Relationship of Pre-Transplant Periodontal Assessment and Post-Transplant Outcomes in Allogeneic Hematopoietic Cell Transplantation

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Abstract

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Background: Global immunosuppression, particularly neutropenia, following allogeneic hematopoietic cell transplantation (HCT) increases the risk of post-transplant (post-TXP) bacteremia. Periodontal infection is highly prevalent in the general and HCT populations. Periodontal bacteria represent a potentially significant source of blood stream infection through compromised gingival epithelium and oral mucosal barriers.

Aim: The primary aim of this study was to examine the relationship between pre-TXP periodontal assessment and post-TXP bacteremia of potential oral/periodontal origin in patients undergoing hematopoietic cell transplantation. Secondarily, maximum periodontal probing depths (PPD) measurements were compared against total inpatient hospitalization days and death within 100 days. Influence of completion of recommended pre-TXP periodontal therapy was also examined in relation to each outcome.

Methods: Medical and dental records were reviewed for 609 consecutive patients treated with allogeneic HCT at Seattle Cancer Care Alliance (SCCA) between 1/27/2005-1/31/2013 who met eligibility requirements. Patients completed pre-TXP oral medicine examination, which included

fixed 12-site partial mouth PPD assessment, as part of standard work-up. In accordance with standard of care protocols, every effort was made to stabilize dental/periodontal infections prior to TXP which included intensive oral hygiene instructions, periodontal scaling, curettage, sulcular antibiotic placement, and dental extractions (EXT). Blood cultures results obtained according to standard center protocol were reviewed for bacteria of potential oral/periodontal origin. All patients received antibacterial prophylaxis per center protocol in anticipation of neutropenia (standard = Levofloxacin 750mg/d).

Results: 416 of 609 patients had maximum PPDs consistent with periodontal disease (≥4mm), including 104 patients with at least one site ≥6mm. 275 patients completed periodontal therapy (including EXT prior to TXP). Incidence of possible/likely oral bacteremia was 37% (Group 1, PPD 2-3mm), 43% (Group 2, and 34% (Group 3, PPD ≥6mm) respectively. No significant differences were noted between periodontal classification and outcomes of interest, though a trend approaching significance was seen in Group 2 [HR bacteremia of possible/likely oral origin: Any = 1.28 (1.0-1.7); Gram(+) = 1.22 (0.9-1.6); Gram(-) 1.45 (0.8-2.6)]. Periodontal therapy was recommended more often in group 3 ($p = 0.000$) and patients in group 3 were significantly more likely to have completed intensive periodontal therapy (regular to heavy scaling, curettage, and local antibiotic therapy) prior to transplant ($p = 0.0000$ for each).

Conclusions: Maximum pre-transplant PPD assessed during partial mouth fixed site periodontal assessment in this setting was not predictive of post-TXP bacteremia of oral/periodontal origin in the SCCA Oral Medicine Service's HCT population. Similarly, maximum PPD was not associated with increased hospitalization within the first 100 days post-transplant or survival at day 100. Though not statistically significant, our results suggest that patients with maximum PPD ≥6mm may be at decreased risk for post-transplant bacteremia compared to those with

intermediate PPDs (4-5mm) due to more aggressive pre-transplant periodontal intervention in those with deeper pockets. HCT patients with pre-transplant PPDs consistent with periodontal disease may be at increased risk for coagulase-negative Staphylococci (CoNS) bacteremia though further study is necessary to confirm an oral source in these infections.

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Dedication

This work is dedicated to my wife Brittany, whose unwavering support defies description,

to my family for continual inspiration,

and to my Dad, who encouraged me to pursue oral medicine even though it meant we wouldn't get to work together every day.

Chapter I: Background and Significance

Hematopoietic Cell Transplantation

Hematopoietic Cell Transplantation has drastically improved the prognosis of hematologic malignancies and immune system disorders since the late-1950s.[1, 2] Historically, HCT represents, "the original stem cell therapy, the first cancer immune therapy and the earliest example of individualized cancer therapy."[1] Today it has become the standard of care in the treatment of many hematologic cancers and hematopoietic disorders.[1-3]

HCT is designed to eradicate malignant and dysfunctional blood-forming cells and re-establish a normal functional marrow (and/or immune system) by replacing aberrant cells with functional stem cells harvested from a donor. Transplants are classified based on the source of the transplanted stem cells. Depending on the disease in question, transplanted stem cells may come from the patient (autologous), an identical twin (syngeneic), or a genetically different individual (allogeneic). Stem cells can be obtained from bone marrow, peripheral blood, umbilical cord, or fetal liver. Prior to the infusion of donor cells, disease-specific chemotherapeutic conditioning protocols (with or without total body irradiation) are utilized to eradicate diseased cells found in hematopoietic, lymphatic, and other tissues throughout the body. In the case of allogeneic transplant, conditioning regimens and/or immunosuppressive drug therapy, also serve to suppress host immune response against the antigenically different donor cells. In time the donated cells will repopulate bone marrow sites and result in engraftment and allow for trilineage hematopoiesis and re-establishment of a functional immune system.[4]

Unfortunately, levels of immunosuppression associated with HCT leave the recipient vulnerable to bacterial, fungal, and viral infections.[5] This risk is especially high in allogeneic protocols that utilize fully myeloablative (MA) conditioning, which eradicates immune system function to a greater degree when compared to reduced intensity conditioning (RIC) protocols. Additionally, though time to tri-lineage engraftment is only one to two days longer than in their autologous counterparts, allogeneic patients remain immunosuppressed much longer post HCT due to systemic immunosuppressant medications that can be given for months to years following transplant to minimize the risk and or damage from graft-versus-host disease (GVHD). On average post HCT GVHD prophylaxis and or treatment will delay immune recovery approximately four to six months in allogeneic patients. Consequently, allogeneic recipients are at high risk for both early and late stage infections, including systemic blood stream infections, following transplant.[4, 6] Due to the high incidence of bacteremia in the allogeneic population it is critically important to identify and eradicate extrinsic and intrinsic sources of potential infection prior to transplantation.

Bacterial Infection in Allogeneic HCT

Several studies have attempted to define the incidence of bacterial infection following allogeneic transplant. A prospective survey at Memorial Sloan-Kettering Cancer Center (MSKCC)[7] identified pre-engraftment bloodstream infection (BSI) in 22% of 298 allogeneic patients and post-engraftment BSI in 19.5%. In the study, 49% of BSIs occurred during the pre-engraftment period with an additional 22% taking place between neutrophil engraftment (mean = 13 days, range 8-37 days) and 90 days post-transplant. Eight patients died as a direct result of these infections. All patients received antibiotic prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX; TMP 10mg/kg/d between day -7 to -3 and after day 50). No standard prophylaxis

was given for neutropenia though febrile neutropenia was treated with ticarcillin and clavulanate, piperacillin and tazobactam, amikacin (with or without cefepime), or vancomycin. Early and late infections were also identified by Mikulska et al.[8] who showed that while 77% of 168 BSIs in their population occurred during neutropenia, 23% were identified later in the post-transplant period (12% during GVHD; 11% under other circumstances). Notably, 30% of bacteremias occurred more than 30 days post-transplant. All patients received standard prophylaxis with ciprofloxacin during neutropenia with the addition of TMP/SMX (960mg bid, 3x/week) between neutrophil engraftment and immunologic recovery. 19 patients with BSIs (11%) died within eleven days of infection. These studies underscore the significant risk of blood stream infection and associated mortality in allogeneic patients even in the context of antibiotic prophylaxis.

Potential Influence of Oral/Periodontal Bacteria in the HCT

In the context of severe immunosuppression the influence of both pathogenic and commensal bacteria must be considered. The oral cavity represents one of the most complex microbial communities in the human body and has been suggested as a likely source of bacteremia in both dental and transplant literature.[9-24] Over seven hundred distinct bacterial species have been isolated in the mouth[25-27]. It is estimated that 415 different species are present in subgingival dental plaque alone.[27] Gram-positive aerobic bacteria of the normal flora make up the majority of these organisms, though dental, gingival, and periodontal pathogens are also exceedingly common[19].

Pathogenic oral bacteria include gram-positive facultative anaerobes (which are the causative organisms in dental caries and gingivitis) and gram-negative anaerobes which predominate in periodontitis. Periodontitis is highly prevalence in the adult population and is estimated to affect

47% of adults (over age 30) in the United States.[28] In patients treated with HCT, periodontal bacteria pose a systemic health risk due to compromises in innate and adaptive immunity.[16, 29] Numerous studies have identified oral and periodontal organisms, including F. nucleatum,[9, 29-31] K. pneumonia,[10, 14, 15] Enterobacter species,[10] and viridians/α-hemolytic streptococci[7, 13, 15, 32-34] as sources of bacteremia in both HCT and non-HCT populations. Neutropenia in particular has been repeatedly associated with bacteremia from oral and non-oral sources in the immunocompromised.[8, 9, 11, 15, 16, 20-22, 29, 30, 35-37] Because local defense against periodontal pathogens is largely mediated by neutrophils[21, 38] it follows that patients with altered neutrophil function may be at increased risk for bacteremia of periodontal origin.[12, 16, 39] In light of these considerations, periodontal infection has been suggested as a potential etiology in neutropenic fevers with no identifiable cause.[21]

Raber-Durlacher and colleagues[21] have reviewed the impact of periodontal disease in immunosuppressed cancer patients. Briefly, periodontal disease produces widespread inflammation in gingival tissues which results in ulceration of the junctional epithelium of the gingival sulcus. In severe, untreated periodontitis the total area of affected tissue is estimated to be up to 35 square centimeters.[21,40] As disease progresses loss of periodontal attachment results in periodontal pocket formation. Pocket formation limits the ability to remove bacterial plaque through standard oral hygiene techniques. With deeper pockets, there is a shift in subgingival microbial composition from the mostly facultative anaerobic Gram-positive bacteria of dental plaque (e.g. Viridans Streptococci, Actinomyces spp., Peptostreptococci) to the facultative and obligate anaerobic Gram-negative species associated with periodontitis (most notably Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Aggregatibacter

actinomycetemcomitans, Treponema spp., and Fusobacterium nucleatum).[25, 26, 41-45] Due to the high prevalence of periodontal disease in both the general[28] and HCT populations,[46] it has been suggested that "of the dental diseases commonly encountered in HCT candidates, inflammatory periodontal diseases (gingivitis and periodontitis) pose the most significant risk for the immunocompromised patient."[39]

Common Oral and Periodontal Bacteria Implicated in Bacteremia

Oral bacteria, particularly Viridans streptococci, have long been implicated in bacteremia in the HCT population. Oral Viridans Streptococci (OVS) are the principle organisms involved in dental plaque formation and plaque-induced gingivitis. They are colonizers of multiple oral environments including dental hard tissue, oral mucosal surfaces, and the subgingival periodontal complex.[27, 47, 48] OVS are also the most common oral organism associated with blood stream infection (BSI) in allogeneic HCT.[7, 13, 15, 32-34] Reported incidence ranges widely (0-46%.[33] but there is general consensus that relative rates began to increase with the advent of novel antibiotic regimens in the 1990s.[11, 12, 34, 49, 50] In the general population systemic morbidity and mortality associated with Viridans bacteremia is relatively low. However, within the HCT population, Viridans streptococci may cause septic shock, cardiorespiratory complications, and death.[11, 34, 50]

Several large studies have investigated Viridans streptococci bacteremia in the HCT population. A prospective analysis of 298 adult and pediatric allogeneic patients treated at MSKCC[7], identified Viridans streptococci as the most common cause of BSI (58 cases/10,000 post-transplant days) and the BSI with the highest mortality rate (24%). Prophylactic microbial coverage was provided with TMP/SMX between day -7 to -3 pre-transplant and after day 50

post-transplant. Villablanca and colleagues[50] isolated Viridans streptococci from the bloodstream or cerebrospinal fluid in 14.8% of 832 bone marrow transplant recipients with two common oral bacteria, S. sanguis and S. mitis, identified as the most likely causative organisms in Viridans bacteremias (75% of cases). A smaller retrospective study by Graber et al.[13] showed a similar result with 61% of 31 bacteremias attributed to Viridians streptococci following MA allogeneic transplant in adults. All patients received standard antibiotic prophylaxis with norfloxacin (400mg po bid) initiated 7-10 days prior to transplant and continued until neutrophil counts were sustained above 1000 cells/μL. TMP/SMX was also provided for Pneumocystis pneumonia (PCP) prophylaxis after day 30. Interestingly, dental pathology was found to be more likely in bacteremic patients (26.3% v. 0%; $p < 0.014$) though periodontal health was not explicitly evaluated in the study.

