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Published in:
Orofacial Supportive Care in Cancer

DOI:
10.1007/978-3-030-86510-8_5

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5.1 Introduction

Oral mucositis (OM) is defined on MeSH as an inflammation of the mucosa with burning or tingling sensation, characterized by atrophy of the squamous epithelium, vascular damage, inflammatory infiltration, and ulceration. Mucositis generally occurs at the mucous lining of the mouth, the gastrointestinal tract, or the airways due to chemical irritations, chemotherapy (CT), or radiation therapy (RT). Actually, this is relevant to any anticancer therapy including combination of chemoradiotherapy (C-RT) and hematopoietic stem cell transplantation (HSCT) [1].

In accordance with the above definition, the profile of OM extended when the targeted therapies were introduced and soon after the associated oral adverse effects were reported. Targeted therapies include antitumor monoclonal antibodies, small molecules, signal transduction receptor inhibitors, and cancer vaccines [2–7].

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R. Nair (ed.), *Orofacial Supportive Care in Cancer*,
https://doi.org/10.1007/978-3-030-86510-8_5

Targeted therapies may be continuously administered for their long-term ability to inhibit tumor growth, progression, cell proliferation, and angiogenesis, and, as such, even mild adverse toxicity is considered burdensome [8]. If targeted therapies are combined with conventional cancer therapies, previously identified toxicities may be increased in severity or duration [9, 10].

The utmost importance of OM stems from the severity of its associated symptoms. In regard to the significance of OM to the patient, 42% of patients undergoing HSCT identified OM as the most significant transplant-related toxicity [11]. In this study, the second most stressful toxicity was nausea and vomiting, described by 13% of the patients [11]. The difference between the proportion of patients affected by OM and the proportion of patients affected by the nausea and vomiting demonstrated the devastating effect of OM on the patients. In another study, OM was described as the most debilitating toxicity by 65% of patients receiving TBI-based regimens, and 84% of the patients reported OM as more severe than expected [12]. This reflects not only the impact of OM on the ability to perform daily tasks but also the risk of systemic consequences such as infection. This is further complicated by its impact on the delivery of anticancer therapy with OM being a significant driver of dose reductions and complete treatment cessation. As such, OM is translated to significant health-care costs due to the overreliance on supportive care measures and hospitalization. Therefore, there is a surge of research in attempt to identify prevention or treatment for OM [13].

This chapter will present a review about the epidemiology, clinical presentation, consequences, pathogenesis, and management approach of OM.

5.2 Epidemiology

The prevalence of OM varies greatly between cancer subpopulations. Generally, the more toxic the anticancer protocol, the higher the risk for OM. The factors that influence the prevalence of OM include both treatment-related variables and patient-related risk factors.

Treatment variables that may affect the prevalence and the severity of OM include the type, dose, and schedule of systemic cytotoxic medications, radiation dose and field, and concomitant use of CT and radiation [14–17].

5.2.1 Radiotherapy for Head and Neck Cancers (HNCs)

The vast majority of patients treated with RT for HNCs develop severe OM [18, 19]. In HNC patients treated with RT or C-RT to the head and neck (H&N), the incidence of OM ranged from 59.4% [20] to 100% [21–26]. In patients receiving altered fractionation RT or high-dose RT, the incidence of grade 3 or 4 OM is 65–85%, and in patients receiving conventional RT, the incidence of grade 3 or 4 OM is 34% [27, 28]. Special radiation techniques may reduce the severity of OM. Several studies reported that grade 4 OM did not develop following volume-modulated arc therapy

(VMAT) [22], proton beam radiation therapy (PBRT) [20], and intensity-modulated radiotherapy (IMRT) [24].

5.2.2 Chemotherapy

OM affects on average 20–40% of patients receiving conventional-dose cytotoxic CT [14, 29–32]. Overall OM frequency for all grades is reported to be between 14.4% and 81.3% depending on the type of tumor and treatment, with most of them being mild OM (grades 1–2), while severe OM (grades 3–4) is generally less than 5% of cases [33–36]. In a study of patients with advanced cancer, the overall prevalence of OM was 22.3% [37]. Data on OM incidence by type of malignancy are limited. One study evaluating OM secondary to conventional chemotherapy as a single modality reported breast cancer to be most associated with OM (76.5% of cases), followed by HNC (67.7%), colorectal cancer (CRC) (63%), and esophageal cancer (57.8%) [33]. Although less frequently described, the risk of severe OM (≥grade 3) has been reported in prostate cancer (14%) and breast cancer patients (0.98–8%) [31, 33].

The incidence of OM depends also on the specific regimen. When using TAC protocol (docetaxel, adriamycin, and cyclophosphamide) for breast cancer, incidence of low-grade OM was 60% with 5% severe OM [38]. When using dose-dense therapy, in which the interval between successive CT cycles is reduced to minimize the likelihood of tumor regrowth and neoangiogenesis between cycles, incidence of grade 1–2 OM reported to be ranged from 15% in patients who received weekly paclitaxel to as high as 59% dose-dense AC → T (adriamycin-cyclophosphamide with sequential taxane). Severe OM reached 14% among those who were treated with weekly AC [38].

For commonly used platinum/gemcitabine in lung cancer, incidence of grade 1–2 OM was 14%, with 1% grade 3 or higher [38].

In various protocols for CRC, the risk of grade 1–2 OM averages 14% with various regimens including FOLFOX (leucovorin, fluorouracil [5-FU], and oxaliplatin), FOLFIRI (leucovorin, 5FU, and irinotecan), and IROX (irinotecan and oxaliplatin). The risk is higher with FOLFIRI (35%). Grade 3–4 OM is low with incidence of 1.35–4.43% [38].

The toxicity of each drug depends on its dosage and the exposure duration, as well as its intrinsic properties [30, 31] and mode of administration (bolus versus continuous infusion) [39]. Many cytotoxic agents have been reported to produce OM [40]; however, few studies have specifically analyzed incidence and severity of the toxicity in relation to these regimens. It is generally accepted that antimetabolites and alkylating agents are associated with a high OM incidence and worse OM severity, although these views have been largely based on anecdotal reports [40–43]. Furthermore, published data on toxicity of various regimens are sometimes inconsistent [43–46].

Chemotherapeutic agents that are DNA cycle-specific (e.g., bleomycin, 5-FU, and methotrexate) are apparently more stomatotoxic than agents that are cell phase

Table 5.1 Cytotoxic agents which incur mucotoxic effect [15, 32]

Category	Cytotoxic agents
Antimetabolites	Methotrexate, 5-fluorouracil, hydroxyurea, cytosine arabinoside
Topoisomerase II inhibitors	Etoposide, irinotecan
Pyrimidine analogs	Cytarabine
Purine analogs	6-Mercaptopurine, 6-thioguanine
Alkylating agents at high doses	Busulfan, melphalan, cyclophosphamide
Intercalating drugs	Idarubicin, doxorubicin, daunorubicin
Antibiotics	Bleomycin, mitomycin
Taxanes	Docetaxel, paclitaxel
Vinca alkaloids	Vinblastine, vincristine

nonspecific [47]. Certain drugs (e.g., etoposide) may be secreted into the saliva, further increasing the potential for stomatotoxicity [48, 49].

