematurely lost?
□ Yes
□ No
□ Unknown
If yes, please identify them:

------------------

Were any of the permanent teeth delayed in their eruption?
□ Yes
□ No
□ Unknown
If yes, please identify them:

------------------
Review of case studies reveals that the first molars of neutropenic patients are often the most severely affected by periodontal disease. We are asking for a brief evaluation of the periodontal status of these teeth in your patient.

| Are any periodontal probing depths greater than 4 mm associated with any of the first molars (place a check in the adjacent box for a probing depth greater than 4 mm)? If so what are the values (write on adjacent line)? |
| Is there any recession noted on the first molars (place a check in the adjacent box for any recession measured from the cemento-enamel junction to the crest of the gingival tissue)? If so what are the values (write on adjacent line)? |

<table>
<thead>
<tr>
<th>Tooth Number</th>
<th>Probing Depth</th>
<th>Recession</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Right First Molar (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Left First Molar (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Left First Molar (36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Right First Molar (46)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you have noted any other teeth with significant attachment loss during your previous examinations of the patient please list them below (with the probing depths and/or the attachment loss)

______________________________________________________________________
______________________________________________________________________

To your knowledge has the patient been prescribed antibiotics for any dental related reasons?
- Yes
- No

To your knowledge, is the patient resistant to any antibiotics?

If so what was/were the reason(s)?
- Periodontal Infection
- Endodontic/Periapical Infection
- Other, please specify:

Please classify the patient’s gingival health by describing the level of inflammation and its localization:
- None
- Localized
- Mild
- Generalized
- Moderate
- Severe

Please describe the nature of bleeding on probing:
- None
- Mild
- Moderate
- Severe

Please describe the patient’s oral hygiene based on plaque and calculus levels:
- No Plaque ± no Calculus
- Minimal Plaque ± Calculus
- Moderate Plaque ± Calculus
- Heavy Plaque ± Calculus

Does your patient present or complain of oral ulcerations?
- Yes
- No

If so, please describe number, frequency, location and history

______________________________________________________________________
Which of the patient’s teeth are mobile / loose?

Mobility is graded using the following Classification

- No mobility
- Tooth moves greater than 1 mm in a buccal-lingual direction

Please circle all teeth that are graded as 1.

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 18 | 17 | 16 | 15 | 14 | 13 | 12 | 11 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
| 48 | 47 | 46 | 45 | 44 | 43 | 42 | 41 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 |

If forwarding radiographs disregard the following questions.

Do the patient’s most current dental radiographs reveal any periodontal bone loss?

☐ Yes
☐ No

Does the bone loss exceed the 50% support level on any tooth?

☐ Yes
☐ No

If yes, please circle the ones involved below:

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 18 | 17 | 16 | 15 | 14 | 13 | 12 | 11 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
| 48 | 47 | 46 | 45 | 44 | 43 | 42 | 41 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 |

Does the bone loss exceed the one-third support level on any tooth?

☐ Yes
☐ No

If yes, please circle the ones involved below:

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 18 | 17 | 16 | 15 | 14 | 13 | 12 | 11 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
| 48 | 47 | 46 | 45 | 44 | 43 | 42 | 41 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 |
Appendix L

Dentist Questionnaire – University of Toronto

Over 16 years of age
**DENTIST QUESTIONNAIRE**  
(Adult, Permanent Dentition)

Comments can be added adjacent to the question, on the reverse side of the page or on an added page.

The F.D.I. tooth numbering system will be used.

- Tooth 18 is the third molar (wisdom tooth) and 11 is the central incisor in the upper right quadrant.
- Tooth 28 is the third molar (wisdom tooth) and 21 is the central incisor in the upper left quadrant.
- Tooth 38 is the third molar (wisdom tooth) and 31 is the central incisor in the lower left quadrant.
- Tooth 48 is the third molar (wisdom tooth) and 41 is the central incisor in the lower right quadrant.