Studies focusing on risk factors for Viridans streptococcal bacteremia identify the oral cavity as a likely point of entry for bacteria into the blood stream. A case-control study at M.D. Anderson Cancer Center[34] identified oral organisms Strep. mitis and Strep. sanguis as the most commonly isolated species in Viridans bacteremia. Severe neutropenia (<100 neutrophils/mm^3; OR= 27.4, multivariate OR= 3.4, $p < 0.0001$) and oral mucositis (OR= 4.3; $p<0.001$) were the greatest risk predictors for infection. Notably, Viridans bacteremia had a 24% mortality rate compared to 4% in patients with other Gram-positive bacteremias ($p < 0.0005$). A literature review by Bochud et al.[11] through 1993 identified oral mucositis and gingivitis as risk factors for OVS bacteremia and implicated OVS as the likely cause of death in 4-18% of cases. Oral ulcerations were also hypothesized as a risk factor by Heimdahl and colleagues,[15] who found an association between Methotrexate (MTX) prophylaxis and alpha-streptococcal bacteremia ($p = 0.01$). 24 of 59

patients (40.7%) with Viridans bacteremia were diagnosed during neutropenia (two of whom died). While the mortality statistics in these studies are striking it is also important to view the results in the broader context of post-transplant care. Bacteremia, regardless of source, prompts significant intervention even in cases of less severe infection. Patients are re-admitted to inpatient care, which increases healthcare cost, and prescribed broad-spectrum antibiotics, which have been associated with medication-related adverse events and increased microbial resistance.

In addition to OVS-related bacteremia, Viridans streptococci may also contribute to systemic infection by periodontal bacteria. When oral hygiene is ineffective, dental plaque accumulates on the surfaces of teeth and in time will calcify to form dental calculus. These "local factors" mechanically increase bacterial colonization and subsequent gingival infection. Viridans streptococci are the principle early colonizers in bacterial plaque and create a biofilm on the tooth surface. The subgingival portion of the biofilm is necessary for adherence and secondary colonization of the gingival sulcus by periodontal pathogens. Subgingival pathogens trigger host immune responses leading to connective tissue destruction and epithelial ulceration.[21, 38] Ulcerated periodontal epithelium provides a potential "point of entry" for periodontal bacteria into systemic circulation[21, 39, 45] Periodontal bacteria have long been implicated in bacteremia in Oncology and Infectious Disease literature. An early case series by Baquero et al.[9] cited severe periodontitis and oral mucositis as risk factors for Fusobacterium nucleatum and Leptotrichia buccalis bacteremia. In their discussion, the authors questioned whether anaerobic-capnophilic bacteria from the oral cavity were supplanting gastrointestinal bacteria as the classic source of neutropenic bacteremia.

Though the assertion is likely overstated, other studies have shown periodontal pathogens to be significant contributors to anaerobic bacteremia in both the HCT and non-HCT populations. A literature review by van Winkelhoff and Slots[45] reported 152 cases of non-oral infection involving endogenous periodontal pathogens A. actinomycetemcomitans (N=136) and P. gingivalis (N=16) in the general population. In a retrospective study by Fanourgiakis et al.,[30] Fusobacterium was identified as the cause of 5% of all bacteremias identified in neutropenic patients over 6.5 period (70% F. nucleatum). These patients included those treated with chemotherapy alone or in conjunction with autologous or allogeneic HCT. 13 of 23 received prophylaxis with ciprofloxacin. "Profound neutropenia, mucosal ulceration, and chemoprophylaxis" were cited as predictive factors for F. nucleatum-bacteremia (statistics not provided). Even more significantly, a matched, retrospective, case-control study by Lark et al.,[29] identified Fusobacterium nucleatum as the most common cause of anaerobic BSI between the start of conditioning and thirty days post-BMT (17 of 22 BSIs). All Fusobacterium infections occurred during neutropenia and severe mucositis was found to be the greatest risk factor for infection (OR= 4.3, 95% CI: 1.3-14.1; $p < 0.01$). The authors in the latter two studies cited Fusobacterium as a potential causative organism in the setting of occult infection, though neither showed increased mortality associated with Fusobacterium bacteremia. However, it is important to keep in mind that these infections are quite rare: a study of over 280,000 consecutive blood cultures at the Mayo clinic identified F. nucleatum bacteremia in only 0.23% of cases.[51].

In addition to oral and periodontal bacteria, improved oral microbial sampling techniques have identified traditionally "non-oral" bacteria such as staphylococci[17, 21, 22, 52-54], pseudomonas[21, 55, 56], and enteric species within the periodontal complex[21, 25, 44, 54]. Coagulase-negative

staphylococci (CoNS) warrant special consideration. CoNS are predominately commensal bacteria of the skin which are recognized as the most common cause of nosocomial BSIs.[52] Murdoch et al.[54] isolated Staph. epidermidis (the predominate species of CoNS) from diseased and healthy subgingival sites in patients with periodontal disease (80.5% and 69.7% respectively) as well as 66.7% of sites in control patients without periodontal disease. Interestingly, a higher percentage of positive cultures were obtained from subgingival locations than extraoral sites (nares= 64.1%, fingertips= 41.2%). These findings are especially relevant in the HCT population where patterns of bacterial colonization vary with length and severity of immunosuppression.[21, 56] Several studies in the immunocompromised (HCT and neutropenic patients) have identified the oral mucosa, gingiva, and periodontium as likely sources in CoNS bacteremia[17, 22, 52] though larger studies are needed to firmly establish the oral cavity as a bona fide site of entry for these bacteria into the bloodstream.

Periodontal Disease and Post-Transplant Bacteremia

Several studies have specifically examined the relationship between periodontal disease and post-transplant bacteremia. A recent prospective study by Raber-Durlacher et al.[22] concluded that allogeneic patients diagnosed with gingivitis and periodontitis prior to transplant were more likely to develop bacteremia of potentially oral origin during neutropenia than those who were periodontally healthy ($p = 0.046$) OVS and CoNS bacteremias were identified in 61% of 16 of patients. Though patients received supportive oral care after transplant it is important to note that pre-transplant periodontal stabilization was not completed in this cohort. Anti-bacterial prophylaxis included general coverage with ciprofloxacin and co-trimoxazole for PCP. A retrospective study of HCT patients by Akintoye and colleagues[32] investigated the risk of blood stream infection in relation to advanced periodontal disease (by measuring alveolar bone loss on

a Panoramic radiograph with a Schei ruler). 34.6% of 81 bacteremias reported in the study were determined to be of likely oral or periodontal origin. However, despite the relatively high incidence of bacteremia, there was no statistical relationship between periodontal bone loss and bacteremia of oral or periodontal origin. Antibiotic prophylaxis included norfloxacin (400mg po bid beginning 7-10 prior to transplant and continuing until ANC >1000mm^3) and TMP/SMX (beginning day 30). It is important to note that the technique used to evaluate periodontal disease in this study, while effective in evaluating horizontal bone loss, unable not to predict periodontal pocket depth or determine the presence of active periodontal.

Early prospective studies[10, 14, 15], though limited by sample size, also identify the oral cavity as a likely source of bacteremia in chemotherapy and BMT patients. Bergmann and colleagues[10] followed consecutive patients with hematologic malignancy (N= 46) who developed fever of unknown origin (FUO). Nine patients developed 19 episodes of blood stream infection during the study. In 10.5% of 19 cases, the causative organisms were only recovered from the mouth (while no other body sites showed signs of infection). Three additional patients had concurrent positive cultures from the mouth and another body site. In a study of non-lymphocytic leukemia patients who developed neutropenic fever, Greenberg et al.[14] identified the oral cavity as the most likely source of BSI in seven of 12 cases. The study evaluated patients both with (N=24) and without (N=9) pre-chemotherapy dental intervention. In the non-intervention group, oral infection was implicated in six of 15 febrile episodes and four of seven cases of bacteremia. These findings prompted modification study protocol to provide pre-chemotherapy dental care to all future patients enrolled in the study. Subsequently, twenty-four patients received dental examination and treatment prior to therapy (periodontal scaling N=3; extraction N=3; scaling +

EXT N=3). 25% of the 24 patients in group 2 had confirmed cases of bacteremia. Severe periodontal disease was cited as the most likely source of bacteria in three cases (statistical significance not reported due to small sample size).

Periodontal Bacteria and Oral Mucositis

Bacteremias of potential oral origin have been most thoroughly studied in the context of oral mucositis and the association between oral mucositis and bacteremia been well-documented.[11, 15, 29-31, 57] Oral mucositis is a well-known complication of both high dose chemo- and radiation therapy that leads to breakdown of intraoral barrier function.[58] Though mucositis is not caused by infection, bacterial colonization of compromised mucosal surfaces can lead to increased mucosal damage, bacterial invasion into tissues, and resulting bacteremia. It is interesting to note that many organisms found in association with oral ulcerations in mucositis are considered potential periodontal pathogens. A prospective observational study by Laheij and colleagues[59] analyzed the microbial composition of oral ulcers in 49 adults undergoing HCT. Fusobacterium nucleatum was the most commonly isolated organism (66% of samples; 86% of patients) while P. gingivalis showed positive predictive value for oral ulceration. Treponema denticola was also associated with mucosal ulcers. These findings support Vidal et al.'s[24] assertion that anaerobic bacteremia should be on the differential diagnosis for febrile neutropenia in all patients with oral mucositis. Myeloablative HCT patients with pre-existing periodontal disease may be at dual risk for bacteremia of periodontal origin through both mucosal ulcerations and ulcerated gingival epithelium.

Global immunosuppression following myeloablative conditioning profoundly increases the risk of bacterial infection in patients treated with allogeneic HCT. Periodontal bacteria found in dental plaque and diseased periodontal tissues are a likely source of bacteremia that may enter

the blood stream through inflamed periodontal tissue or through secondary colonization of mucosal ulcerations during oral mucositis. Pre-transplant diagnosis of periodontal disease and targeted periodontal therapy may decrease the risk of bacteremia in the HCT population.

Hypothesis

The primary objective of this study is to analyze the relationship between pre-transplant periodontal assessment and incidence of oral/periodontal bacteremia between day 0 and day 100 post-HCT who had undergone pre-HCT periodontal and dental disease stabilizing treatment. We hypothesize that patients presenting to our clinic with maximal pre-transplant periodontal probing depths (PPDs) consistent with periodontal disease (i.e. ≥4mm) would have higher incidence of post-HCT bacteremia of potential oral/periodontal origin than those judged to have healthy periodontal tissue (i.e. all PPD = 2-3mm).

Secondarily, we hypothesize that periodontal patients with deeper PPDs (≥6mm) would have greater number of inpatient hospitalization days between day 0 and day 100 post-HCT than those with no evidence of periodontal disease during pre-transplant assessment.

Aims

1) To assess the relationship between maximum pre-transplant PPD and bacteremia of potential oral origin between day 0 and day 100 post-HCT.
2) To assess the relationship between maximum pre-transplant PPD and total inpatient hospitalization days between day 0 and day 100 post-HCT.
3) To assess the relationship between maximum pre-transplant PPD and survival at day 100.
4) To examine the aforementioned outcomes in patients who did and did not complete prescribed periodontal therapy prior to transplant.

5) To evaluate differences between periodontal probing groups with respect to degree of pre-transplant periodontal intervention.
6) To evaluate whether differences in post-transplant outcomes varied between periodontal groups based on relative degree of myeloablation (MA v. RIC conditioning).

Chapter II: Materials and Methods

A list of consecutive patients treated with allogeneic HCT at Seattle Cancer Care Alliance (SCCA, Seattle, WA USA) between January 1, 2004 and March 26, 2013 was generated by Fred Hutchinson Cancer Research Center (FHCRC) Clinical Research Data Systems division and reviewed for eligibility. January 31, 2013 was designated as the end limit for review purposes (due to availability of patient records) and historical records were reviewed until target sample size was attained (N= 600). Patients younger than 21 years of age were *a priori* excluded due to inconsistent gathering of periodontal data and overlap in post-transplant evaluation between SCCA and Seattle Children's Hospital. Physical records from the Oral Medicine Services clinic at SCCA (OMS SCCA) were reviewed against this list to identify all patients completing pre-transplant oral medicine examination prior to transplant. Oral medicine examination (described in detail below) was part of standard pre-hematopoietic cell transplantation (HCT) protocol at SCCA designed to identify and eliminate potential sources of infection in the oral cavity prior to transplant.