The most recognized mucotoxic agents are listed in Table 5.1 [15, 32]. The literature indicates that treatment regimens containing 5-FU and adriamycin-cyclophosphamide pose high risk for OM [33]. Specifically, 5-FU has been reported to cause grade 3–4 OM with incidence of more than 15% [31].

In selected regimens for solid tumors, the prevalence of OM is reported to be less than 10% [50]. This low prevalence of OM in patients treated for solid tumors is attributed in part to underreporting for various reasons: monitoring protocols in outpatients that is less intensive, low- and moderate-level OM that may not require palliative treatment, and patient's and clinician's preference to avoid cancer treatment interruption [1].

Of note, when CT is administered in multiple cycles, the risk of OM increases at each course owing to residual changes in the biological structure of the oral mucosa (e.g., angiogenesis) [31, 33, 51].

OM was found in 90% of all patients diagnosed with acute leukemia who were treated with induction CT, with grades 3–4 in 20%, and in 12.5% for consolidation CT with 0% grades 3–4 [52]. Patients with acute myeloid leukemia (AML) treated with standard anthracycline-based regimens develop profound myelosuppression and OM (10–15% of cases) [53]. In this setting, liposomal daunorubicin seems to reduce the incidence of mucositis [54], while more aggressive protocols were associated with a higher incidence. The FLAG (fludarabine, cytarabine, G-CSF) protocol induces mucosal damage in 50% of patients [55], a rate that rose to 70% in patients treated with idarubicin-containing FLAG [56]. In patients with acute promyelocytic leukemia treated with trans-retinoic acid (ATRA) and idarubicin, the incidence of OM is about 10% [57, 58].

In non-Hodgkin's lymphoma (NHL), OM was reported in 2–11% for various CT protocols [15, 59, 60]. Other studies in NHL patients reported a higher incidence of 22.2% [52] and up to 42.9% [33]. Grade 3–4 OM in NHL patients is reported to range from 0 [33, 52] up to 6.6% [38].

As for various protocols in NHL patients, grade 3–4 OM has been reported in 4–5% of CHOP-treated patients (cyclophosphamide, doxorubicin, vincristine, and prednisone) [38, 61]. The addition of rituximab (R-CHOP) does not appear to

modify the risk for OM [31]. Dose intensification of the CHOP regimen, achieved by increasing the cyclophosphamide dose, results in a slight increase in the risk (7.9%) [38]. The addition of etoposide to CHOP, however, more than doubles the risk for grade 3–4 OM in a similar patient population (10.4%). Other protocols CEOP/IMVP-Dexa (cyclophosphamide, epirubicin, vincristine, prednisone, ifosfamide, methotrexate, etoposide, dexamethasone) produce similar rates of grade 3–4 OM to those reported with CHOP (4.17%) [38].

The differences in incidence of OM between acute leukemia and NHL patients may be related to the underlying degree of immunosuppression. The first induction of CT is aggressive, aiming to eradicate malignant clones. Furthermore, in most studies, NHL patients were admitted for a short stay at the hospital with limited follow-up during the ambulatory period [33, 52].

In regard to Hodgkin's lymphoma, OM incidence was reported to be 3% in patients who received the ABVD protocol (doxorubicin, bleomycin, vinblastine, and dacarbazine) and 8% in patients treated with hybrid multidrug regimens [62].

5.2.3 Hematopoietic Stem Cell Transplantation (HSCT)

OM is undoubtedly one of the most debilitating toxicities of hematopoietic stem cell transplantation and reported in up to 99% of patients undergoing HSCT, 67.4% of which are grade 3 or 4 [11, 46, 63–65]. This was consistently reported in other studies in HSCT patients with all OM grades being 70–86.8% [66–68]. OM grade 3 was reported to be 12.9% and 30.5% [67, 68], and OM grade 4 is reported to be 8.2% and 13.7% [67, 68].

Factors associated with the development of OM during HSCT are summarized in Table 5.2 [12, 31, 46, 69–77]. Multivariate analysis showed that the conditioning regimen is the most significant determinant of OM [15, 71]. Regimens containing

Table 5.2 Factors associated with the development of OM during HSCT [12, 31, 46, 69–77, 299]

Class	Factor
Conditioning regimen administered	CT type and dose and use of TBI
Hematopoietic progenitor source	PBPC leads to higher OM incidence compared to allo-BMT, which leads to higher OM incidence compared with auto-BMT
Previous exposure to drugs	Methotrexate for prophylaxis of GVHD, as well as other drugs such as anthracyclines, vinca alkaloids, cyclophosphamide, fludarabine, platinum analogs, and etoposide in the mobilizing regimen
Gender	Female
Type of disease	Leukemia (compared to various indications for allo-BMT and auto-BMT) NHL (compared to MM and HD undergoing auto-BMT)

CT chemotherapy, *TBI* total body irradiation, *PBPC* peripheral blood progenitor cells, *allo-BMT* allogeneic bone marrow transplant, *auto-BMT* autologous bone marrow transplant, *GVHD* graft versus host disease, *MM* multiple myeloma, *HD* Hodgkin's disease, *NHL* non-Hodgkin's lymphoma

busulfan or melphalan or total body irradiation (TBI) were associated with the worst OM [15, 71].

The type of HSCT may also be related to severity of OM. While some studies reported an increased severity of OM in allo-BMT compared to auto-BMT patients, others found no differences in OM severity and duration [43, 45, 46]. Incidence of OM in auto-BMT was reported to be 40–86.8%, with 9.6–44.2% grade 3 or 4 OM [67, 78–80]. In contrary, in allo-BMT, OM incidence was 70.4–95.7% for all-grade OM and 20–51.3% for grade 3 or 4 OM [81–84].

In reduced intensity conditioning (RIC) protocols, the treatment rationale is largely based on triggering an immunity-mediated graft-versus-malignancy effect rather than by the cytotoxic treatment itself [85]. Accordingly, OM incidence in myeloablative conditioning is higher than in RIC. Specifically, the OM incidence in myeloablative conditioning is reported to be 83.4%–88.2% with 33.4–78.4% grade 3–4 OM [81, 82, 86, 87]. In contrast, the OM incidence in RIC is 56.3–75.7% for all OM grades and 4–32.9% for grade 3–4 OM [81, 82, 86–88].

