

Microbial colonization in hematopoietic stem cell transplantation-induced oral mucositis: A systematic review

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is a treatment modality for patients with hematological malignancy. Oral mucositis is the most serious complication in these group of patients. Among various risk factors for oral mucositis, oral microbial colonization is considered the most important factor which greatly affects the quality of life in these patients. A systematic review was carried out to assess the colonization of microbes in individuals who developed oral mucositis following to HSCT. The literature study was done using PubMed, Medline, Google Scholar, Cochrane databases with keywords of oral mucositis, bacteria, fungi, viruses, hematologic malignancy, and HSCT, from the January 1989 to June 2017. Furthermore, hand searches were taken from the back references for assessing microbial colonization in oral mucositis following HSCT. Data extraction done from the included studies. The study quality was assessed using Ottawa-Newcastle scale. Four studies investigating microbial colonization in oral mucositis following HSCT were included. The available literature shows no clear pattern or association between oral mucositis and oral microflora in patients undergoing HSCT as a treatment modality for various hematological malignancies. Future research is needed to determine the relationship between the nature of oral microflora and its role in the development of mucositis subsequent to HSCT therapy. Data from such work would direct toward the development and testing of selective antimicrobial therapies for the prevention and management of mucositis subsequent to HSCT.

Keywords: Oral mucositis, stomatitis, mucositis, hematopoietic stem cell transplantation, stem cell transplantation, hematopoietic stem cell transplant, oral microbes

Introduction

Hematopoietic stem cell transplantation (HSCT) is a treatment modality for patients with hematological malignancy such as acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, and Hodgkin's lymphoma. Earlier, it was called bone marrow transplantation; however, hematopoietic stem cells can be obtained from a variety of sources such as bone marrow, peripheral blood, and umbilical cord blood. Hence, the term bone marrow transplant been replaced by hematopoietic stem cell transplantation.^[1]

Hematopoietic stem cell can be obtained from the patient him/herself which is called autologous transplantation. When it is obtained from

an identical twin, it is referred as synergetic transplant, and transplant other than identical twin/from patient himself is called allogeneic transplantation.

In patients receiving HSCT, most serious complication is oral mucositis^[2] which is almost seen in 70–90% of patients who receive HSCT^[3,4] and 30–50% of patients with HSCT complain that mucositis is their most significant toxicity. There is 4 phase pathophysiological models in the development of oral mucositis: Phase 1 - vascular phase (1–3rd day), Phase 2 - epithelial phase (4–5th day), Phase 3 - ulcerative phase (6–12th day), and Phase 4 - healing phase (12th day onward)^[5] which has been replaced by a 5 phase pathobiological model^[6,7] beginning with (i) initiation, (ii) upregulation and message generation, (iii) signal amplification, (iv) ulceration, and (v) healing.

Oral mucositis has severe physical and mental disability during the course of treatment. Among various risk factors for oral mucositis, development of bacterial, viral, and fungal infections is considered the most important factor^[2] which greatly affects the quality of life in these patients. It has been suggested that the microbes on the ulcerated surface are active contributors of mucositis process.^[8] The endotoxins released by the microorganisms penetrate the submucosa which exerts a chemotactic activity on polymorphonuclear