Eligibility Requirements/Study Population

All eligible individuals must have completed pre-transplant oral medicine evaluation including measurement of periodontal probing depths (PPDs) prior to bone marrow transplant (BMT) or peripheral blood stem cell transplant (PBSCT) at SCCA. Umbilical cord transplants and transplants completed at other centers were not included in this study. Additionally, recent dental radiographs or radiographs obtained concurrently with oral medicine examination were required for inclusion. Eligible radiographs must have demonstrated alveolar bone level in all quadrants (i.e. panoramic or intraoral equivalent). Individuals were also excluded if they lacked pre-transplant periodontal assessment (defined in detail below) or oral medicine departure

examination (including oral mucosal GVHD diagnosis prior to release from SCCA). Patients in whom departure examination was precluded by relapse, graft failure, release to palliative care/hospice, or death were not excluded to minimize omission of potential negative outcomes (“intent to analyze”). Edentulous patients were exempted from periodontal assessment but were excluded from periodontal analysis. Edentulous patients were included in the study for comparative purposes as they possessed risk for bacteremia of oral “mucosal origin” but not bacteremia of “periodontal origin”. If an individual completed multiple allogeneic transplants during the study period (N= 20) only the first transplant was evaluated. Data pertaining to second allogeneic transplants were included if patients lacked oral medicine data related to the first transplant (N= 2). Further transplants were censored from analysis. Patients who completed autologous transplant prior to allogeneic transplantation as part of planned “tandem transplantation” were included if SCCA OMS evaluation was completed between transplants (N= 1). All individuals provided consent according to FHCRC protocol #884 (Oral Complications of Transplant) and #999.209 (Master Protocol for Use of Medical Records).

Pre-Transplant Oral Medicine Evaluation

Pre-transplant examinations were completed by SCCA Oral Medicine staff (attending dentists and/or hygienists). Nine different examiners completed at least one assessment (though 89% were performed by the service’s two principle attending doctors). Examinations included inspection and palpation of head and neck structures and intraoral hard and soft tissues, as well as periodontal screening examination, oral hygiene assessment, and dental radiography (panoramic with or without intraoral radiographs, see below). Supplemental dental radiographs provided by extra-mural dental offices were evaluated where applicable. All patients received individualized oral hygiene instruction (OHI), and verbal and written education related to oral

complications of transplant (e.g. oral mucositis, hyposalivation, taste changes). Oral hygiene instruction was re-enforced at regular intervals in the immediate peri-transplant period (Day -1 to 21).

Periodontal/Gingival Assessment

A standardized periodontal screening examination was carried out according to SCCA OMS protocol. PPDs were measured using a Marquis periodontal probe (banded in 3mm increments) for three teeth per quadrant (first premolar, first and second molar) at either the mesiobuccal (Teeth #12,14,28,30,31) or distobuccal line angle (Teeth #2,3,5,15,18,19,21). If pre-defined teeth were absent, the most similar tooth in the quadrant was substituted. Additional probing sites were recorded if potential for significant periodontal pocket depth was identified based on clinical or radiographic examination. Radiographs were reviewed and additional PPDs were obtained at the discretion of the examiner in attempts to identify clinically significant periodontal pocketing (i.e. ≥5mm) not assessed during standard examination. All PPDs were recorded to the nearest whole number. Gingivitis and local factors (plaque, supra- and subgingival calculus) were assessed using oral hygiene definitions defined in internal documents utilized in the SCCA OMS clinic (Figure 1). Additionally, all patients completed the SCCA OMS Dental History Questionnaire (Figure 2) which included self-reported frequency of brushing and flossing, time since last dental visit, and oral concerns selected from a list of common intra- and extra-oral problems. Oral hygiene assessment and self-reported information were utilized to determine personalized oral hygiene interventions.

Pre-Transplant Periodontal Therapy

Pre-transplant periodontal treatment plans were created by OMS attending dentists to stabilize oral disease prior to conditioning. Potential periodontal interventions included 1) mechanical

debridement (scaling, spot curettage, plaque removal), 2) antimicrobial therapy (Chlorhexidine gluconate), 3) local minocycline therapy (Arestin^{TM} – OraPharma Horsham, PA USA), and 4) Tooth extraction. Pulpal and periapical infection were identified and appropriately treated with root canal therapy or dental extraction whenever possible. Dental caries judged to put the patient at risk for pain or pulpal infection within the ensuing calendar year were treated with definitive restoration or stabilized with temporary restorative material. Factors affecting the ability to complete recommended therapy included (but were not limited to) neutropenia, thrombocytopenia, financial limitations, and factors related to fragile underlying health condition (e.g. hospital re-admission, medical deferment). Supportive measures including prophylactic antibiotics, platelet transfusions, and/or other interventions were pursued where indicated to allow for completion of treatment prior to HCT. Prophylactic antibiotics were utilized if patients presented with any of the following indications: neutropenia (based on discretion of clinical examiner, generally ANC <750/mm^3), Hickman line, periodontal abscess, artificial joint, risk for bacterial endocarditis (according to American Heart Association guidelines).

For purposes of analysis periodontal scaling was scored on a 1-5 categorical scale based on the degree of intervention (light, light-regular, regular, regular-periodontal, periodontal) as judged by the clinical attending. Curettage, local antibiotic therapy, and dental extractions were classified by number of affected teeth. Treatment completion was confirmed through review of SCCA OMS hygiene records and clinic scheduling manifests or records from outside providers where available. Where discrepancies existed between the treatment recommendation and clinical treatment notes, the intervention with the higher score was included. Treatment visits for which notes were unavailable were excluded from analysis (N= 5).

Demographic Information

Date of birth, recipient sex, hematologic diagnosis, stem cell source, donor relationship, degree of Human Leukocyte Antigen (HLA) match, history of prior transplant, and conditioning regimen were obtained from Electronic Health Records (ORCA, University of Washington Medical Center, Seattle, WA USA; Powerchart, Cerner Corporation, Kansas City, MO USA). Systemic health conditions (e.g. Diabetes Mellitus) and habits (e.g. smoking) known to influence periodontal health were also recorded. Individuals were classified as current smokers if they reported smoking within the 6 months preceding OMS SCCAS examination.

HCT Protocols

33 distinct MA (544 patients) and RIC conditioning protocols (65 patients) were utilized in our cohort (Table 3). Protocols included combinations of the following agents/interventions: anti-thymocyte globulin (ATG), busulfan, carmustine (BCNU), clofarabine, cyclophosphamide (CY, Cytoxan), cytarabine (Ara-C), etoposide (VP-16), fludarabine, melphalan (L-Pam), rituximab, total body irradiation (TBI), thiotepa, and treosulfan.

Prophylactic GVHD regimens were also highly varied within our cohort. The most common prescribed prophylactic medications were primarily corticosteroids, cyclosporine (CSP, Neoral), cyclophosphamide (CY, Cytoxan), methotrexate (MTX), mycophenolate mofetil (MMF), sirolimus (RAPA, rapamune), and tacrolimus (FK-506) therapy. 40 different protocols were used in total.

Standard antibacterial, antifungal, and antiviral prophylaxis were provided per standard of care according to SCCA Infectious Disease protocols [Antibacterial: levofloxacin during initial

neutropenia (750mg po or IV per day) and trimethoprim/sulfamethoxazole (TMP/SMX) conditioning until day ≥180; Antifungal: Fluconazole conditioning until day 75 (400mg po qd); Antiviral: acyclovir (ACV, 800mg po bid) or Valacyclovir (VACV, 500mg po bid) continued to ≥1 year. Alternative medications were utilized in situations of allergy or sensitivity)]. Surveillance blood cultures were obtained two times per week throughout inpatient care and once per week during the outpatient period when patients were receiving steroid therapy (≥1mg/kg/d). Daily blood cultures were also completed during febrile episodes. Cultures were collected with paired sets of aerobic, anaerobic, and mycobacterial/fungal bottles containing culture medium.

Post-Transplant Outcomes

The primary outcome measure in the study was bacteremia of potentially oral origin. For each patient, blood cultures were reviewed from the start of conditioning through Day 100. Total number of positive bacterial cultures, date(s) of positive cultures, and causative organism(s) were identified. Microbial details were recorded to the maximum level of specificity provided by laboratory results (e.g. cellular morphology, genus, species). Only positive cultures classified to the genus or species level were included in our analysis. Multiple positive cultures obtained on the same date were reviewed for duplication. In situations where multiple cultures appeared to represent a single organism, the most specific result was scored as a single positive result. Blood cultures were obtained during the normal course of patient care. As such they were not designed to determine the oral origin of infection. For purposes of analysis, organisms were categorized as “likely periodontal origin”, “likely oral origin”, “possible oral origin”, and “likely non-oral origin” based on a review of literature (Figure 3).[21, 22, 25, 26, 32, 38, 43, 44] Proposed groupings were reviewed and modified by a physician specializing in Infectious Disease (M.B.)

blinded to individual patient data (including pre-transplant periodontal status). Administrative records were reviewed by FHCRC's Clinical Research Data Systems division to determine length of inpatient hospital stay and Day 100 survival.

Figure 1 – SCCA OMS Oral Hygiene Definitions

Excellent

- No plaque or calculus evident
- No gingival inflammation or bleeding or edema
- Gingiva: smooth marginal gingiva, normal color, and shape
- Periodontal: attachment less than or equal to 3mm

Good

- Gingiva is of normal color and shape
- No evidence of periodontal abnormality, pocket depths generally <3mm, isolated 4mm
- Isolated areas with plaque (<1/3 tooth surface), particularly with difficult access areas, <4 areas (teeth); association with marginal tissue inflammation (grade 1 or less) change
- Only occasional plaque
- Supra gingival calculus <1mm, <6 teeth

Fair

- Moderate to heavy generalized plaque 1/3 to 2/3 surface
- Calculus supragingival and subgingival on 1/3 to 1/2 teeth
- Moderate edema, inflammation, bleeding >1/3 teeth
- Positive inflammation, <8 teeth with bleeding on probing, pocket depths generally 3-4mm, isolated 5-6mm

Poor

- Inflamed, red, swollen gingiva
- Heavy plaque and calculus and periodontal tissue break down
- Plaque, calculus, debris
- Heavy plaque (>2/3 tooth covered with plaque/calculus) on over 75% of teeth; severe gingival inflammation (grade 2+) with bleeding, edema

Revised 9/2004, reviewed 9/2008

Figure 2 – SCCA OMS Dental History Questionnaire

ORAL MEDICINE PRE-TRANPLANT DENTAL HISTORY

Do you have a history of any of the following (circle all that apply):

Heart Murmur Mitral Valve Prolapse History of Rheumatic Fever Endocarditis Artificial joint Splenectomy

If yes, do you take antibiotics prior to dental treatment: No Yes Medication name _____

Have you taken: Zometa Aredia Fosamax Boniva **Dates:** _____

Allergies: Penicillin Anesthetics Latex **Other:** _____

Previous Chemotherapy No Yes **Date of last treatment:** _____

Prior Transplant: No Yes **Type:** _____ **Date:** _____

Please circle type and date of most recent dental treatment(s):

Dental cleaning Date _____

Fillings/Crowns Date _____ **How Many**_____

Root Canals Date _____ **How Many**_____

Extractions Date _____ **How Many**_____

Are you currently experiencing any of the following problems: (circle)

Toothaches	**Gum disease**	**Dry mouth**	**Frequent headaches**
Tooth decay	**Bleeding gums**	**Bad taste in mouth**	**Jaw pain**
Broken Teeth	**Wisdom tooth problem**	**Mouth sores**	**TMJ problems**
Abscessed Teeth	**Mouth pain**	**Cold sores**	**Jaw swelling**
Loose teeth	**Exposed bone**	**Canker sores**	
Tooth sensitivity (circle: hot cold sweets)		**Oral yeast (Thrush)**	

Any other oral problems: _____

Comments:_____

Routine Oral Hygiene

Manual Type: Soft Med Hard **Electric:** Crest-Spin Oral B Sonicare **Other** _____

- **How often do you usually brush your teeth?** _____ **#times per day or** _____**#times per week**
- **Do you floss your teeth?** No Yes _____ **#times per day or** _____**#times per week**
- **Do you routinely use a mouth rinse?** No Yes **Brand Name:**_____
- ***For children*: Does parent brush child's teeth?** No Yes _____ **# times per day Floss teeth?** No Yes

Revised 8/2012

Table 1 – Bacteremia groupings: periodontal, oral (possible/likely)

Oral – possible (448)*	**Oral – likely (26)[1]**	**Periodontal (5)[1]**
coagulase(-) Staphylococci (268)	Capnocytophaga sputigena (1)	Acinetobacter junii (0)[2]
corynebacterium (not jeikeium) (2)	Gemella haemolysans (5)	Acinetobacter ursingii (2)
Escherichia coli (12)	Lactobacillus casei (0)[2]	Acinetobacter baumannii (1)
Enterobacter cloacae (9)	Leptotrichia buccalis (1)	Acinetobacter johnsonii (1)
Enterococcus casseliflavus (1)	Leptotrichia species (1)	Actinomyces odontolyticus (1)
Enterococcus faecalis (26)	Rothia mucilaginous (1)	
Enterococcus faecium (31)	Streptococcus gordonii (1)	
Enterococcus gallinarum (1)	Streptococcus milleri group (6)	
Enterococcus species (10)	Streptococcus mitis (1)	
Klebsiella pneumoniae (24)	Streptococcus parasanguinis (1)	
Pseudomonas aeruginosa (22)	Streptococcus salivarius (1)	
Staphylococcus aureus (24)	Streptococcus (fastidious) (1)	
Stenotrophomonas maltophilia (18)	Streptococcus (non-hemolytic) (0)[2]	
	Viridans Streptococci (5)	

*values in brackets indicate total number of positive cultures
[1]see Table 12
[2]signifies initial culture re-classified as a different bacterial species

Chapter III: Statistical Analysis

Individuals were divided into three groups based on maximum PPD recorded in the pre-transplant examination: Group 1 (2-3mm), Group 2 (4-5mm), Group 3 (≥6mm). Divisions between periodontal groups used the same PPD criteria defined in the WHO Community Index of Periodontal Treatment Needs (CPITN)[60] though PPDs pertaining to extracted teeth were not included in PPD group classification (as the potential source of infection had been eliminated).