Interestingly, a systematic review found that RIC regimens led to a high incidence of OM similar to that of myeloablative regimens [66]—86.5% vs. 73.2% for all grades of OM and 57.4% vs. 63.2% for grade 3 or 4, respectively. Moreover, it was found that there is an increased risk of developing grade 3 and 4 OM over grade 1 and 2 OM in the RIC group. Of note, none of the included studies reported whether radiation therapy was included in the conditioning regimen, and only some studies included information regarding previous cycles of CT or HSCT. Therefore, these results should be interpreted with caution due to possible residual confounding factors [66].

5.2.4 Targeted Therapy

The epidemiology of mucositis or stomatitis due to targeted therapy is summarized in Table 5.3. The oral complications associated with these new classes of anticancer agents are distinctly different compared to those induced by traditional cytotoxic agents. Despite this, they are largely referred to as OM.

Epidermal growth factor receptor inhibitors (EGFRI) have been investigated in the treatment of epithelial cancers including breast, colorectal, oropharyngeal, non-small cell lung cancer, and renal cell carcinoma (RCC) [89–94], with oral complications remaining poorly characterized.

Cetuximab is a recombinant human/murine mAbs directed toward EGFR and is FDA approved for treatment of head and neck squamous cell carcinoma (HNSCC) and CRC [95, 96].

In a trial of metastatic CRC (mCRC) comparing irinotecan plus cetuximab to cetuximab alone, fewer patients experienced grade 3 or 4 stomatitis in the cetuximab alone group (0.9%) versus cetuximab plus irinotecan (2.4%, nonsignificant difference, $p = 0.67$) [97].

In recurrent or metastatic HNSCC, cetuximab may be used alone or in combination with RT [98]. Concurrent administration of cetuximab and RT makes the

Table 5.3 Targeted therapy-induced oral mucositis/stomatitis

Mode of action	Agent	Brand name	FDA-approved indications	OM/stomatitis-related clinical signs and symptoms	
EGFRI	Cetuximab	Erbitux	HNSCC and CRC	Stomatitis	0.9% grades 3–4 [97]
				Mucositis, HNCSCC	93% (Cetuximab with RT) 56% grades 3–5 94% (RT alone) 52% grades 3–5 [8]
				Mucositis, various indications	52.7% all-grade RT plus EGFR [99]
				Mucositis, concurrent RT HNC	23% <grade 2 77% grade 3 [100]
	Panitumumab	Vectibix	Wild-type RAS mCRC	Stomatitis	7–23% [113–115]
	Erlotinib	Tarceva	mNSCLC Metastatic pancreatic cancer Malignant gliomas	Stomatitis	19% vs. 3% placebo 1% >grade 3 [119]
	Afatinib	Gilotrif	mNSCLC	Stomatitis	72% all-grade, 9% ≥grade 3 [122]
mTORI	Everolimus	Afinitor, Zortress	*A*dvanced RCC after failure with sunitinib or sorafenib *H*ormone receptor-positive, HER2-negative breast cancer *P*rogressive NET in pancreas and nonfunctional NET of GI or lung *T*SC: renal angiomyolipomas and subependymal giant cell astrocytoma *K*idney and liver transplant rejection	Stomatitis	40–44% vs. 8% in placebo 3–5% grade 3 [103, 125–127]
				Mucosal inflammation	14% grade 2 vs. 2% in placebo 1% grade 3 [103]
	Sirolimus	Rapamune	Kidney transplant rejection Lymphangioleiomyomatosis	Stomatitis	71% ≥grade 2 4% grade 3 [130]
	Temsirolimus	Torisel	Advanced RCC	Various	19–41% stomatitis/mucositis 1–3% grades 3–4 4% aphthous stomatitis, 3% ulcers [132, 133]
	Deforolimus	None	Has not been approved to date	Ulcerations • Include oral pain, mucosal inflammation, and stomatitis	63% grades 1–2 16% grades 3–4 [134]

(continued)

Table 5.3 (continued)

Mode of action	Agent	Brand name	FDA-approved indications	OM/stomatitis-related clinical signs and symptoms	
TKI, MKI and others	Imatinib mesylate TKI of abl-bcr fusion gene, PDGF-R, and c-kit kinases	Gleevec/ Glivec	*P*hiladelphia chromosome positive ALL and CML *M*yelodysplastic/myeloproliferative diseases with specific PDGF-R gene rearrangements *H*ypereosinophilic syndrome and/or chronic eosinophilic leukemia *M*etastatic dermatofibrosarcoma protuberans *A*ggressive systemic mastocytosis Advanced malignant GIST	Various	10.6% stomatitis [138] 2.8% mouth ulcers 0.7% mucosal sensitivity [135]
	Sorafenib tosylate MKI of VEGF, PDGF, and TK	Nexavar	Advanced RCC Hepatocellular carcinoma Advanced thyroid cancer refractory to radioactive iodine treatment	Stomatitis/ mucositis	11–38% 2–9% ≥grade 2 [96, 142–147]
				Mucosal sensitivity	14.5% [135]
	Sunitinib malate TKI of VEGF and PDGF	Sutent	Advanced RCC GIST after failure with imatinib Advanced pancreatic NET	Stomatitis	17–38% grades 1–2 1–4% grade 3 [156–159]
				Mucosal sensitivity	23% [135]
				Ulcers	8.7% [135]
				Aphthous-like ulcers	33–43% [150]
	Bevacizumab Anti-VEGF mAbs	Avastin, Mvasi	*m*RCC (in combination with interferon alfa-2a) *m*CLC (in combination with 5-fluorouracil) *A*dvanced mNSCLC *M*etastatic cervical cancer (with combination CT) *O*varian, fallopian tube, or peritoneal cancer (with combination CT) *R*ecurrent glioblastoma	Various	5.7% ulcers 6.3% mucosal sensitivity [135]
	Pazopanib TKI of VEGF and PDGF	Votrient	Advanced RCC Advanced soft tissue sarcoma	Various	4.6% ulcers 10.6% mucosal sensitivity [135]
	Cabozantinib MKI of RET, MET, VEGFR-1, VEGFR-2, and VEGFR-3, KIT, TrkB, FLT-3, AXL, and TIE-2	Cometriq, Cabometyx	Advanced RCC Metastatic medullary thyroid cancer	Various	26.1% ulcers 34.8% mucosal sensitivity [135]
	Lapatinib TKI of EGFR and HER2	Tykerb	HER2-overexpressing metastatic breast cancer (in combination with capecitabine) Hormone-positive and HER2-positive advanced breast cancer (in combination therapy with letrozole)	Stomatitis	13% grade 1 [162, 163] 21% grade 2 [164]

EGFRI epidermal growth factor receptor inhibitor, *HNSCC* head and neck squamous cell carcinoma, *CRC* colorectal cancer, *RT* radiation therapy, *mNSCLC* metastatic non-small cell lung cancer, *mTORI* mammalian target of rapamycin inhibitor, *RCC* renal cell carcinoma, *NET* neuroendocrine tumor, *GI* gastrointestinal, *TSC* tuberous sclerosis complex, *PDGF-R* platelet-derived growth factor receptor, *GIST* gastrointestinal stromal tumor, *TKI* tyrosine kinase inhibitor, *MKI* multikinase inhibitor, *VEGF* vascular endothelial growth factor, *mAbs* monoclonal antibodies, *CT* chemotherapy

etiology of oral side effects difficult to distinguish. A 2006 phase III trial involving 400 patients compared patients treated with RT alone and RT plus cetuximab. The reported grade 3 and above adverse events (AEs) did not differ significantly between these two groups [8].