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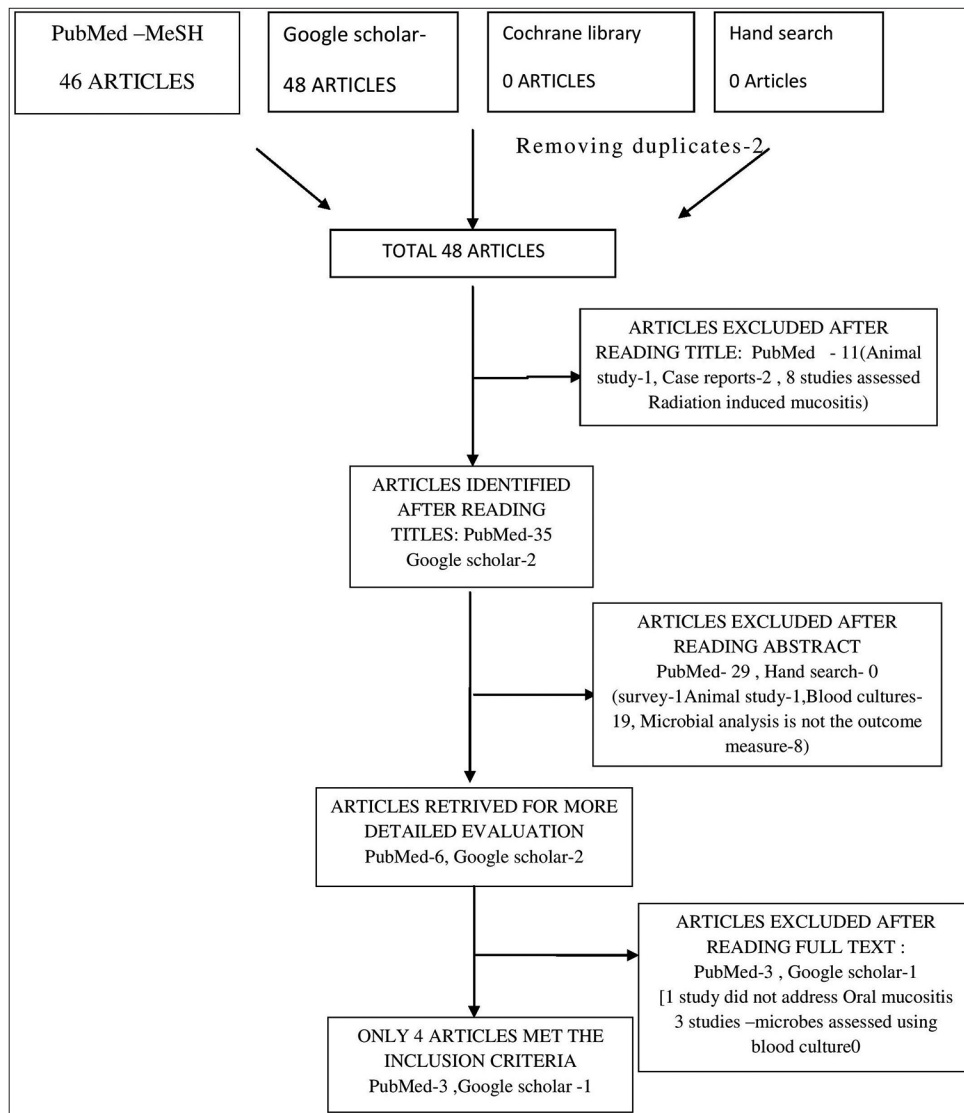


Figure 1: PRISMA flowchart for selection of studies

leukocytes and macrophages and stimulates further pro-inflammatory cytokines that intensifies the inflammatory process as well as exacerbates the ulcer.^[9] Therefore, we need a better understanding of the role of oral microflora in the development of oral mucositis which begins with identifying changes in the oral flora during HSCT therapy.

Thus, the objective behind carrying out this systematic review was to assess the microbial colonization in patients developing oral mucositis following HSCT.

Materials and Methods

The literature search was done using the keywords of “oral mucositis” with “HSCT” and “oral microbes” in databases of PubMed, Medline, Cochrane library, and Google Scholar from January 1989 to 20th June 2017 for English language publications. After database search reference lists were hand-searched to identify additional studies.

Research methodology

Inclusion and exclusion criteria of this review were set a priori

A studies published in English between January 1st 1989 and June 20th 2017. Studies discussing microbial colonization from samples taken from oral cavity in patients developing oral mucositis following HSCT were included. Experimental studies, observational studies, and systematic reviews involving human subjects only were included in the study. While case reports, case series, animal studies, studies in which patients developed oral mucositis following radiotherapy, and studies that assessed microbial colonization from blood samples were excluded from the study.

Data retrieval

After the initial literature search, the authors reviewed all titles and abstracts to identify suitable articles for inclusion. All articles identified as suitable were read in their entirety and considered for inclusion and were summarized based on study design, sample population, methodology, results, and conclusion.