<table>
<thead>
<tr>
<th>Are you a dental specialist?</th>
<th>If yes, please indicate below your specialty:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes</td>
<td>□ Periodontist</td>
</tr>
<tr>
<td>□ No</td>
<td>□ Pediatric dentist</td>
</tr>
<tr>
<td></td>
<td>□ Other, please specify: _________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient's Name:</th>
</tr>
</thead>
<tbody>
<tr>
<td>___________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Does the patient have Neutropenia?</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Which of the patient's teeth are missing? (Circle tooth number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
</tr>
<tr>
<td>85</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>48</td>
</tr>
</tbody>
</table>

| 21  | 22  | 23  | 24  | 25  | 26  | 27  | 28  |
| 31  | 32  | 33  | 34  | 35  | 36  | 37  | 38  |

<table>
<thead>
<tr>
<th>Were any teeth congenitally missing?</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>If yes, please identify them:</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Were any of the primary teeth prematurely lost?</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>If yes, please identify them:</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Were there any retained primary teeth?</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>If yes, please identify them:</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Were any of the permanent teeth delayed in their eruption?</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>If yes, please identify them:</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Review of case studies reveals that the first molars of neutropenic patients are often the most severely affected by periodontal disease. We are asking for a brief evaluation of the periodontal status of these teeth in your patient. (Please fill out the following section even if your patient does not suffer from neutropenia)

Please draw a line through the tooth number for any missing tooth & circle ones that are unerupted.

Are any periodontal probing depths greater than 4 mm associated with any of the first molars (place a check in the adjacent box for a probing depth greater than 4 mm)? If so what are the values (write on adjacent line)?

<table>
<thead>
<tr>
<th>Tooth</th>
<th>Probe Depth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Right First Molar (16)</td>
<td></td>
</tr>
<tr>
<td>Upper Left First Molar (26)</td>
<td></td>
</tr>
<tr>
<td>Lower Left First Molar (36)</td>
<td></td>
</tr>
<tr>
<td>Lower Right First Molar (46)</td>
<td></td>
</tr>
</tbody>
</table>

Is there any recession noted on the first molars (place a check in the adjacent box for any recession measured from the cemento-enamel junction to the crest of the gingival tissue)? If so what are the values (write on adjacent line)?

<table>
<thead>
<tr>
<th>Tooth</th>
<th>Recession</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Lower Right First Molar (46)</td>
<td></td>
</tr>
</tbody>
</table>

If you have noted any other teeth with significant attachment loss during your previous examinations of the patient please list them below (with the probing depths and/or the attachment loss)

______________________________________________________________________

To your knowledge has the patient been prescribed antibiotics for any dental related reasons?

- ☐ Yes
- ☐ No

To your knowledge, is the patient resistant to any antibiotics?

______________________________________________________________________

Please classify the patient’s gingival health by describing the level of inflammation and its localization:

- ☐ None
- ☐ Localized
- ☐ Mild
- ☐ Generalized
- ☐ Moderate
- ☐ Severe

Please describe the nature of bleeding on probing:

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

Please describe the patient’s oral hygiene based on plaque and calculus levels:

- ☐ No Plaque ± no Calculus
- ☐ Minimal Plaque ± Calculus
- ☐ Moderate Plaque ± Calculus
- ☐ Heavy Plaque ± Calculus

Does your patient present or complain of oral ulcerations?

- ☐ Yes
- ☐ No

If so, please describe number, frequency, location and history

______________________________________________________________________
Which of the patient’s teeth are mobile / loose?

Mobility is graded using the following Classification

- No mobility
- Tooth moves greater than 1 mm in a buccal-lingual direction

Please circle all teeth that are graded as 1.

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<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>47</td>
<td>46</td>
<td>45</td>
<td>44</td>
<td>43</td>
<td>42</td>
<td>41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
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<td>32</td>
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<td>34</td>
<td>35</td>
<td>36</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

If forwarding radiographs disregard the following questions.

Do the patient’s most current dental radiographs reveal any periodontal bone loss?

- Yes
- No

Does the bone loss exceed the 50% support level on any tooth?