However, a review and meta-analysis reported EGFRI plus RT to a have higher reported prevalence of mucositis compared to RT alone (1.76 risk ratio) [99]. A small study of 13 patients reported exacerbated toxicity with cetuximab in HNC with grade 3 OM in ten patients (77%), while the remaining three patients developed grade 2 OM [100]. Numerous studies about cetuximab do not describe the oral AEs which limits the understanding about the role of cetuximab in OM [101–109].

Panitumumab is a fully humanized IgG2 mAb EGFRI, approved for treatment of wild-type RAS mCRC (in both KRAS and NRAS) [110, 111]. Several studies reported stomatitis as "mild to moderate" [112] and to develop in 7–23% of patients [113–115].

Erlotinib is a small molecule tyrosine kinase inhibitor (TKI) of EGFR, approved for metastatic non-small cell lung cancer (NSCLC), locally advanced, unresectable, or metastatic pancreatic cancer, and malignant gliomas [116–120]. A study of previously treated NSCLC patients found 19% of patients experienced OM—compared to 3% in the placebo group, 1% had above grade 3 [119]. A meta-analysis reported an increased risk of all-grade OM (3.2 adjusted relative risk), with no significant risk for high-grade OM [121].

Afatinib blocks signaling from the EGFR (erbB1), EGFR2 (HER2/erbB2), and erbB4, which has been approved for mNSCLC with nonresistant EGFR mutations. Higher rates of stomatitis (72% all-grade, 9% grade 3 or worse) are reported with afatinib, compared to combination of cisplatin and pemetrexed [122].

mTOR inhibitors (mTORI) are drugs that inhibit the mammalian target of rapamycin and are used in the treatment of RCC and various other indications and demonstrate high level of efficacy with acceptable tolerability [123]. In a meta-analysis of randomized controlled clinical trials (RCTs) of patients receiving mTORI, the incidence of all-grade (grade 1–4) stomatitis was 33.5%, and the incidence of high-grade stomatitis (grade 3–4) was 4.1% [124]. The incidence of high-grade stomatitis significantly varied with tumor types (increased risk in breast cancer (RR: 11.18) and progressive neuroendocrine tumor (RR: 28.52)). In comparison with controls, mTORI significantly increased the risk for developing all-grade stomatitis (RR: 4.04) and high-grade stomatitis (RR: 8.84) [124].

The mTORI that were reported to cause oral mucosal injury include everolimus, sirolimus, temsirolimus, and deforolimus.

Stomatitis with **everolimus** was reported in 30–44% of patients vs. 8% in the placebo group, with 2.2–5% experiencing grade 3 reactions [103, 125–127]. Mucosal inflammation of grade 2 or less was reported in 14% of patients (vs. 2% in placebo), with 1% of patients reporting grade 3 events [103]. In a phase III RCT evaluating everolimus in patients with metastatic RCC, the incidence of stomatitis was approximately 39% with the majority of cases resolving within 3 days [128, 129]. Out of 277 patients, 13 required dose modification or interruption, 49 patients required supportive therapy, and everolimus was permanently discontinued in one patient [128, 129].

A phase I study of **sirolimus** as a major metabolite reported 71% with grade 2 and below stomatitis and only 4% with grade 3 mucositis. These oral ulcers were dose dependent and resolved despite continued drug therapy [130, 131].

Among patients on **temsirolimus**, 19–20% reported stomatitis/mucositis, with 1% grade 3 mucositis, 4% aphthous stomatitis, and 3% mouth ulceration [132]. Another study reported stomatitis/mucositis in 41% of patient, with 3% grade 3 mucositis [133]. Almost all mucositis-type AEs were low grade and manageable with supportive measures.

A phase I trial of **deforolimus**, currently investigated for use/treatment in solid tumors, sarcoma, cancer/tumors (unspecified), endometrial cancer, prostate cancer, and bone metastases, with 32 patients, reported mouth sores, including mouth pain, mucosal inflammation, and stomatitis in 79% of patients, with 16% grades 3–4. Ulcers were more frequent at high doses. Three dose-limiting toxicity events of grade 3 mouth sores were reported. The patients were treated symptomatically and usually achieved complete recovery. These reactions appear less frequent and severe at subsequent administration [134].

Stomatitis or OM is also reported due to multikinase inhibitors, including imatinib, sorafenib, sunitinib, bevacizumab, and lapatinib. Among patients treated with VEGFR-directed multi-targeted TKI, the most commonly reported oral AE was oral mucosal sensitivity or pain, occurring in 12% of patients [135]. Approximately one-quarter resulted in at least one dose alteration in part attributable to the oral AE. Among these alterations, 16.2% led to dose interruption, 11.0% led to dose modifications, and 6.3% resulted in drug discontinuation. The majority (65.9%) of dose alterations were associated with sunitinib or sorafenib [135].

Imatinib mesylate is a TKI that selectively targets the abl-bcr fusion gene, platelet-derived growth factor receptor (PDGF-R), and c-kit kinases [136, 137]. Stomatitis was reported in 10.6% of patients [138]. Mouth ulcers were reported in 2.8% and mucosal sensitivity in 0.7% [135].

Sorafenib tosylate is a multikinase which inhibits VEGF, PDGF, and TK. Stomatitis was reported in 11–38% of cases [96, 139–150], with 2–9% grade 2 or more [151–154]. Mucosal sensitivity was reported in 14.5% of cases [135]. In 7% and 18% of cases, dose was interrupted or reduced due to oral AEs, respectively [150, 155]. A meta-analysis reported an increased risk of all-grade OM (3.3 adjusted relative risk), with no significant risk for high-grade OM [121].