Table 1: Characteristics of included studies

Study/no of patients	Title/journal/year	Sample/oral mucositis assessed	Study design	Frequency of sample collection/method of isolation	Statistical method used	Results (organisms isolated)	Quality score	Author's conclusion
Laheij <i>et al.</i> /49 samples	Oral bacteria and yeasts in relationship to oral ulceration in HSCT recipients. Support Care Cancer 2012;20: 3231-3240	Oral rinse Yes	Cohort	Twice weekly Multiplex real-time PCR	Explanatory variables for oral ulcerations were calculated using multilevel generalized estimated equations technique	% positive samples <i>F. nucleatum</i> - 66%, <i>P. micra</i> - 43% <i>T. forcythia</i> - 31% <i>T. denticola</i> - 15% <i>P. gingivalis</i> - 11% <i>P. intermedia</i> - 8% <i>A. comitans</i> - 0 <i>C. albicans</i> - 88% <i>C. glabrata</i> - 54% <i>C. tropicalis</i> - 58% <i>C. kefyra</i> - 56% <i>C. krusei</i> - 26% <i>C. parapsilosis</i> - 8%	4	Significant relationship between yeast and bacteria associated with periodontitis to the oral ulceration in HSCT recipients
Westbrook/121 samples	Microbiology and epidemiology of oral yeast colonization in hematopoietic progenitor cell transplantation recipients. OOOE, 2013;115 (3).	Oral swish and oral swab Yes	Cohort	Before transplant/during/at discharge Mono plex real-time PCR	Fischer's exact test	<i>C. albicans</i> - 44% <i>C. glabrata</i> - 35% <i>C. krusei</i> - 3% <i>C. dubliniensis</i> - 11% <i>C. tropicalis</i> - 11% <i>S. cerevisiae</i> - 2% <i>C. parapsilosis</i> - 2%	4	<i>C. albicans</i> and <i>C. glabrata</i> were predominant organisms/ <i>C. Krusei</i> and <i>C. glabrata</i> shows elevated MIC for fluconazole and are associated with fungemia. When these organisms are found in oral colonization in HSCT recipients, modification of antifungal prophylaxis should be considered
Vokurka <i>et al.</i> /37 samples	Gelclair on oral microbial colonization and pain control compared with other rinsing solution in patients with oral mucositis after allogeneic stem cell transplantation. Med Sci Monit 2011;17 (10).	Oral swabs Yes	Cohort	Once a week, pre OM phase, OM phase, post OM phase culture	Fisher's exact test and unpaired t-test	During OM phase Gelclair - Potentially pathogenic - 36% Pathogenic - 5% (<i>E. faecalis</i>) Control - Potentially pathogenic - 60% Pathogenic - 40% (<i>E. faecalis</i>) During pre-OM phase and post-OM phase <i>E. faecalis</i> and <i>C. glabrata</i> were predominant pathogenic species present about 18% and 55% and potentially pathogenic species of about 82% and 36% in pre and post-OM phase respectively Potentially pathogenic-colonies of <i>Streptococcus viridians</i> or <i>Neisseria</i> species or <i>Staphylococcus coagulase</i> negative	4	<i>E. faecalis</i> and <i>C. glabrata</i> were predominant pathogenic species found which was significantly reduced during OM phase in treatment group
Beek <i>et al.</i> /49 samples	Viral loads and antiviral resistance of herpesviruses and oral ulceration in hematopoietic stem cell transplantation. Bone Marrow Transplantation 2012;47:1222-8	Oral rinse and swab Yes	Cohort	Twice a week real-time PCR	Repeated measures logistic regression	Percentage of positive HSV-1 viral samples *Ulcerative mucositis - 39% *No ulcerative mucositis - 23% *Ulceration on keratinized mucosa - 69% *No ulceration on keratinized mucosa - 19% Percentage of positive EBV samples	3	HSV-1 DNA - predictors of ulcerative mucositis in keratinized and non-keratinized mucosa EBV DNA is a predictor of ulcerative mucositis in keratinized mucosa only CMV DNA is not a significant predictor of ulcerative mucositis non keratinized and keratinized mucosa

(Contd...)