Differences in demographic values across PPD groups were assessed by chi-squared analysis and Fischer's exact test. Differences in number of infections and number of inpatient days across PPD groups were assessed by Kruskal-Wallis one-way analysis of variance. Differences in the proportion of patients with infection and the proportion of patients dying within 100 days of transplant were assessed by chi-squared analysis. Cox regression was used to further assess differences in incidence of infection during the first 100 days after transplant. Analysis was repeated after exclusion of patients conditioned with RIC protocols to assess the influence of conditioning protocol on outcomes of interest.

A sample size of 200 patients per group was calculated to provide 80% power to detect significant difference between PPD groups (i.e. for a true difference in a binary endpoint between 8%, the expected incidence of gram-negative versus non-CoNS gram-positive bacteremia in the control group, versus 13% in any other group) at the 2-sided 0.05 level of significance.

Analysis was performed using SAS (Cary, NC) and Microsoft Excel (Microsoft, Seattle WA USA)

Chapter IV: Results

Patient Demographics

973 patients were evaluated in SCCA OMS prior to allogeneic HCT and completed TXP between January 27, 2005 and January 31, 2013. 620 patients were eligible for analysis after exclusion of patients who failed to meet eligibility criteria (Figure 3). 609 patients in the cohort were dentate, while 11 were edentulous. Approximately 90% of patients in the dentate group were conditioned with myeloablative conditioning protocols. The majority of patients were male (55.8%) and ranged in age between 21.5 and 74.1 years old (mean = 46.6 years). Peripheral blood stem cells were the most common stem cell source (79.8%). The majority of donors were not related to the recipient (60.3%). Matched unrelated donors (MURDs) were the most common donor group with respect to HLA-classification (54.7% of total donors). Acute myelogenous leukemia (37.8%) and myelodysplastic syndrome (18.2%) were the most commonly treated conditions (Table 1).

Periodontal Classification

68.3% of 609 patients had at least one PPD consistent with periodontal disease (i.e. ≥4mm). 104 patients had maximum PPDs ≥6mm (Group 3; 17.1%). No statistical differences were noted between PPD groups with regard to sex, hematologic diagnosis, stem cell source, HLA-match, donor relationship, hematologic diagnosis (Table 2), conditioning regimen (Table 3), GVHD prophylaxis (Table 4), or diabetes status (Table 5). However, patients in Group 3 were statistically older ($p < 0.0002$) (Table 2) and more likely to be current or former smokers ($p < 0.01$ (Table 5).

Periodontal Classification versus Outcomes of Interest

No statistical differences were found between periodontal classification (categorized by either maximum or mean PPD) and incidence of bacteremia, length of inpatient hospitalization stay, or death within the first 100 days post-transplant (Table 6) though a trend toward significance was observed in Group 2 (max PPD = 4-5mm) with respect to risk of bacteremia of potential oral/periodontal origin [Hazard Ratio = 1.28 (1.0-1.7); $HR_{G(+)}$ = 1.22 (0.9-1.6); $HR_{G(-)}$ (0.8-2.6)]. (Table 7). Comparison of group 2 and group 3 (max PPD ≥6mm) demonstrated a reverse trend for bacteremia with lower risk in the more severe PPD group [(HR = 0.96 (0.7-1.4); $HR_{G(+)}$ = 1.01 (0.7-1.5); $HR_{G(-)}$ = 0.54 (0.2-1.6)] (Table 7). Bacteremia results were consistent when patients conditioned with RIC protocols were excluded from analysis (Table 8)

Completion of Pre-Transplant Periodontal Therapy

45 patients did not complete prescribed periodontal therapy prior to transplant. No statistical differences in post-transplant outcomes were observed between those who did and did not complete recommended therapy (Table 9). Bacteremia characteristics (possible/likely oral, gram-positive, gram-negative) also did not differ based on treatment completion (Table 10).

When considering all interventions collectively, patients in each periodontal group were equally likely to complete recommended treatment prior to transplant ($p < 0.38$). Treatment was more likely to be prescribed in group 3 (PPD ≥6mm; $p = 0.0000$) than in the other groups. Patients in Group 3 were also statistically more likely to have completed intensive periodontal therapy including moderate to heavy scaling, spot curettage, and/or local antibiotic therapy (p values for each intervention <0.0001, Table 11).

"Non-Treatment" Subgroup

Though the "non-treatment group" in our cohort is insufficient for meaningful statistical analysis, it does provide a *de facto* control group for comparative purposes. Among patients who did not complete recommended treatment with at least one PPD ≥6mm (N=16), there were 13 bacteremias diagnosed in six patients. 92.3% of bacteremias in this subgroup were of possible oral origin with the great majority (84.6%) representing coagulase-negative staphylococci.

Common Bacterial Isolates

Overall incidence of possible/likely oral bacteremia was 38.6%. When evaluating the entire cohort, CoNS were the most commonly isolated organism in bacteremia (41.9% of 639 bacteremias). Interestingly, 82.3% of the 268 CoNS bacteremias were isolated in patients with at least one periodontal probing depth greater than 4mm ($N_{\geq 6mm}$= 110, $N_{4\text{-}5mm}$= 112). Incidence of oral/periodontal bacteremia decreased to 5.7% if CoNS was excluded from analysis. Other potentially oral bacteremias in our population included K. pneumonia (N= 24 total positive cultures) and Enterobacter cloacae (N= 9). There was no statistical difference in increase of either bacteremia based on PPD measurement (K. pneumonia: $N_{\geq 6mm}$= 6, $N_{4\text{-}5mm}$= 5, $N_{<4mm}$= 13; E. cloacae: $N_{\geq 6mm}$= 1, $N_{4\text{-}5mm}$= 3, $N_{<4mm}$= 6).

Bacteremia Not Otherwise Specified

Positive cultures were excluded from analysis of periodontal group versus bacteremia if they were not classified to the genus or species level. Excluded cultures included one anaerobic gram negative rod, eight alpha hemolytic strep, two alpha hemolytic strep (not enterococci), seven alpha hemolytic strep (not enterococci or pneumoniae), and 15 alpha hemolytic strep (not

enterococci, pneumoniae or milleri group) which may have represented oral bacteria. Most of these cultures were recovered in patients with at least one PPD ≥4mm (Table 8).

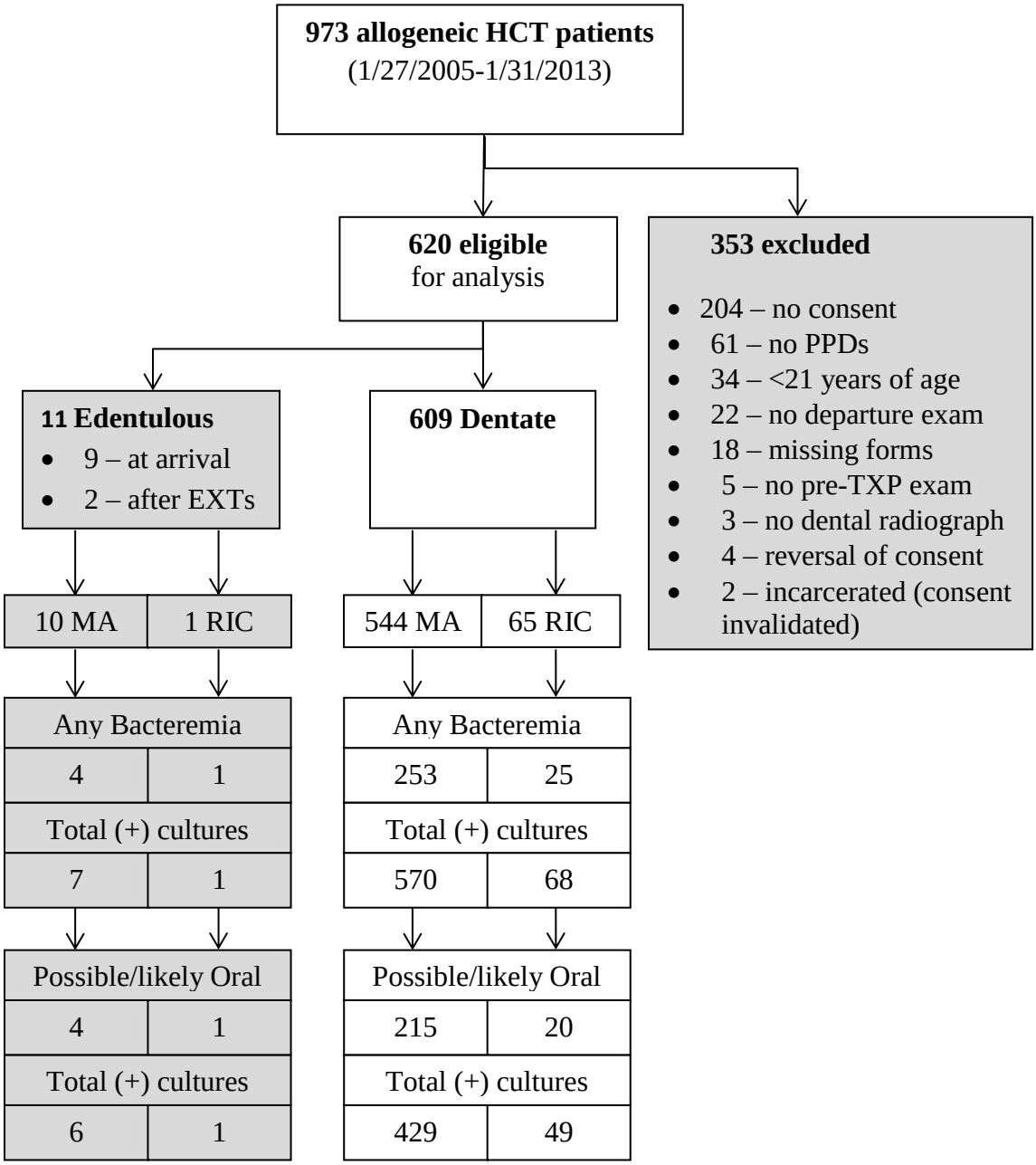
Edentulous Patients

Five of 11 edentulous patients had eight confirmed bacteremias (mean = 0.73, median = 0). 87.5% of bacteremias were of possible/likely oral origin (Figure 3). CoNS (N = 3) was the most commonly isolated organism. Acinetobacter ursingii, a likely periodontal pathogen, was identified in one case despite lack of dentition (day 73, WHO mucositis scale = 0). Duration of inpatient hospitalization ranged from 13 to 43 days (mean = 28.5d). The small size in the edentulous cohort precludes meaningful statistical analysis though findings were similar to those observed in periodontal analysis (which can be reviewed in Table 6).

Death Within 100 Days

62 dentate (10.2%) and one edentulous patient died within the first 100 days post-transplant (9.1%). The most common cause of death in dentate patients was residual or refractory malignant disease (N = 16), followed by bacterial infection (N = 9) and complications of GVHD (N = 7). Other bacteria-related causes of death included combined bacterial/fungal infection (N = 2), aspiration pneumoniae (N = 1) and suspected culture-negative sepsis (N = 5). The single death in the edentulous group was due to complications of Klebsiella pneumoniae bacteremia.