For **sunitinib malate**, grade 1 or 2 stomatitis has been reported in 17–38% and grade 3 stomatitis in 1–4% [150, 156–159]. Mucosal sensitivity was reported in 23% of cases [135]. Others report oral ulcers in 8.7% [135]. Aphthous-like ulcers are reported in 33–43% of cases [150]. In 9% and 26% of cases, dose was interrupted or reduced due to oral AEs, respectively [150]. For sunitinib, an increased risk for all-grade OM was reported in a meta-analysis (7.7 adjusted relative risk), with no increased risk for high-grade OM [121].

Bevacizumab is an anti-VEGF mAbs that inhibits angiogenesis used for various indications [160, 161]. Mucosal sensitivity was reported in 6.3% of cases [135], with ulcers reported in 5.7% [135]. A meta-analysis showed that bevacizumab led

to an increased risk of all-grade OM (1.8 adjusted relative risk), but no significant difference was found for high-grade OM [121].

Stomatitis in patients treated with **lapatinib**, a TKI of EGFR and HER2, was reported to reach 13% grade 1 [162, 163] and 21% grade 2 [164].

5.3 Risk Factors

Patient-related variables that may influence the risk for OM include age, gender, body mass index, smoking, genetic factors, the tumor itself, oral environment related factors and comorbidities [14, 50]. Risk factors for OM are outlined in Table 5.4.

5.3.1 Age

Conflicting data exist regarding the effect of patient age on development of OM. One study reported younger age as a risk factor for overall oral complications, without referring specifically to OM [165]. A prospective cohort study in 63 patients reported a trend for increased prevalence and severity of OM in older patients [166]. Likewise, a phase III study in 439 patients treated with 5-FU identified a significant correlation of moderate and severe OM with advancing age [167]. A small study of 50 patients receiving high-dose antineoplastic therapy found that increasing age was a risk factor for developing OM [168]. Possible interpretation of these results could be that in the very young age, there is increased cell turnover rate, and in the old age there is decreased rate of healing [169, 170].

Table 5.4 Risk factors for OM

Age	Trends for increased risk in older age
Gender	Trends for increased risk in females
Body Mass Index	Lower BMI
Smoking	Mixed reports
Genetic factors	MTHFR polymorphism TSMT polymorphism TNF-alpha polymorphism DPYD polymorphism GST polymorphism
Oral environment	Poor oral hygiene Hyposalivation
Comorbidities	Addison's disease increases risk Poor renal function increases risk Psoriasis lowers risk

BMI body mass index, *MTHFR* methylenetetrahydrofolate reductase, *TSMT* thiopurine *S*-methyltransferase, *TNF* tumor necrosis factor, *DPYD* dihydropyrimidine dehydrogenase, *GST* glutathione *S*-transferase

5.3.2 Gender

There are inconsistent reports on gender as a risk factor for OM. A study reporting 1074 patients treated with 5-FU for colorectal carcinoma found that female gender confers increased toxicity in terms of number of different types of toxicity experienced, average maximum toxicity grade, and incidence of severe toxicities. Females had 1.59 OR for developing OM, 1.8 OR for hematologic toxicities, and 1.92 OR for GI toxicities [171]. Other clinical trials also found that female patients have approximately a 2–2.37-fold higher risk for severe FU-related OM as compared with male patients, after adjusting for dose, body mass index, and age [39, 167, 172]. Other studies found no gender-related difference [77, 166].

5.3.3 BMI

Some studies have reported low body mass to be associated with an increased risk of OM [34, 173, 174]. It is postulated that poorly nourished individuals are more likely to experience increased breakdown and delayed healing [169]. However, another study reported no association of OM with patients' body surface area [166, 175].

5.3.4 Smoking

Smoking was reported to be associated with an increased risk of OM in radiation-induced OM for HNC patients [174, 176] and in CT for solid tumors [36]. Smoking affects microcirculation and can potentially delay healing. Conversely, nonsmokers were found to have a 2.70-fold increase in risk for severe OM, in oropharyngeal SCC patients undergoing concurrent CT and RT [26]. Another study showed a protective effect of smoking in patients undergoing HSCT [177]. Some evidence shows that smoking was associated with reduced pain due to OM, presumably due to loss of nociceptive receptors [36]. Other studies found no association between smoking and risk for OM [166, 178].

5.3.5 Genetic Factors

It becomes clear that genetic factors play a role in toxicity risk [19]. Differences in drug metabolism, absorption, distribution, and excretion, due to the genetic variants of several families of enzymes, seem to have pronounced effects [179].

Genetic determinants of OM risk include genes that regulate the availability of active CT drug metabolites. It seems that enzyme deficiencies may be relatively rare, and rather polymorphism and differences in the expression of genes associated with biological pathways that drive OM are more common.

For example, evaluation of genetic variation in folate-metabolizing enzymes may help to identify patients at greater risk for methotrexate toxicity [178]. The administration of methotrexate, a highly mucotoxic agent, was associated with different rates of OM in patients undergoing allo-BMT according to patient's genotype of a polymorphism in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene; patients with the *MTHFR* TT genotype have lower MTHFR activity and were noted to have more severe OM than patients with wild-type enzymes [180].

Moreover, genetic polymorphisms for thiopurine *S*-methyltransferase (TSMT) are a major factor responsible for large individual variations in both the toxicity and therapeutic effect of thiopurine [181].

Similar findings of genetic polymorphisms associated with the expression of inflammatory mediators such as TNF-alpha have been implicated in severe toxicities in patients undergoing allo-BMT [182]. Curiously, TNF-alpha polymorphism influenced significantly toxicity risk more than aggressive conditioning regimens (17.2 vs. 6.9 OR) [182].

A clinical trial that included 683 patients with cancer, treated with 5-FU monotherapy, showed patients with the dihydropyrimidine dehydrogenase (DPYD) polymorphism had a 5.8 fold higher risk of OM [39]. It is unclear if this study included OM exclusively or combined OM and gastrointestinal mucositis.

Glutathione *S*-transferase (GST) protects against oxidative stress, a key component in the initiation of OM. In a study of 699 patients undergoing BMT, a deletion polymorphism in one or two GST genes (GSTM1 and GSTT1) was significantly associated with increased occurrence of overall toxicity (71% versus 56%) and OM (74% versus 55%).

5.3.6 The Tumor

The site and stage of HNC determine the radiation plan and the addition of chemotherapy, which influence on the risk for OM [184]. Several studies aimed at the role of the tumor itself on the response to RT and CT. Additionally, the tumor itself is biologically active and might contribute to OM risk [185, 186]. Both tumor parenchyma and stroma are sources of molecules (peptides, MMPs), which influence cell behavior, and could directly modify normal cell response and enhance the breakdown of the local tissue environment [51]. Studies about the interaction between the tumor and the host are warranted.