Table 1: (Continued)

Study/no of patients	Title/journal/year	Sample/oral mucositis assessed	Study design	Frequency of sample collection/method of isolation	Statistical method used	Results (organisms isolated)	Quality score	Author's conclusion
						*Ulcerative mucositis - 10% *No ulcerative mucositis - 23% *Ulceration on keratinized mucosa - 27% *No ulceration on keratinized mucosa - 14% Percentage of positive CMV samples *Ulcerative mucositis - 10.2% *No ulcerative mucositis - 2.4% *Ulceration on keratinized mucosa - 6.8% *No ulceration on keratinized mucosa - 4.4%		

HSCT: Hematopoietic stem cell transplantation, PCR: Polymerase chain reaction, *F. nucleatum*: *Fusobacterium nucleatum*, *P. micra*: *Prevotella micra*, *T. forcythia*: *Tannerella forsythia*, *T. denticola*: *Treponema denticola*, *P. gingivalis*: *Porphyromonas gingivalis*, *Candida albicans*, *P. intermedia*: *Prevotella intermedia*, *A. comitans*: *Aggregatibacter actinomycetemcomitans*, *C. albicans*: *Candida albicans*, *C. glabrata*: *Candida glabrata*, *C. tropicalis*: *Candida tropicalis*, *C. kefir*: *Candida kefir*, *C. krusei*: *Candida krusei*, *C. parapsilosis*: *Candida parapsilosis*, MIC: Minimum inhibitory concentration, *S. cerevisiae*: *Saccharomyces cerevisiae*, *C. dubliniensis*: *Candida dubliniensis*, *E. faecalis*: *Enterococcus faecalis*, HSV: Herpes simplex virus, EBV: Epstein-Barr virus, CMV: Cytomegalovirus

Quality assessment

The authors evaluated the quality of the included studies using a published scoring system. Newcastle–Ottawa quality assessment scale, a 9-item checklist, was used to score cohort studies. Their scores were summarized in Table 1.

Results

The database search and the hand search identified 48 studies. After initial title screening, 11 were excluded, and after abstract screening, 29 abstracts were excluded. The remaining 8 articles were retrieved, and the full text was reviewed. Of these, 4 articles were excluded. Of the 4 studies excluded at this stage, 3 were excluded because they assessed microbes in blood samples while 1 study was excluded because it did not specifically investigate oral mucositis. The entire data have been tabulated according to PRISMA flowchart [Figure 1]. The remaining 4 articles that assessed microbial colonization in oral mucositis following HSCT were included in the present study, and their characteristics are described in Table 1.

Levels of evidence

The included observational studies showed the level of evidence - II-B.

Grading of oral mucositis - All 4 included studies used standardized scoring system – the WHO scoring system to assess mucositis in all 4 studies additionally OMAS and visual analog scale were used in 2 studies.

The 4 studies retrieved from the literature assessed bacterial, fungal, and viral colonization using oral samples. However, it is difficult to compare studies as considerable heterogeneity was observed

between the studies. The available literature showed no clear pattern or association between oral mucositis and oral microflora in patients undergoing HSCT as a treatment modality for various hematological malignancies.

Discussion

One of the most important complications of HSCT is oral mucositis occurring in 75–99% of patients.^[10-13] It usually develops 6–10 days after transplantation that greatly affects the quality of life in these patients. The commonly involved sites are buccal mucosa, labial mucosa, floor of the mouth, ventral surface of the tongue, and esophageal mucosa.^[7,14] The phase initiates with basal cell damage and release of reactive oxygen species followed by which there is activation of transcription factors and upregulation of genes and production of destructive proteins and pro-inflammatory cytokines leading to apoptosis and cell injury, also there is positive feedback loop (signal amplification) which leads to destructive process, and there is break in oral epithelium and ulcerates where infective process comes into play complicates. It is the ecological shift in the oral microbes that complicate the oral mucositis.^[15,16] Thus, in this review, we have analyzed the studies assessing the oral microbial colonization in oral mucositis among hematopoietic stem cell transplant recipients.