- Yes
- No

If yes, please circle the ones involved below:

<table>
<thead>
<tr>
<th>18</th>
<th>17</th>
<th>16</th>
<th>15</th>
<th>14</th>
<th>13</th>
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<tr>
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<td>42</td>
<td>41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
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<td>32</td>
<td>33</td>
<td>34</td>
<td>35</td>
<td>36</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

Does the bone loss exceed the one-third support level on any tooth?

- Yes
- No

If yes, please circle the ones involved below:

<table>
<thead>
<tr>
<th>18</th>
<th>17</th>
<th>16</th>
<th>15</th>
<th>14</th>
<th>13</th>
<th>12</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
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<td>44</td>
<td>43</td>
<td>42</td>
<td>41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
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<td>32</td>
<td>33</td>
<td>34</td>
<td>35</td>
<td>36</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>
Appendix M

Neutropenia group

Breakdown of patient questionnaire responses based upon severity of neutropenia
<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Unclassified idiopathic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shwachman-Diamond</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic neutropenia</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cyclic neutropenia</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current or previous medical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocyte colony-</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>stimulating factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Has ever been to pediatric dentist?</strong></td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frequency of dental appointments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 3 months</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 6 months</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 9 months</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 12 months</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 24 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not been to dentist in over</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>24 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not answered</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotics given for dentally related reason</strong></td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periodontal infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endodontic/periapical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis prior to extractions</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tooth extractions</strong></td>
<td>3</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Decay/cavities</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Loose</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crowding</td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Wisdom teeth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Do you get mouth sores?</strong></td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Do your gums bleed when brushing?</strong></td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>
Appendix N

Neutropenia group

Breakdown of results from dental examination based upon severity of neutropenia
<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gingival health: level of inflammation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plaque and calculus levels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No plaque or calculus</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Minimal plaque and calculus</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Moderate plaque and calculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy plaque and calculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pathologic tooth mobility</strong></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Periodontal bone loss</strong></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix O

Post-hoc power calculations for results from patient questionnaire, dental and radiographic examination
<table>
<thead>
<tr>
<th>Variable</th>
<th>Post-hoc power calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.80%</td>
</tr>
<tr>
<td>Mouth sores</td>
<td>83%</td>
</tr>
<tr>
<td>Bleeding gums while brushing</td>
<td>95.30%</td>
</tr>
<tr>
<td>Given antibiotics</td>
<td>40.40%</td>
</tr>
<tr>
<td>Dental extractions</td>
<td>39.4%</td>
</tr>
<tr>
<td>Frequency of appointments</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>N/A</td>
</tr>
<tr>
<td>3 months</td>
<td>N/A</td>
</tr>
<tr>
<td>6 months</td>
<td>31.70%</td>
</tr>
<tr>
<td>9 months</td>
<td>N/A</td>
</tr>
<tr>
<td>12 months</td>
<td>6.70%</td>
</tr>
<tr>
<td>24 months</td>
<td>N/A</td>
</tr>
<tr>
<td>Never been</td>
<td>4.80%</td>
</tr>
<tr>
<td>Seen by paediatric dentist</td>
<td>40.20%</td>
</tr>
<tr>
<td>Gingival health</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>21.50%</td>
</tr>
<tr>
<td>Mild</td>
<td>55.40%</td>
</tr>
<tr>
<td>Moderate</td>
<td>40.30%</td>
</tr>
<tr>
<td>Severe</td>
<td>N/A</td>
</tr>
<tr>
<td>Plaque and calculus</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>40.30%</td>
</tr>
<tr>
<td>Mild</td>
<td>58.40%</td>
</tr>
<tr>
<td>Moderate</td>
<td>6.30%</td>
</tr>
<tr>
<td>Severe</td>
<td>N/A</td>
</tr>
<tr>
<td>Primary dentition caries</td>
<td></td>
</tr>
<tr>
<td>dmft</td>
<td>91.60%</td>
</tr>
<tr>
<td>dmft/t</td>
<td>94.70%</td>
</tr>
<tr>
<td>Permanent dentition caries</td>
<td></td>
</tr>
<tr>
<td>DMFT</td>
<td>9.20%</td>
</tr>
<tr>
<td>DMFT/T</td>
<td>18.20%</td>
</tr>
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