5.3.7 Oral Environment

The oral cavity is a complex environment, which includes a wide range of microbiota comprised of bacteria, fungi, and viruses and saliva on all its components. Many studies have shown that local environmental factors might influence the course of OM but are not considered as the primary etiology of OM [50, 51].

The oral microflora has been conceptually linked to severity of OM for many years. As a result, several studies have addressed oral decontamination as a prophylactic or therapeutic intervention for OM; however, these studies presented conflicting results [187–194].

It is recognized that mucosal injury precedes increase in bacterial load [51]. During OM ulceration phase, there is an increase in gram-negative organisms, indicating that an increase in bacterial load is insufficient to hold the healing phase. Moreover, reestablishment of normal bacterial flora seems to be necessary for spontaneous ulcer resolution, irrespective of bacterial numbers [195]. The ulcerated mucosa represents a desirable colonization site, possibly contributing to increased severity and delayed healing at highly corroded areas. Thus, the oral microflora is currently considered to play a secondary role in the pathogenesis of OM.

This is also the case for other oral microorganisms, with purely correlative findings linking certain infections and OM. For example, candidiasis is a common finding in patients receiving H&N RT or myeloablative CT; however, candida has not been substantiated as a risk factor for OM and is therefore considered a coinciding condition rather than causal. Correspondingly, antifungals as interventions for RT-associated OM in HNC patients have not been effective in preventing OM [196].

Similarly, the role of HSV in OM remains unclear, despite increasing evidence of higher HSV rates in OM. For example, HSV was found in higher rates among cancer patients treated with CT who developed clinically evident mucositis, compared to patients who did not develop clinical lesions [197]. Other studies showed that OM development was unrelated to HSV antibody status or positive viral cultures, that acyclovir prophylaxis was ineffective in preventing OM, and that there was no relationship between the rate of viral reactivation and the presence or absence of OM [198, 199]. Furthermore, poor overall predictive value (both positive and negative) was reported for surveillance cultures of the oral microflora, and it was concluded that their significant expense does not support their routine use [200].

Regarding salivary flow, xerostomia was reported to be one of the two best predictors for development of OM in 5-FU-treated patients [166]; however, therapeutic approaches directed at stimulating salivary flow have not been successful. Pilocarpine was ineffective in modifying the incidence or course of OM in HNC patients and HSCT patients [201, 202]. Moreover, two studies reported that propantheline, an anticholinergic drug, protected patients from etoposide-induced OM [48, 49]. The authors indicated that propantheline may have protected oral mucosa from salivary-excreted etoposide and thus reduced prevalence of OM.

5.3.8 Comorbidities

Preexisting conditions may also impact OM risk and disease course. In a study of patients receiving induction therapy for leukemia, OM risk was compared among

individuals who had precancer diagnoses of psoriasis and Addison's disease [51]. The authors found that psoriasis patients had a significantly lower risk of OM and Addison's disease patients had significantly higher risk for OM, compared to controls. These results could be interpreted due to inherent effect of psoriasis on epithelial proliferation and due to the fact that Addison's disease patients present with high preexisting pro-inflammatory cytokine levels. In addition, decreased renal function with elevated blood urea nitrogen and creatinine was associated with increased risk for OM [168].

These data indicate the potential importance of the patient's underlying condition on OM risk.

5.4 Pathogenesis

The pathogenesis of OM was conceptually defined in 2004 [30, 203, 204], in which a series of independent yet overlapping phases were used to describe the complex interactions underpinning mucositis development. This has undoubtedly been the gold standard model for OM for over a decade, shaping approaches to intervention design and guiding its clinical management [178, 205]. Introduction of this model saw a greater appreciation placed on non-epithelial mechanisms, a great leap forward in our understanding, with mucositis typically considered a strictly epithelial phenomenon. Over the years, our understanding of mucositis development has grown exponentially, particularly with regard to the oral microbiome, and has learned to adapt to the ever-changing landscape of cancer medicine in which the idiosyncrasies of newer targeted and immune therapies present supportive care experts with new challenges.

Although the clinical symptoms of mucositis are primarily driven by epithelial injury, the condition itself is the consequence of a dynamic series of biological events that take place throughout the different cellular and tissue compartments of the mucosa and submucosa. These biological stages are defined as initiation, upregulation (primary damage response), signal amplification, ulceration, and healing [206].

5.4.1 Five-Phase Model

DNA and non-DNA damage, caused by traditional anticancer agents (CT and radiotherapy), **initiates** direct cellular damage in highly proliferative basal epithelial and submucosal stem cells resulting in p53-dependent apoptosis [207, 208]. Simultaneously, reactive oxygen species (ROS) production drives a cascade of secondary signals which indirectly contribute to mucosal injury and biological dysfunction [209]. Critical to the transduction of this response is the activation of nuclear factor kappa B (NFκB), widely considered the gatekeeper of mucositis development, regulating over 200 downstream genes associated with mucosal injury [210, 211]. NFκB defines the **primary damage response,** in which an intense inflammatory response is observed, characterized by increased local and systemic levels of interleukin 1β (IL-1β), tumor necrosis factor-α

(TNFα), and IL-6 [212]. These cytokines are suggested to drive endothelial injury, connective tissue dysfunction, and mesenchymal signaling resulting in reduced epithelial oxygenation, confounding the initial direct injury to basal epithelial cells. Furthermore, it is well demonstrated that a number of downstream molecules produced in the primary damage response phase exert a positive feedback effect on NFκB, thus exacerbating the primary insult initiated by CT and radiotherapy [30]. This **signal amplification** is coupled with additional downstream activation of mitogen-activated protein kinase (MAPK) signaling and the activation of JNK, which in turn regulates the transcriptional activity of AP1 [213]. This pathway ultimately results in the activation of caspase 3, resulting in a second wave of NFκB-dependent apoptosis. NFκB is also a potent activator of cyclooxygenase (COX) 2 resulting in the production of matrix metalloproteinases (MMPs) [214]. Despite this tsunami of pro-inflammatory signaling occurring on a biological level, it is important to note that the clinical scenario remains quiescent. The oral mucosa may show signs of erythema during these phases; however, tissue integrity remains unaffected, and there are negligible oral symptoms.

The **ulcerative** stage is universally recognized as the most clinically relevant for the patient, caregivers, and oncology support staff. It represents the cumulative effect of direct cell death caused by the anticancer therapy, coupled with a cascade of potentially lethal cytokines, chemokines, kinases, and proteinases that ultimately destroy the integrity of the oral mucosa [30], although the true mechanisms underpinning tissue injury remain poorly defined. Patients present with painful, ulcerative lesions affecting almost all regions of the oral mucosa. Symptoms such as pain, xerostomia, and dysphagia severely impact on the ability of the patient to perform daily tasks, with eating, drinking, and speaking commonly affected [215]. Oral lesions are prone to superficial colonization with the many microorganisms that inhabit the oral cavity, increasing the risk of infection and sepsis particularly in neutropenic patients [216, 217]. Even in the absence of microbial translocation, bacterial products easily penetrate into the submucosa, aided by frank ulceration and compromised epithelial barrier function, activating innate immune responses and the further release of proapoptotic genes [218]. This promotes the migration of immune cells to the area of insult and the subsequent production of inflammatory signals.