Figure 3 – Flow Diagram of General Patient Characteristics



EXT = extraction; HCT = hematopoietic cell transplantation; MA = myeloablative conditioning; PPD = periodontal probing depth; RIC = reduced intensity conditioning

Table 2 – Patient Demographics

	Maximum PPD	Group 1 (2-3mm)	Group 2 (4-5mm)	Group 3 (≥6mm)	p-value
Sex	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**	0.10
Male	**340**	150 (52.3)	123 (56.4)	67 (64.4)	
Female	**269**	137 (47.7)	95 (43.6)	37 (35.6)	
Age	**Years old**				0.00[1]
Mean	**46.6**	45.5	46.4	51.1	
Median	**48.5**	47.3	47.8	52.6	
Range	**21.5-74.1**	21.5-74.1	21.5-69.8	23.0-69.0	
Conditioning Protocol[2]	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**	0.11
Myeloablative	**544**	264 (92.0)	191 (87.6)	89 (85.6)	
RIC	**65**	23 (8.0)	27 (12.4)	15 (14.4)	
Source	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**	0.26
PBSC	**486**	222 (77.7)	176 (80.7)	88 (84.6)	
BM/Combination[3]	**123**	65 (22.3)	42 (19.3)	16 (15.4)	
Donor	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**	0.13
MURD	**333**	166 (57.8)	113 (51.8)	54 (51.9)	
MRD[4]	**229**	103 (35.9)	81 (37.2)	45 (43.3)	
Mismatched Donor[5]	**47**	18 (6.3)	24 (11.0)	5 (4.8)	
Donor Relationship	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**	0.36
Non-Related	**367**	181 (63.1)	128 (58.7)	58 (55.8)	
Sibling	**235**	103 (35.9)	86 (39.4)	46 (44.2)	
Other[6]	**7**	3 (1.0)	4 (1.9)	0 (0.0)	

Ag= (human leukocyte) antigen; BM= bone marrow; MMRD= mismatched related donor; MMURD= mismatched unrelated donor; MRD= matched related donor; MURD= matched unrelated donor; PBSC= peripheral blood stem cell; PPD= periodontal probing depth; RIC= reduced intensity conditioning

[1] P = 0.0002 (one way ANOVA)
[2] see Table 3 "Conditioning Protocols" for further detail
[3] Includes BM + PBSC (N=1)
[4] Includes syngeneic (N=2)
[5] MMRD 0Ag (N= 3), 1Ag (N= 4), 3Ag (N= 6); MMURD 1Ag (N= 34)
[6] Child (N= 3), Parent (N= 3), Half-sibling (N= 1)

Table 2 – Patient Demographics (continued)

	Maximum PPD	Group 1 (2-3mm)	Group 2 (4-5mm)	Group 3 (≥6mm)
Hematologic Diagnosis	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**
AML	**230**	111 (38.7)	77 (36.7)	42 (37.5)
MDS	**111**	45 (15.7)	41 (18.8)	25 (24.0)
ALL	**90**	51 (17.8)	28 (12.8)	11 (10.6)
Myelofibrosis	**61**	33 (11.5)	18 (8.3)	10 (9.6)
CML	**55**	22 (7.7)	25 (11.5)	8 (7.7)
Aplastic Anemia	**15**	8 (2.8)	6 (2.8)	1 (1.0)
NHL	**14**	3 (1.0)	7 (3.7)	4 (2.9)
Multiple Myeloma	**6**	1 (0.3)	5 (2.3)	0 (0.0)
CMML	**5**	1 (0.3)	1 (0.5)	3 (2.9)
MPS	**5**	2 (0.7)	2 (0.9)	1 (1.0)
T-cell Lymphoma	**5**	3 (1.0)	1 (0.5)	1 (1.0)
APL	**4**	2 (0.7)	2 (0.9)	0 (0.0)
T-cell Prolymphocytic Leukemia	**2**	1 (0.3)	0 (0.0)	1 (1.0)
Acute Undifferentiated Leukemia	**1**	1 (0.3)	0 (0.0)	0 (0.0)
Biphenotypic Leukemia	**1**	0 (0.0)	1 (0.5)	0 (0.0)
CLL	**1**	1 (0.3)	0 (0.0)	0 (0.0)
Common variable immunodeficiency with aplasia	**1**	1 (0.3)	0 (0.0)	0 (0.0)
Hemophagocytic lymphohistiocytosis	**1**	0 (0.0)	0 (0.0)	1 (1.0)
NK Cell Leukemia	**1**	1 (0.3)	0 (0.0)	0 (0.0)

ALL= acute lymphoblastic leukemia; AML= acute myelogenous leukemia; APL= acute promyelocytic leukemia; CLL= chronic lymphoblastic leukemia; CML= chronic myelogenous leukemia; CMML= chronic myelomonocytic leukemia; MDS= myelodysplastic syndrome; MPS= myeloproliferative syndrome; NHL= non-hodgkin's lymphoma; NK= natural killer (cell); PPD= periodontal probing depth

Table 3 – Conditioning Protocols

	Maximum PPD	Group 1 (2-3mm)	Group 2 (4-5mm)	Group 3 (≥6mm)
Conditioning Protocol				
MA	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**
Busulfan, Cytoxan	**246**	118 (19.3)	86 (39.4)	42 (40.4)
Cytoxan, HD-TBI(1200cGy)	**83**	42 (14.6)	31 (14.2)	10 (9.6)
Busulfan, Fludarabine	**59**	28 (9.8)	17 (7.8)	14 (13.5)
Cytoxan, LI(400), HD-TBI(1200cGy)	**51**	26 (4.3)	17 (7.8)	8 (7.7)
Treosulfan, Fludarabine, TBI(200cGy)	**51**	26 (4.3)	17 (7.8)	8 (7.7)
Busulfan, Fludarabine, ATG	**16**	5 (1.7)	7 (3.2)	4 (6.7)
Thiotepa, Fludarabine, HD- TBI(1320cGy)	**10**	7 (2.4)	3 (1.4)	0 (0.0)
Busulfan, L-PAM	**5**	1 (0.3)	4 (1.8)	0 (0.0)
Cytoxan, Fludarabine, RAB, TBI(200cGy)	**4**	0 (0.0)	4 (1.8)	0 (0.0)
Thiotepa, LI(400), Fludarabine, HD-TBI(1320cGy)	**4**	1 (0.3)	0 (0.0)	3 (2.9)
HD-TBI(1200cGy)	**3**	3 (1.0)	0 (0.0)	0 (0.0)
Cytoxan, ATG	**2**	2 (0.7)	0 (0.0)	0 (0.0)
BEAM (BCNU, VP-16, ARA-C, L-PAM)	**1**	0 (0.0)	1 (0.5)	0 (0.0)
BEAM (BCNU, VP-16, ARA-C, L-PAM),LI(1600)	**1**	0 (0.0)	1 (0.5)	0 (0.0)
Busulfan, Cytoxan, Campath	**1**	1 (0.3)	0 (0.0)	0 (0.0)
Busulfan, Cytoxan, TBI(200cGy)	**1**	1 (0.3)	0 (0.0)	0 (0.0)
Busulfan, LI(1800), Fludarabine	**1**	1 (0.3)	0 (0.0)	0 (0.0)

Ara-C = cytarabine; ATG = anti-thymocyte globulin; BC8SA = streptavidin-conjugated anti-CD45 antibody; BCNU = carmustine; BEAM = carmustine (BCNU), etoposide (VP-16), cytarabine (Ara-C), melphalan (L-pam), cGy = centigray; HD-TBI(cGy); = high-dose total body irradiation; L-Pam = melphalan; LI(cGy) = localized irradiation; RAB = radiolabeled antibody (not otherwise specified); RDB = radio-labeled dota-biotin; TBI(cGy); = total body irradiation; VP-16 = etoposide

Table 3 – Conditioning Protocols (continued)

	Maximum PPD	Group 1 (2-3mm)	Group 2 (4-5mm)	Group 3 (≥6mm)
Conditioning Protocol	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**
MA				
Cytoxan, LI(1400), HD-TBI(1200cGy)	**1**	0 (0.0)	1 (0.5)	0 (0.0)
HD- TBI(1200cGy), LI(400),	**1**	1 (0.3)	0 (0.0)	0 (0.0)
Treosulfan, Fludarabine, LI(800)	**1**	0 (0.0)	1 (0.5)	0 (0.0)
RIC	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**
Treosulfan, Fludarabine	**24**	6 (2.1)	12 (5.5)	6 (5.8)
Fludarabine, RAB, TBI(200cGy)	**19**	6 (2.1)	6 (2.8)	7 (36.8)
Cytoxan, ATG, TBI(200cGy)	**6**	4 (1.4)	2 (0.9)	0 (0.0)
Cytoxan, Fludarabine, ATG, TBI(200cGy)	**6**	2 (0.7)	3 (1.4)	1 (1.0)
BC8SA, RDB, Fludarabine, TBI(200cGy)	**2**	1 (0.3)	1 (0.5)	0 (0.0)
Fludarabine, TBI(200cGy)	**2**	2 (0.7)	0 (0.0)	0 (0.0)
Treosulfan, Fludarabine, ATG	**2**	1 (0.3)	0 (0.0)	1 (1.0)
Cytoxan, Fludarabine, RAB, LI(1400), TBI(200cGy)	**1**	1 (0.3)	0 (0.0)	0 (0.0)
Fludarabine, RAB, LI(1400), TBI(200cGy)	**1**	0 (0.0)	1 (0.5)	0 (0.0)
L-PAM, Fludarabine, TBI(200cGy)	**1**	0 (0.0)	1 (0.5)	0 (0.0)
Rituximab, Fludarabine, RAB, TBI(200cGy)	**1**	0 (0.0)	1 (0.5)	0 (0.0)

Ara-C = cytarabine; ATG = anti-thymocyte globulin; BC8SA = streptavidin-conjugated anti-CD45 antibody; BCNU = carmustine; BEAM = carmustine (BCNU), etoposide (VP-16), cytarabine (Ara-C), melphalan (L-pam), cGy = centigray; HD-TBI(cGy); = high-dose total body irradiation; L-Pam = melphalan; LI(cGy) = localized irradiation; RAB = radiolabeled antibody (not otherwise specified); RDB = radio-labeled dota-biotin; TBI(cGy); = total body irradiation; VP-16 = etoposide

Table 4 – GVHD Prophylaxis

	Maximum PPD	Group 1 (2-3mm)	Group 2 (4-5mm)	Group 3 (≥6mm)
GVHD Prophylaxis	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**
MTX, FK506	**365**	156 (54.4)	138 (63.3)	70 (68.3)
MTX, FK506, Steroids	**66**	42 (14.6)	18 (8.3)	5.8 (9.1)
CY	**29**	17 (5.9)	6 (2.8)	6 (5.8)
FK506	**18**	10 (3.5)	5 (2.3)	3 (2.9)
MMF, FK506	**16**	6 (2.1)	9 (4.1)	1 (1)
CSP, MTX, Neoral	**14**	6 (2.1)	8 (3.7)	0 (0.0)
CSP, CY	**12**	10 (3.5)	1 (0.5)	1 (1.0)
Neoral, MMF	**12**	1 (0.3)	5 (2.3)	6 (5.8)
CSP, MTX	**10**	8 (2.8)	1 (0.5)	1 (1.0)
MTX, MMF, FK506	**10**	5 (1.7)	3 (1.4)	2 (1.9)
CSP, MTX, FK506	**9**	3 (1.0)	5 (2.3)	1 (1.0)
CSP, MMF	**7**	4 (1.4)	3 (1.4)	0 (0.0)
CSP, Neoral, MMF	**5**	2 (0.7)	2 (0.9)	1 (1.0)
CY, MMF, FK506	**4**	1 (0.3)	3 (1.4)	0 (0.0)
CSP, MTX, Neoral, FK506	**3**	1 (0.3)	2 (0.9)	0 (0.0)
MTX, [CSP-Ophth (Blind study drug)], FK506	**3**	1 (0.3)	1 (0.5)	1 (1.0)
MTX, RAPA, FK506	**3**	0 (0.0)	2 (0.9)	1 (1.0)
CSP, MTX, MMF, FK506	**2**	2 (0.7)	0 (0.0)	0 (0.0)
MTX, MMF, FK506, Steroids	**2**	0 (0.0)	1 (0.5)	1 (1.0)
Neoral	**2**	1 (0.3)	0 (0.0)	1 (1.0)
CSP, CY, FK506	**1**	0 (0.0)	1 (0.5)	0 (0.0)
CSP, CY, RAPA	**1**	1 (0.3)	0 (0.0)	0 (0.0)
CSP, MMF, FK506	**1**	1 (0.03)	0 (0.0)	0 (0.0)
CSP, MTX, FK506, Steroids	**1**	1 (0.03)	0 (0.0)	0 (0.0)
CSP, MTX, MMF	**1**	1 (0.3)	0 (0.0)	0 (0.0)
CSP, MTX, Steroids, FK506	**1**	0 (0.0)	1 (0.5)	0 (0.0)
CSP, MTX, [Mycophenolate sodium], Neoral	**1**	1 (0.3)	0 (0.0)	0 (0.0)
CSP, [Mycophenolate sodium], Neoral, MMF	**1**	1 (0.3)	0 (0.0)	0 (0.0)

ATG = anti-thymocyte globulin; CY = cyclophosphamide (Cytoxan); CSP = cyclosporine; CSP-Ophth = ophthalmic cyclosporine; FK506 = tacrolimus; MMF = mycophenolate mofetil; MTX = methotrexate; Neoral = cyclosporine; RAPA = rapamune (Sirolimus)

Table 4 – GVHD Prophylaxis (continued)