The primary outcome measure in the 4 included studies was assessing the microbial colonization. In a study involving 49 HSCT recipients by Laheij *et al.*,^[17] the authors found that *Fusobacterium nucleatum* was the most frequent bacteria isolated and *Porphyromonas gingivalis* was consistently isolated from the samples. *Candida albicans* was the most frequent fungi isolated, and the study concluded that there was a significant relationship between yeast and bacteria associated with periodontitis to the oral mucositis in hematopoietic stem cell

transplant recipients. Moreover, *Candida kefyr*, a rare species but very high colonization rate (94% of patients), is found among the study population.

Furthermore, the authors stated that there is the absence of *Actinobacillus actinomycetemcomitans* in the study samples which is normally present in subgingival biofilm of 15–30% of healthy population. It is important to note that this study had the lower quality score because follow-up was not adequate and explanation for the absence of *A. actinomycetemcomitans* was not given; however, this could be due to the use of antibiotics.

In a prospective cohort study, Westbrook *et al.*^[18] evaluated oral yeast colonization in patients undergoing stem cell transplantation who received fluconazole prophylaxis. *C. albicans* and *Candida glabrata* were predominant organisms. Both *Candida krusei* and *C. glabrata* showed elevated MIC for fluconazole and are associated with fungemia. This finding concluded that when these organisms are found in oral colonization in HSCT recipients, modification of antifungal prophylaxis should be considered.

In a prospective observational study involving 37 HSCT recipients, Vokura *et al.*^[19] found that *Enterococcus faecalis* and *C. glabrata* were the predominant pathogenic organisms in 15 patients and these organisms were significantly reduced during oral mucositis phase in 22 patients who were given Gelclair. However, this study assessed microbial colonization by culture-based method.

van der beek *et al.*^[20] found that the presence of HSV-1 DNA was found to be a predictor of ulcerative mucositis in keratinized and non-keratinized. Furthermore, antiviral-resistant strains were isolated from the samples. EBV was found to be a predictor of ulcerations in the keratinized mucosa only. CMV was not a significant predictor of ulcerative mucositis on the non-keratinized and keratinized mucosa. It is important to note that this study had lowest quality score of included studies because follow-up of cohorts not adequate and no information regarding loss of follow-up given in the study.

Method of collecting samples is not uniform in all 4 studies where 2 studies used both oral swish and oral swab as collection method while other two involved only oral rinse and oral swab for collecting sample. Furthermore, the methodology for detection and quantification of microflora in the included studies shows the molecular biologic technique in 3 studies while one employed culture-based isolation of microbes which is less sensitive than real-time PCR, so low loads could be missed.

All patients who underwent HSCT in the included studies developed oral mucositis, and they were all given different conditioning regimen as prophylaxis for graft versus host disease.

Although oral prophylaxis was given in all 4 included studies, consistent increase in microbes found during mucositis phase. This may be due to the selection of inappropriate antimicrobials and the way it is administered. When antimicrobials are given orally, patients might have difficulty in sucking due to dry mouth which could be the reason for low compliance of prophylactic antimicrobials.

Not all included studies evaluated the relationship between WBC counts and quantitative oral flora changes. Combination of oral mucositis and granulocytopenia increases the risk of systemic infection.

The studies included in this review assessed bacterial, fungal, and viral colonization using oral samples. However, it is difficult to compare studies since they differ on the population that were studied, conditioning regimen administered, sample collection methods and intervals, sample analysis methods, microorganisms studied. The available literature shows no clear pattern or association between oral mucositis and oral microflora in patients undergoing HSCT as a treatment modality for various hematological malignancies.

Conclusion

Future research is needed to determine the relationship between the nature of oral microflora and its role in the development of mucositis subsequent to HSCT therapy. This would give a better understanding of the potential role oral microflora in the development and exacerbation of oral mucositis. Data from such work would direct toward the development and testing of selective antimicrobial therapies for the prevention and management of mucositis subsequent to HSCT.

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