In many cases, mucositis is a self-limiting condition, with **healing** evident after the cessation of anticancer treatment. However, healing is thought to be more complex than purely the removal of the initial insult, with submucosal and extracellular matrix (ECM) remodeling critical in governing the rate of repopulation and differentiation of the oral epithelium [178].

5.4.2 Emerging Evidence

The five-phase model of mucositis has instrumentally enhanced our understanding of mucositis development, with the appreciation for non-epithelial mechanisms

seeing it maintained as the gold standard model for almost two decades. However, with greater research efforts and an increasing awareness for the importance of supportive oncology, it is becoming increasingly clear that the mechanisms of mucositis extend far beyond the mucosa. Advances in our understanding have undoubtedly centered on the role of the ECM, in both the initiation and healing phases, the importance of maintaining epithelial barrier function, and the role of resident microflora.

Cellular Kinetics: Disruption to homeostatic mechanisms that regulate cellular kinetics has always been central to our understanding of mucositis development. In 2013, emerging evidence on the pathobiology of mucositis suggested that maintenance of the ECM was critical across all phases of the model [178]. For example, it was demonstrated that augmented cellular kinetics during the initiation of mucositis were not only characterized by apoptosis but also cellular cytostasis, fibronectin loss, and collagen deposition during the ulcerative phase [36]. This understanding was also complimented by comprehensive characterization of MMP changes throughout the mucosa and submucosa following CT [26]. Mechanistically, the causal relationship between MMPs and symptoms remains unclear; however, it has been suggested that MMPs contribute to mucositis development via regulation of the mesenchymal-epithelial communication, epithelial proliferation/differentiation, and destruction of epithelial barrier function [30, 178, 219, 220].

Epithelial Barrier Function: Epithelial barrier integrity is critical for any epithelium, particularly those of the alimentary tract. Tight junctions maintain barrier integrity, ensuring strict control of paracellular transport [221]. A variety of physiological and pharmacological stimuli can modulate the integrity of tight junctions, including MMPs, pro-inflammatory cytokines, and bacterial byproducts (e.g., lipopolysaccharide), leading to hyperpermeability and compromised barrier integrity.

Despite a wealth of preclinical and clinical data indicating alterations in *intestinal* barrier function following a variety of anticancer therapies [222], translation of this mechanisms to the *oral* cavity is scarce. This likely reflects the challenges in quantifying barrier function in a stratified oral mucosa and the relative magnitude of clinical consequences that arise from altered barrier dysfunction in the gut. To date, only morphological changes in oral barrier function have been identified, with proteolysis and translocation of key tight junction proteins in the buccal epithelium of patients undergoing standard dose CT for a range of solid malignancies [223]. Importantly, correlations between peak barrier dysfunction, pro-inflammatory cytokine production, and MMP signaling were evident, supporting the mechanistic hypothesis that barrier dysfunction occurs secondarily to the initiation of mucositis. These findings also compliment previous research demonstrating the efficacy of antrum mucosal protein (AMP)-18 in mitigating OM via regulation of tight junction assembly [224]. As such, epithelial barrier dysfunction is considered central to the pathogenesis of mucositis; however, the clinical consequences are considered more profound in the gastrointestinal tract given the abundance of luminal microbes and its contribution to diarrhea.

Host-Microbe Interactions: The historical paradigm of OM, which was predicated on indiscriminate clonogenic cell death of highly proliferative cell

populations, has clearly been overturned in favor of a more complex cascade of biological events [225]. The appreciation of the oral microbiome has certainly been a clear driver of this new biological approach to mucositis, with increasingly sophisticated genomic technology enabling in-depth analysis of the complex ecosystem that resides throughout the alimentary tract (mouth to anus). A growing body of evidence supports microbial interference with key mechanisms of *gastrointestinal* mucositis such as intestinal barrier function, mucin production, ROS activation, and inflammatory signaling. Unfortunately, the same mechanistic appreciation for the microbiome in the development of OM is lacking, with conclusions clouded by variations in patient populations, sample collection, culturing/processing, and bioinformatic approaches [226]. Nonetheless, it can be concluded that the oral microbiome shifts in its composition with a gram-negative dominant phenotype [227–229]. An interesting finding from some studies is the elevation in species diversity following anticancer therapy, due to the emergence of opportunistic strains. This is in stark contrast to the significant drop in species diversity seen in the fecal microbiome, suggesting that although dysbiosis is a common trait of oral and gastrointestinal mucositis, the complexities of these changes are region-specific.

Mechanistically, the understanding of the causal relationship between oral dysbiosis and mucositis symptomology is unclear, and the "chicken or the egg" puzzle is frequently raised [225]. However, it has been suggested that certain microbial subtypes are critical in the local activation of certain anticancer drugs, in turn regulating their efficacy and toxicity [177]. Furthermore, it is also likely that these shifts in the oral microbiome drive innate immune signaling, thus enhancing chemotactic recruitment of immune cells and initiating local innate immune responses [230]. Of particular interest is the interaction between resident microbes and Toll-like receptors (TLRs), with bacterial signals (e.g., PAMPs/DAMPs) potent activators of TLR subtypes, many of which have been implicated in the pathobiology of mucositis [231]. Similarly, evidence also suggests that some bacterial subtypes linked with mucositis, as well as oxidative stress, can elicit robust inflammasome assembly characterized by caspapse-1 activation and the proteolytic cleavage of pro-inflammatory cytokines [232]. Although this mechanism has been studied in greater detail in the gastrointestinal tract [233], it is likely that core mechanisms translate to the oral cavity.

5.4.3 A New Era of Oral Complications

The emergence of newer targeted and immune-based anticancer therapies has drastically altered the current supportive care landscape, with newly defined adverse toxicities underpinned by largely unclear mechanisms. This is certainly the case for OM among the most common side effects of these new wave anticancer therapies [206, 228]. There remains no pathobiological model for oral complication of non-cytotoxic therapy, despite their increasing prevalence. Current evidence suggests that "off-target" tyrosine kinase inhibition mediated through endothelial growth

factor receptor (EGFR) and HER2 is central to the oral complications associated with targeted therapies [206], while monoclonal antibody targeting of programmed cell death ligand-1 (PD-L1) contributes to oral complications of immune checkpoint inhibitors [234].