	Maximum PPD	Group 1 (2-3mm)	Group 2 (4-5mm)	Group 3 (≥6mm)
GVHD Prophylaxis	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**
CSP, Neoral, MMF, FK506	**1**	1 (0.3)	0 (0.0)	0 (0.0)
CY, [Mycophenolate sodium], MMF, FK506	**1**	0 (0.0)	1 (0.5)	0 (0.0)
MMF, [Mycophenolate sodium], RAPA, FK506	**1**	0 (0.0)	1 (0.05)	0 (0.0)
MTX, [ATG (Blind study drug)], FK506	**1**	1 (0.3)	0 (0.0)	0 (0.0)
MTX, [Budesonide], ATG, FK506	**1**	1 (0.3)	0 (0.0)	0 (0.0)
MTX, [CSP Ophth (Blind study drug)], FK506, Steroids	**1**	1 (0.3)	0 (0.0)	0 (0.0)
MTX, [CSP-Ophth emulsion], FK506	**1**	0 (0.0)	1 (0.5)	0 (0.0)
MTX, MMF, RAPA, FK506	**1**	0 (0.0)	0 (0.0)	1 (1.0)
MTX, Neoral, FK506	**1**	1 (0.3)	0 (0.0)	0 (0.0)

ATG = anti-thymocyte globulin; CY = cyclophosphamide (Cytoxan); CSP = cyclosporine; CSP-Ophth = ophthalmic cyclosporine; FK506 = tacrolimus; MMF = mycophenolate mofetil; MTX = methotrexate; Neoral = cyclosporine; RAPA = rapamune (Sirolimus)

Table 5 – Periodontal Classification versus Systemic Factors Influencing Pre-existing Periodontitis

	Maximum PPD	Group 1 (2-3mm)	Group 2 (4-5mm)	Group 3 (≥6mm)	P-value
DM Type	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**	0.068
None	**568**	267 (93.0)	203 (93.1)	98 (94.2)	
Type 1	**6**	4 (1.4)	1 (0.5)	1 (1.0)	
Type 2	**33**	14 (4.9)	14 (6.4)	5 (4.8)	
Other[1]	**2**	2 (0.7)	0 (0.0)	0 (0.0)	
Smoking	**N total**	**N1 (%)**	**N2 (%)**	**N3 (%)**	[2]0.01*
Never	**382**	194 (67.6)	138 (63.3)	50 (48.1)	
Current	**54**	18 (6.3)	21 (9.6)	15 (14.4)	
Former	**158**	69 (24.0)	54 (24.8)	35 (33.7)	
Unknown	**15**	6 (2.1)	5 (2.3)	4 (3.8)	

*statistically significant
DM= diabetes mellitus; PPD= periodontal probing depth
[1]Includes diabetes insipidus (N=1) and gestational diabetes (N=1)
[2]Unknown status excluded from analysis

Table 6 – Periodontal classification versus Total Bacteremias, Inpatient Hospitalization Days, and Death within 100 Days

PPD[1]	N	Any Bacteremia (%)	N of Bacteremia median (range)	Inpatient days median (range)	Death w/in 100 days (%)
Maximum					
Group 1 (2-3 mm)	287	43	0 (0-14)	27 (0-103)	8
Group 2 (4-5 mm)	218	50	1 (0-16)	27 (0-106)	12
Group 3 (≥6 mm)	104	44	0 (0-13)	27 (0-85)	13
P-value		0.27	0.12	0.85	0.15
Mean (nearest 0.5mm)					
2-2.5mm	162	45	0 (0-14)	28 (1-106)	9
3-3.5mm	371	46	0 (0-16)	27 (0-104)	11
≥4mm	76	43	0 (0-7)	26 (2-85)	12
P-value		0.88	0.72	0.62	0.71

Table 7 – Periodontal Classification versus Bacteremia characteristics

All infections		**Any type**		**Gram (+)**		**Gram (-)**	
PPD[1]							
Maximum	N	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)
Group 1 (2-3mm)	287	43	1.0	38	1.0	11	1.0
Group 2 (4-5mm)	218	50	1.28 (1.0-1.7)	44	1.24 (0.9-1.6)	13	1.21 (0.7-2.0)
Group 3 (≥6mm)	104	44	1.11 (0.8-1.6)	41	1.18 (0.8-1.7)	6	0.52 (0.2-1.2)
P-value			0.18		0.29		0.12
Possible/likely oral		**Any type**		**Gram (+)**		**Gram (-)**	
PPD[1]							
Maximum	N	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)
Group 1 (2-3mm)	287	37	1.0	33	1.0	7	1.0
Group 2 (4-5mm)	218	44	1.28 (1.0-1.7)	38	1.22 (0.9-1.6)	10	1.45 (0.8-2.6)
Group 3 (≥6mm)	104	34	0.96 (0.7-1.4)	32	1.01 (0.7-1.5)	4	0.54 (0.2-1.6)
P-value			0.16		0.43		0.12

[1]including standard and additional sites
PPD= periodontal probing depth

Table 8 - Periodontal Classification versus Bacteremia Characteristics [RIC protocols excluded]

All infections		Any type		Gram +		Gram -	
PPD[1]							
Maximum	N	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)
Group 1 (2-3mm)	264	45	1.0	40	1.0	11	1.0
Group 2 (4-5mm)	191	50	1.22 (0.9-1.6)	45	1.21 (0.9-1.6)	13	1.15 (0.7-2.0)
Group 3 (≥6mm)	89	44	1.06 (0.7-1.5)	40	1.10 (0.8-1.6)	6	0.52 (0.2-1.3)
P-value			0.35		0.43		0.20
Possible/likely oral		Any type		Gram +		Gram -	
PPD[1]							
Maximum	N	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)
Group 1 (2-3mm)	264	39	1.0	34	1.0	8	1.0
Group 2 (4-5mm)	191	43	1.18 (0.9-1.6)	38	1.15 (0.8-1.6)	10	1.38 (0.7-2.6)
Group 3 (≥6mm)	89	34	0.90 (0.6-1.4)	31	0.95 (0.6-1.4)	4	0.62 (0.2-1.8)
P-value			0.35		0.58		0.27

[1]including standard and additional sites
PPD= periodontal probing depth

Table 9 – Pre-transplant Periodontal Therapy versus Bacteremia, Inpatient Hospitalization Days, and Death within 100 days

Treatment (n=5, missing)	N	Any Bacteremia (%)	N of Bacteremia median (range)	Inpatient days median (range)	Death w/in 100 days (%)
None	263	44	0 (0-12)	27 (0-106)	11
Not completed	45	40	0 (0-5)	26 (3-103)	2
Completed	296	47	0 (0-16)	27 (0-104)	11
P-value		0.57	0.69	0.91	0.18

Table 10 – Pre-transplant Periodontal Therapy versus Bacteremia Characteristics

Possible/likely oral Bacteremia		Any type		Gram (+)		Gram (-)	
Treatment (N = 5 missing)	N	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)
None	263	38	1.0	35	1.0	7	1.0
Not completed	45	33	0.86 (0.5-1.4)	27	0.73 (0.4-1.3)	9	1.22 (0.4-3.6)
Completed	296	40	1.11 (0.8-1.4)	35	1.06 (0.8-1.4)	8	1.08 (0.6-2.0)
P-value			0.56		0.43		0.93

Table 11 – Periodontal Classification versus Pre-Transplant Periodontal Intervention

	Group 1 (2-3mm)	Group 2 (4-5mm)	Group 3 (≥6mm)	P-value (all)	P-value (G2 vs. G3)
Prescribed Therapy	**N1 (%)**	**N2 (%)**	**N3 (%)**	[1]0.00*	[1]0.00*
None	182 (63.4)	79 (36.2)	4 (3.8)		
Any	105 (36.6)	139 (63.8)	100 (96.2)		
Completed Therapy (N = 5 missing)[2]	**N1 (% of prescribed)**	**N2 (% of prescribed)**	**N3 (% of prescribed)**	0.38	0.18
Not Completed	13 (12.4)	15 (10.8)	17 (17.0)		
Completed	91 (86.7)	121 (87.1)	82 (82.0)		
Unknown	1 (1.0)	3 (2.2)	1 (1.0)		
Scaling (N = 5 missing)[2]	**N1 (%)**	**N2 (%)**	**N3 (%)**	0.00*	0.08
None	206 (71.8)	104 (47.7)	38 (36.5)		
Any	80 (27.9)	111 (50.9)	65 (62.5)		
Unknown	1 (0.3)	3 (1.4)	1 (1.0)		
	N1 (%)	**N2 (%)**	**N3 (%)**	0.00*	[3]0.00*
<Moderate	252 (87.8)	158 (72.5)	51 (49.0)		
Moderate	33 (11.5)	51 (23.4)	26 (25.0)		
Heavy	1 (0.3)	6 (2.8)	26 (25.0)		
Unknown	1 (0.3)	3 (1.4)	1 (1.0)		
Curettage (N = 5 missing)[2]	**N1 (%)**	**N2 (%)**	**N3 (%)**	0.00*	0.00*
No	286 (99.7)	197 (90.3)	41 (39.4)		
Yes	0 (0.0)	18 (8.3)	62 (59.6)		
Unknown	1 (0.3)	3 (1.4)	1 (1.0)		
Arestin™ (N = 4 missing)[4]	**N1 (%)**	**N2 (%)**	**N3 (%)**	0.00*	0.00*
No	285 (99.3)	211 (96.8)	52 (50.0)		
Yes	1 (0.3)	4 (1.8)	52 (50.0)		
Unknown	1 (0.3)	3 (1.4)	0 (0.0)		

*statistically significant (all P <0.0000)
[1] computed by Fischer's Exact Test (all others comparisons by Chi-squared)
[2]completion of prescribed periodontal therapy was unknown in five patients (N1 = 1; N2 = 3; N3 = 1)
[3]P-value <0.0001
[4]Arestin™ was completed in one unknown patient (Group 3)

Table 12 – Periodontal classification versus bacteremia lacking genus identification

[excluded from oral/periodontal classification]

	Anaerobic GNR	**alpha-hemolytic Streptococci**			
Maximum PPD	NOS	NOS	non-Enterococci	non-Enterococci or Pneumoniae	non-Enterococcus, Pneumoniae, or Milleri group
Group 1 (2-3 mm)	0	3	0	2	6
Group 2 (4-5 mm)	0	3	0	3	7
Group 3 (≥6mm)	1	2	2	2	2

NOS = not otherwise specified

Chapter V: Discussion

This study was designed as an initial evaluation of the relationship between pre-transplant periodontal assessment and post-transplant bacteremia of potential oral origin, total inpatient hospitalization days within the first 100 days post-transplant, and day 100 survival in a cohort of patients treated with allogeneic hematopoietic cell transplantation (HCT). If associations were discovered using this study design, periodontal screening criteria could be refined and subjected to more rigorous evaluation in a prospective cohort study to ascertain the predictive of the exam. In this study, periodontal health was assessed via a standardized periodontal screening examination completed as part of oral medicine evaluation during routine pre-transplant assessment. In contrast to earlier works in dental[10, 15, 20] and oncology[8, 9, 29-31] literature, within our population every effort was made to stabilize periodontal, pulpal, and periapical health prior to transplant. This included both professional periodontal therapy as well as individualized oral hygiene instruction. Although compliance was not rigorously assessed, elimination of local plaque and calculus by dental scaling and emphasis on personal oral hygiene are believed to decrease active gingival and periodontal infection (this assertion is supported by a recent study in allogeneic HCT patients which showed decreases in plaque index, gingival inflammation and periodontal probing depths following similar interventions[61]). Furthermore, patients with compromised periodontal health were often re-evaluated after engraftment (and in some instances, retreated with Arestin™ where indicated – Arestin™ has been shown to dramatically reduce periodontal pocket microbial colonization for several weeks, and when administered immediately before conditioning for HCT could clearly have provided antibacterial benefits through the period of most profound neutropenia). Though the findings in our study support the null hypothesis that no difference existed between pre-transplant periodontal assessment and

post-transplant bacteremia of oral/periodontal origin it is logical to hypothesize that aggressive pre-transplant therapy may have dramatically reduced incidence of bacteremia within our cohort.

Though not statistically significant, a trend approaching significance was observed in Group 2 (PPD 4-5mm) in relation to bacteremia of potential oral/periodontal origin. Interestingly, the risk of patients in Group 2 was greater than that seen in Group 3 (PPD ≥6mm) though patients in the latter group had deeper periodontal pockets. This reverse trend may relate to patient management prior to transplant. Patients presenting with less severe signs of periodontal disease could be considered to have been treated less aggressively than those with frank, more severe disease. This in turn may have put the intermediate group at greater risk for periodontal-related blood stream infection. Our findings are consistent with this interpretation. Patients in Group 3 were statistically more likely to have been prescribed periodontal therapy prior to transplant and, when degree of periodontal treatment was considered, were found to have received more intensive intervention (e.g. moderate-heavy periodontal scaling, curettage, and Arestin^{TM}). It is worth noting that completion of any scaling was very nearly statistically significant as well ($p < 0.08$).

Though results supported the null hypothesis, there are several very important considerations to be entertained. All periodontal data reviewed in this study was gathered as part of a standard screening examination; collected data was then subsequently analyzed without specific intent to support or reject our hypothesis. Even though medical and dental records were analyzed retrospectively, pre-transplant oral health data was gathered prospectively and following a consistent protocol. The availability of 609 patients to study represents a very large cohort of

allogeneic HCT patients to study and thus allow for meaningful analysis with respect to periodontal health.

Partial Mouth Periodontal Assessment

The design of the study did present several inherent limitations that should also be considered. The most obvious from an oral health perspective is the lack of "full mouth" periodontal data for disease assessment. In periodontal literature, complete examination includes the measurement of six periodontal probing depths (PPDs) per tooth (192 sites if all 32 teeth are present)[62] in addition to other specific markers of periodontal disease including clinical attachment loss, furcation involvement, and tooth mobility. Gingival health is also evaluated by recording plaque levels on each tooth surface and assessing bleeding on probing for all periodontal sites. This process takes 25 to 45 minutes to complete and may be prohibitively time consuming.[62] PPDs recorded in the SCCA OMS clinic were limited to 12 standard sites (with additional sites included at the discretion of the examiner when periodontal bone loss was identified on radiographic examination). This fixed site partial mouth protocol was designed as an efficient and consistent clinical approach to assess periodontal health within the context of complete head and neck and intraoral examination of pre-HCT patients. From a practical standpoint our examination method is felt to have successfully identified patients in need of periodontal therapy and helped facilitate disease stabilization prior to transplant. Furthermore, it is important to realize that though our examination protocol assessed a subset of teeth, all patients referred for periodontal treatment completed "whole mouth" therapy. That is, treating hygienists consistently examined all periodontal sites. Additional areas of concern identified received targeted interventions (e.g., scaling, curettage, local antimicrobials) whether or not they were identified during screening examination. Partial mouth assessment methods like ours have been shown to be effective at

classifying disease severity but are less adept at determining prevalence of periodontal disease.[63] As such our examination may successfully identify patients at high risk for periodontitis-related complications while simultaneously underestimating the burden of disease in our population.

It is well established in periodontal literature that partial mouth probing methods underestimate overall PPD when compared to complete mouth assessment.[62, 63] The most accurate partial mouth fixed site method appears to be Ramfjord's Periodontal Disease Index (PDI) [64] which measures six individual sites for six "index teeth" (#3, 9, 12, 19, 25, 28; 36 total sites). Though bias is low (-0.88%[62] to 1.9%[63]) the PDI increasingly underestimate periodontal probing depth as severity of periodontal disease increases (30.3%for PPD ≥4mm, 54.9% ≥6mm compared to comprehensive assessment).[62] Furthermore, random protocols that analyze approximately the same number of sites recorded in our exam underestimate PPD values to a greater degree than the Ramfjord method (Random 10 site: 50.6% underestimate PPD ≥4mm, 68.8% ≥6mm; Random 15: 40.8% ≥4mm, 60.1% ≥6mm)[62]. In light of these considerations, maximum periodontal probing depths were likely underestimated in a proportion of our patients. This may have blurred the distinction between patients in group 2 and 3 and contributed to the reverse trend for bacteremia of oral origin seen in group 2. However, additional studies would be necessary to determine the degree of underestimation of significant disease associated with the examination and treatment techniques utilized in our protocol versus more involved periodontal disease examination techniques.

Lack of Control Group

Another consideration in the study is the lack of a control group that either did not complete periodontal assessment and intervention prior to HCT or did not receive systemic antimicrobial prophylaxis prior to transplant. In a group of patients at high risk for systemic infection, the use of a non-treated control group poses significant ethical considerations. Blood stream infections in the allogeneic population are associated with potentially significant morbidity, mortality, and health care cost.[8, 34, 65, 66] As such, SCCA standard of care oral health protocols prescribe pre-transplant interventions and antimicrobial prophylaxis with a goal of reducing/eliminating active disease and minimize risk for systemic infection. In general, pre-transplant dental, gingival, and periodontal therapies have been established as the standard of care to eliminate active oral infection in HCT patients [12, 21, 39, 46, 56] Complications associated with dental interventions are considered to be less severe than those related to emergent dental infections during immunosuppression (though there are no specific controlled trials that substantiate this claim).[12, 39] Potential risks associated with deferred treatment prevent centers from designing and implementing controlled studies in which individuals are randomized into treatment and non-treatment arms. Therefore, in studies like this one, we are dependent on observational designs and analysis of surrogate markers to characterize associations between periodontal status and post-transplant complications. At the same time, many HCT transplant centers do not utilize vigorous pre-HCT patient assessments for dental or periodontal disease and/or do not provide definitive disease-stabilizing/eliminating treatment.

Sample Size

In retrospect, it is clear that our study was underpowered to detect significant difference between periodontal probing groups with respect to bacteremia. Our power calculation was established on

the assumption that effect size would be at least 50% (based on baseline gram-negative and/or non-CoNS gram-positive bacteremia rates of 8%). This was a reasonable assumption to make after review of the limited literature available in the field. We now know, based on findings in the present study, that increase in bacteremia in select groups may be much lower (at closer to 25%). Therefore, a much larger study would be needed to detect differences of that magnitude.

Pre-Transplant Periodontal Therapy

We attempted to address the impact of pre-transplant periodontal therapy by comparing patients who were and were not able to complete recommended periodontal therapy prior to transplant. Many considerations prevent patients from completing prescribed therapy in the weeks before transplantation. In our population emergent health concerns, logistical challenges, lack of dental insurance, and inability to delay HCT (due to fragile health due underlying malignancy or complications resulting from recent cancer care) were commonly cited factors. Limited time to complete dental treatment is an especially significant challenge in HCT patients. Elad and colleagues[67] reported an average of 21 days between initial dental evaluation and HCT in which to adequately treat dental and periodontal infections (median = 15d). However, for many centers, patients may not arrive until several days prior to conditioning. Practically this usually does not allow for sufficient time for diagnosis and management of periodontal disease. While it is often recommended that all patients presenting to these centers see a dentist prior to arrival to have all necessary infections treated, this is often not the case. Therefore, in settings were oral treatment is not part of standard pre-transplant protocol at the treating center, it is critical to educate oral health care providers regarding periodontal health objectives and special oral health considerations in the HCT population.

Despite numerous challenges, nearly 90% of the 342 patients in our study who were prescribed periodontal therapy prior to transplant were able to be completely treated (including 85% of those with PPD ≥4mm). Those who were unable to complete treatment represented only a small portion of our total cohort (N=44 of 609). Only 5.1% of the patients who were unable to complete recommended therapy had PPDs consistent with periodontal disease ($N_{\geq 6mm}$= 16; N_{4-5mm}= 15). One additional patient completed periodontal scaling but not local Arestin™ therapy (in pockets measuring 5 and 6mm respectively).

Oral Hygiene and Post-HCT Outcomes

Previous prospective studies in allogeneic HCT patients have shown reduced oral mucositis severity, decreased incidence of febrile neutropenia, and lower blood levels of C-reactive protein (a non-specific marker of inflammation) in patients receiving periodontal therapy with intensive oral hygiene instruction. A randomized clinical trial by Borowski and colleagues[68] showed a 70% decrease in moderate/severe mucositis in patients receiving intensive pre-operative therapy (INT) when compared those receiving only limited therapy (LIM; $p<0.01$ after adjustment for TBI and pre-treatment intraoral status). Intervention included scaling/root planning and EXT of compromised teeth and gingival brushing during aplasia (the LIM group received no dental intervention unless lack of treatment was deemed life-threatening).

Two recent Japanese studies support and expand on these findings. In both studies allogeneic HCT patients were treated with pre-transplant dental therapy, periodontal scaling, individualized oral hygiene instruction, and supportive care during oral mucositis. Intervention groups in both studies were compared to historical control groups treated at their respective centers immediately

prior to implementation of new oral care protocols. Soga and colleagues[69] reported a decreased incidence of mucositis from 76% in 13 historic control to 20% in 15 patients who received oral intervention prior to conditioning. Kashiwazaki et al.[70] also found decreased mucositis incidence (93.5% control group v. 66.7% intervention group; $p < 0.001$) in addition to decreased febrile neutropenia (82.3% v. 60.3%; $p < 0.01$) and maximum C-reactive protein (CRP; 7.10 v. 2.64; $p < 0.035$). In the later study only mucositis remained significant in multivariate analysis [OR= 7.58 (2.45-23.3); $p < 0.001$]. Of the two protocols, Kashiwazaki's appeared to be more extensive with each patient receiving weekly professional brushing, flossing, and mucosal cleansing (with a sponge brush) in addition to follow-up examination to ensure effective personal compliance. Though neither study specifically evaluated bacteremia the author's reported decreased mucosal ulceration[68-70], febrile neutropenia[70], and CRP.[70] Each of these factors either directly relates to risk of bacterial blood stream infection (oral mucositis) or may occur as a result of infection (febrile neutropenia, CRP). Therefore, it seems reasonable to assume that similar interventions in our population decreased microbial load and gingival inflammation to a degree that impacted the overall incidence of bacteremia.

A significant difficulty in interpreting the results of these above studies arises from the inability to meaningfully compare the pre-transplant patient oral health between various centers, and thus determine the potential for reducing the risk for complications stemming from oral health influences. That is to say, that if the general oral health of patients in the above studies tended to be much worse than the general oral health at say our center, it would seem unlikely that a similar significant reduction in oral complications would be appreciated at our center where there is less pre-existing disease. But this should not distract from the clear importance of establishing

and maintaining consistent and focused pre HCT oral health examinations and the provision of complete oral health stabilization and maintenance of oral health post HCT.

Bacteremia and Oral Mucositis

Though the aforementioned studies suggest a relationship between periodontal treatment and oral mucositis, the exact relationship between periodontal disease, oral bacteremia, and oral mucositis remains unclear.[71, 72] Oral mucositis additional must be considered an important variable to be considered in all studies that seek to characterize the relationship of periodontal disease and bacteremia in HCT patients. Compromised barrier function caused by oral mucositis is an established risk factor for bacteremia of oral origin. Studies have also shown close association between oral mucosal ulcers and organisms implicated in periodontal disease.[59] In cases of periodontal bacteremia it is extremely challenging to determine whether the organism entered systemic circulation though compromised gingival epithelium or damaged mucosal barriers. We did not address the influence of oral mucositis in our study, but chose instead to focus broadly on bacteria commonly associated with gingival and periodontal disease. However, we appreciate that any study attempting to conclusively determine bacterial origin from the oral cavity into the bloodstream must account for mucositis.

Potential Oral/Periodontal Bacteria

In our cohort, coagulase-negative staphylococci (CoNS) were the most commonly observed cause of bacteremia (41.9% of 639 total bacteremias). Though high incidence of CoNS bacteremia is not surprising in the HCT population, subgroup analysis revealed that the majority of these infections occurred in patients with PPDs ≥4mm (82.3% of 268 CoNS bacteremias, Group 2 = 112; Group 3 = 110). Raber-Durlacher et al.[22] reported a similar finding with in a

prospective study of allogeneic HCT patients in which ten of the 18 individuals developed CoNS-bacteremia. 90% of those developing CoNS bacteremia had pre-transplant gingivitis (N=2) or concurrent gingivitis and periodontitis (N=7).

When considering these findings it is important to re-emphasize that most CoNS reside on skin surfaces and that central venous catheters remain the most common point of entry for staphylococci into the bloodstream. However, CoNS colonizing the alimentary tract, including the oral cavity, have also been associated with systemic infection.[52] Additionally, during the post-transplant period CoNS replace alpha-hemolytic streptococci on the buccal mucosa which may contribute to the risk of staphylococcal bacteremia during mucositis.[53] At least one case study has confirmed mucositis-related CoNS bacteremia of oral origin through the use of molecular methods.[17] Furthermore, Murdoch et al.[54] have confirmed the presence of CoNS in gingival sulci of both periodontal patients and healthy controls. Ulcerated pocket epithelium in periodontitis may allow subgingival staphylococci to enter the bloodstream more readily in patients with periodontal disease.[21, 22] Future studies attempting to characterize the association between CoNS bacteremia and periodontitis will have to differentiate between bacteria originating within periodontal pockets versus those that normally colonize the skin.

In contrast to staphylococci, many of the principle bacteria implicated in periodontal disease are anaerobic gram negative rods (i.e. Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, and Fusobacterium nucleatum).[25, 26, 42-44] Of these bacteria, only F. nucleatum has been specifically implicated in bacteremia in HCT patients.[9, 24, 29-31] This may relate to challenges

inherent in culturing anaerobic bacteria, the effectiveness of levofloxacin prophylaxis against gram-negative rods, or a relative lack of species determination after identification of gram-negative bacilli in laboratory practice. In our study, one unidentified anaerobic gram negative rod was isolated in a patient with periodontal disease (who presented with one 8mm and four 4-5mm PPDs at arrival). Prevotella, Bacteroides, and Fusobacterium species (including F. nucleatum) are the most common infectious organisms among anaerobic gram negative rods.[73] By limiting analysis to only cultures with genus and/or species identification we may have excluded a bacteremia of periodontal origin. Similarly, this restriction may have under-reported the incidence of oral viridans streptococcal bacteremia (Table 12).

Conditioning Protocols (MA versus RIC)

One final consideration in our study design relates to difference in immunosuppression between Myeloablative (MA) and Reduced-intensity conditioning (RIC) regimens. MA and RIC protocols differ in degree and timing of immunosuppression. Patients treated with MA protocols are immunosuppressed by marrow ablation. Consequently, they will experience more profound neutropenia in the early transplant period than their RIC counterparts. Differences in neutrophil function may impact the incidence of bacteremia and associated infectious complications between the two groups. In contrast, RIC patients experience less severe marrow ablation but must be maintained on intensive immunosuppressive regimes following transplant to prevent relapse of disease. This in turn may contribute to increased risk for late onset bacteremia in RIC patients. Future studies in this area and time-to-event analysis within our cohort may help elucidate differences in timing of oral-source bacteremias in those conditioned with MA versus RIC protocols.

Future Research

Additional analyses within our cohort may provide further insight into our study aims. When designing this study, Day 100 was chosen as an empiric end-point for analysis. This time-point is well-established in HCT literature in relation to survival and hospitalization parameters. However, in light of the significant influence of neutropenia on bacterial infection, oral/periodontal bacteremia may have been more accurately assessed earlier in the post-transplant course. By extending measurement of bacteremia over 100 days we may have diluted an early effect. Time-to-event analysis assessing shorter intervals (e.g. pre-engraftment, 30 days post-transplant, 50 days post-transplant) may provide additional information to guide future research in this area. Additionally, subset analysis of patients with prolonged severe neutropenia (ANC <500 cells/mm^3 for greater than 10 days) should be completed to assess whether patients with significant neutrophil compromise are more prone to oral and/or periodontal bacteremia.

When our results are considered in light of other studies, one can clearly entertain the notion that periodontal therapy prior to transplant reduces the risk for post-transplant bacteremia of dental origin. However, to adequately address this question a larger negative control group is necessary. With ethical considerations in mind, a multi-center study design may be the most appropriate to address this. A collaborative study could compare patients receiving HCT through centers with established periodontal protocols against others treated in centers where periodontal therapy is not the recognized standard of care. Periodontal treatment standards are determined in part by regional and socioeconomic differences meaning that national and/or international collaboration may be required to find appropriate institutions. In this case, every effort should be made to

match patient demographics between centers to minimize confounding. Examiners from each site could be calibrated to administer a standardized pre-transplant periodontal exam measuring PPD, gingival inflammation, and local plaque and calculus levels. Patients would then complete periodontal therapy (or lack of therapy) according to the standard of care at their respective institutions. Individuals would be followed prospectively for outcomes of interest (e.g. fever of unknown origin, bacteremia, hospital readmission) and compared to those with matched periodontal condition treated at other sites. This would be particularly interesting in the case of severe periodontitis (≥8mm). At our center teeth with 8mm PPDs are almost uniformly extracted (serial local antibiotics are employed when extractions are refused or contraindicated). This is not the case in other areas of the world. A multi-center design would allow for a larger cohort of patients in "high risk groups" to be evaluated with greater variation in pre-transplant stabilization therapy.

Furthermore, despite major consistencies in transplantation techniques across centers (including conditioning regimens, donor HLA-matching, and other factors), significant differences still exist which must be considered in future study designs. For instance, some centers do not routinely provide general antibiotic, antifungal, and anti-viral prophylaxis for all patients. In other instances medication dose, duration of use, or spectrum of coverage may vary. In the case of antibiotics, the effect of these characteristics on oral (and more specifically periodontal bacterial) colonization patterns must be considered. Researchers in microbiology and infectious disease have also raised the question of whether routine antibiotic prophylaxis is appropriate given concerns of increased microbial resistance. Therefore, an alternate multi-center design could compare patients treated in centers with different antibiotic prophylaxis protocols even if

periodontal therapy is consistent across centers. Potential centers could include those that limit general antibiotic use or those that utilize antibiotics with decreased periodontal coverage. Periodontal coverage must also be considered in the context of bacterial culture. In most transplant centers, empiric antibiotics are initiated with onset of fever of unknown origin. Future studies attempting to assess post-transplant periodontal bacteremia must consider whether therapeutic antibiotics influence the sensitivity of anaerobic cultures in detecting periodontal bacteremia.

Ideally, future studies examining periodontal parameters and bacteremias would include specific microbial analysis to confirm the periodontium as the definitive source of systemic infection. Even if these studies did not examine a particular screening method (as in our study), confirmation of the role of periodontal bacteria in post-transplant bacteremia would greatly influence the dental management of HCT patients. Nevertheless, the level of microbial detail required to confirm the periodontium as a source of bacteremia presents inherent challenges. Microbial studies of the oral cavity often utilize oral rinses[55, 59] or mouth swabs[17,55] to obtain general oral cultures. Though overlap exists between organisms colonizing dissimilar oral sites, succession within periodontal pockets creates uniquely anaerobic population over time.[27, 41, 42, 54] Anaerobic species are more challenging to culture than their aerobic counterparts. Furthermore, adult can patients routinely possess between 28 and 32 teeth. Culturing every periodontal pocket for anaerobic organisms would be cost-prohibitive and exceedingly time intensive. One strategy to reduce this burden would be to restrict the study population to patients at higher perceived risk of infection secondary to compromised periodontal health (i.e. multiple PPD $\geq$6mm).

A pilot study using a non-invasive periodontal microbial assay, such as micro-Ident® (Hain Diagnostics LLC, Midland, TX, USA), could be completed to compare differences in sub-gingival colonization patterns at initial examination, one day following dental scaling, and 21 days after completion of therapy. Samples could also be obtained from "periodontal control group", without pocketing, before and after local plaque and calculus. This would provide specific information about periodontal microbial succession in the HCT population, in healthy and diseased sites in the context of periodontal therapy. Groups could also be followed prospectively after HCT for the development of bacteremia. Isolated organisms could be compared against findings of the periodontal assay. Alternatively, in cases of bacteremia in which an oral source is suspected, comparative subgingival microbial samples could be empirically collected from the deepest PPD sites detected during initial examination. Depending on study resources, subgingival cultures could be obtained from all sites ≥6mm, ≥4mm, or a pre-determined number of sites identified on initial exam. If bacteremia occurs concurrently with oral mucosal ulceration, tissue cultures could be obtained along with subgingival samples. Where subgingival or oral cultures identify organisms consistent with those detected by blood culture, DNA samples could be extracted and compared by polymerase chain reaction (with species specific primers)[74] or pulsed field gel electrophoresis.[17]

Chapter VI: Conclusions

Our study found no significant association between maximum pre-transplant periodontal probing depth (PPD) and post-transplant bacteremia of potential oral or periodontal origin when patients were vigorously treated for pre-existent periodontal disease. The primary conclusion in this study is that pre-transplant periodontal disease is not predictive of post-transplant bacteremia of oral/periodontal origin and that maximum PPD was not associated with increased hospitalization within the first 100 days post-transplant or survival at day 100. It is plausible to conclude, however, that attempts at eliminating or reduce potential periodontal sources of bacteremia was effective in reducing the risk of bacteremia in our patient population when our results are compared to other studies.

It should still be noted that there was a trend toward increased oral/periodontal bacteremia in patients with intermediate PPDs (4-5mm) combined with significantly greater completion of intensive periodontal therapy by those with maximum PPD ≥6mm. This again suggests that patients with the most severe pre-transplant periodontal involvement may be at less risk for post-transplant bacteremia due to aggressive pre-transplant intervention. Additionally, sites with less severe periodontally pocketing could represent a source of bacteremia in patients, especially while neutropenic.

A relatively high percentage of CoNS bacteremia in patients with PPD ≥4mm also suggests that HCT patients with pre-transplant PPDs consistent with periodontal disease may be at increased risk for staphylococci bacteremia. Further study is necessary to confirm an oral source in these infections.

Appendix: Conditioning Protocols

Myeloablative (MA)	
Busulfan, Cytoxan	**Bu (12.8mg/kg), Cy (120mg/kg)**
Cytoxan, HD-TBI(1200cGy)	**Cy (120mg/kg), TBI (1200cGy)**
Busulfan, Fludarabine	**Bu (12.8mg/kg), Flu (120mg/m^2)**
Cytoxan, LI(400), HD-TBI(1200cGy)	**Cy(120mg/kg), LI (400cGy), TBI (1200cGy)**
Treosulfan, Fludarabine, TBI(200cGy)	**Treo (42 gm/m^2), Flu (270mg/m^2), TBI (200cGy)**
Busulfan, Fludarabine, ATG	**Bu (12.8mg/kg), Flu (120mg/m^2) ATG (3mg/kg)**
Thiotepa, Fludarabine, HD-TBI(1320cGy)	**Tepa (10mg/kg), Flu (125mg/m^2), TBI (1320cGy)**
Busulfan, L-PAM	**Bu (14mg/m^2, L-PAM (120mg/m^2)**
Cytoxan, Fludarabine, RAB, TBI(200cGy)	**Cy (79mg/kg), Flu (150mg/m^2), BC8, TBI (200cGy)**
Thiotepa, LI(400), Fludarabine, HD- TBI(1320cGy)	**Tepa (10mg/kg), Flu (125mg/m^2), LI (400cGy), TBI (1320cGy)**
HD-TBI(1200cGy)	**TBI (1200cGy)**
Cytoxan, ATG	**Cy (200mg/kg), ATG (90mg/kg)**
BEAM (BCNU, VP-16, ARA-C, L-PAM)	**BCNU (300mg/m^2), VP-16 (800mg/m^2), Ara-C (400mg/m^2), L-PAM (140mg/m^2)**
BEAM (BCNU, VP-16, ARA-C, L-PAM),LI(1600)	**BCNU (300mg/m^2), VP-16 (800mg/m^2), Ara-C (400mg/m^2), L-PAM (140mg/m^2), LI (1600cGy)**
Busulfan, Cytoxan, Campath	**Bu (**12.8mg/kg**), Cy (120mg/kg), Campath (40mg/kg)**
Busulfan, Cytoxan, TBI(200cGy)	**Bu (16mg/kg), Cy (120mg/kg), TBI (200cGy)**
Busulfan, LI(1800), Fludarabine	**Bu (800-900ng/ml), Flu (160mg/kg), LI (1800cGy)**
Cytoxan, LI(1400), HD-TBI(1200cGy)	**Cy (120mg/kg), LI (1400cGy), TBI (1200cGy)**
HD-TBI(1200cGy), LI(400)	**LI (400cGy), TBI (1200cGy)**
Treosulfan, Fludarabine, LI(800)	**Treo (42 gm/m^2), Flu (270mg/m^2), LI (800cGy)**

BC8 = 131-I-labelled-ant9-CD45 antibody

Reduced Intensity Conditioning (RIC)	
Treosulfan, Fludarabine	**Treo (42 gm/m^2), Flu (270mg/m^2)**
Fludarabine, RAB, TBI(200cGy)	**Flu (90mg/m^2), BC8. TBI (200cGy)**
Cytoxan, ATG, TBI(200cGy)	**Cy (250mg/kg), ATG (120mg/kg), TBI (200cGy)**
Cytoxan, Fludarabine, ATG, TBI(200cGy)	**Cy (50mg/kg), Flu (120mg/m^2), ATG (9mg/kg), TBI (200cGy)**
BC8SA, RDB, Fludarabine, TBI(200cGy)	**BC8-SA, Y-90, Flu (90mg/m^2), TBI (200cGy)**
Fludarabine, TBI(200cGy)	**Flu (90mg/m^2), TBI (200cGy)**
Treosulfan, Fludarabine, ATG	**Treo (42 gm/m^2), Flu (150mg/m^2), ATG (3mg/kg)**
Cytoxan, Fludarabine, RAB, LI(1400), TBI(200cGy)	**Cy (30mg/kg), Flu (90mg/m^2), BC8, TBI (200cGy)**
Fludarabine, RAB, LI(1400), TBI(200cGy)	**Flu (90mg/m^2), BC8, LI (1400cGy) TBI (200cGy)**
L-PAM, Fludarabine, TBI(200cGy)	**L-PAM (100mg/m^2), Flu (90mg/m^2), TBI (400mg)**
Rituximab, Fludarabine, RAB, TBI(200cGy)	**Ritux, Flu (90mg/m^2), Zevalin, TBI (200cGy)**

BC8 = 131-I-labelled-ant9-CD45 antibody

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