5.5 Clinical Presentation

OM typically manifests as erythema, swelling, atrophy, ulceration, and pseudomembranous formations (Fig. 5.1) [14]. The ulcerative phase of OM presents clinically with irregular and often confluent ulceration that is typically preceded by regional erythema. The nonkeratinized mucosae of the cheeks, lips, soft palate, ventral surface of the tongue, and the floor of the mouth are frequently affected [14, 46, 173].

Figure 5.2 illustrates the expected time course of OM caused by various anticancer therapies. CT may be delivered over a short time, in which case the injury to mucosal tissues tends to be immediate and acute. CT-induced OM usually develops within 4–7 days after initiation of cytotoxics and peaks within 2 weeks, usually resolving within 3 weeks of treatment [15, 51, 173]. RT has a more gradual clinical course since it is most often administered in small fractions given over weeks. Thus, RT-induced OM takes longer both to develop and to heal, with clinical manifestations typically beginning at cumulative doses of about 15 Gy (after about 10–14 days), typically reaching full severity at 30 Gy. RT-induced OM usually resolves in 3–4 weeks but may last months after treatment has ended [51, 173].

Historically, OM caused by allo-HSCT was reported to last up to day +21; however, with the shift to RIC-HSCT, OM tends to be shorter [86]. In allo-HSCT cohorts, clinical evidence of oral injury begins 2–5 days following transplant, lasting approximately 6–9 days and resolving by 12–15 days post-HSCT [40, 44, 45, 64, 235, 236]. In actuality, injury begins with the initiation of the conditioning

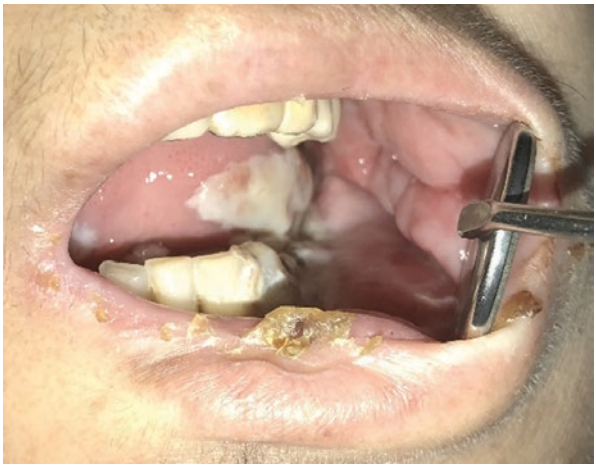

Fig. 5.1 Oral mucositis. Chemotherapy-related oral mucositis, presenting as confluent ulcerations covered with yellowish pseudomembrane

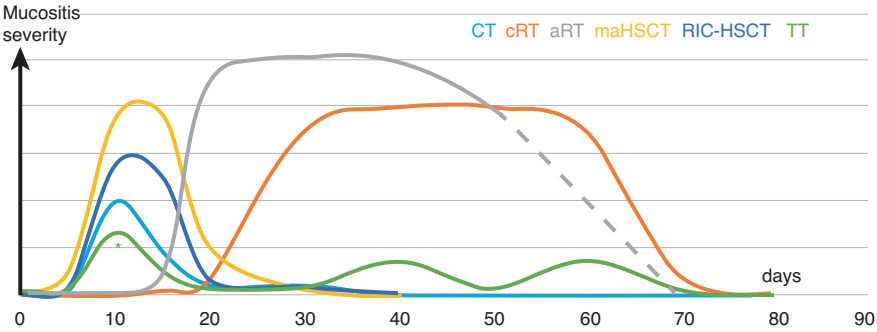

Fig. 5.2 Dynamics over time of OM severity due to various cancer therapies. *CT* chemotherapy, *cRT* conventional radiotherapy, *aRT* accelerated radiotherapy, *maHSCT* myeloablative hematopoietic stem cell transplantation, *RIC-HSCT* reduced intensity conditioning for hematopoietic stem cell transplantation, *TT* targeted therapy. In RT, the onset of OM is later than CT. Severity of OM in RIC-HSCT is usually lower than in maHSCT. Estimated course of aRT (dashed line). Following adjustment of dose (asterisk) of TT, an improvement in OM severity occurs. Thereafter, lesions may wax and wane as long as the patient receives the medication

regimen, with subclinical changes occurring in the oral cavity [12]. In some cases, oral ulcers may persist beyond day 15 post-HSCT and after recovery of the neutrophil count particularly in patients who initially develop more severe ulcerations [46]. While the regeneration of the oral mucosa begins 9–14 days after injury, the resolution of the OM usually coincides with the time of neutrophil engraftment following HSCT, when granulocyte counts exceeded 500/mm^3 [46, 237]. Epithelial cell regeneration is also associated with the return of a normal oral bacterial flora [12].

A chronic form of OM was described [238], in patients, who underwent C-RT for squamous cell carcinoma in the oral cavity. The chronic OM was defined as appearing more than 3 months following the completion of the C-RT. Two patients presented with long-lasting ulcers persisting from unresolved acute lesions, named *persistent form*. Two patients presented with new discrete ulcers that were episodic in nature, named *recurrent form*. Prior to diagnosing the oral mucosal injury as chronic OM, other etiologies need to be ruled out. It was suggested that the persistent form stems from delayed wound healing, and the lesions of the recurrent form are due to the friability of the postradiation mucosae. A prospective multi-central study reported chronic OM to have an incidence of 8.1% in post-RT patients [239].

Pain associated with OM is a also major concern for clinicians and patients due to its impact on daily tasks such as eating, swallowing, and talking [1]. Other symptoms are dysphagia, which may be mild or severe, drooling, and infections. Although pain is the hallmark of OM, the issue of pain related to OM has been poorly addressed. The incidence of OM-related pain is 40–70% among patients treated with CT, 100% in those receiving RT for HNC, and 60–89% in the setting of allo-BMT [64, 240]. Pain in allo-BMT, on average, begins 4–4.5 days posttransplant, although it may begin several days prior to transplant, lasts 6.5–9.5 days, and

resolves by 11–13 days posttransplant [46, 64, 241]. Pain is described as "tender," "irritating," and "sore" [46]. The pain can range from a sense of burning in the initial phases up to severe pain and are caused by a mixture of different types of pain [15].

In a model adopted from oral mucosal injury, it was suggested that the main components are nociceptive pain, mediated by C fibers and relievable by opioids, and incidental pain, caused by movement and contact with the mucosal surface, mediated by the fast-conducting A-δ fibers [242]. The latter component is insensitive to analgesics, and the only effective pain treatment is the functional exclusion of the anatomic parts involved until the resolution of the ulcers and full recovery of the mouth's functionality.

Oral AEs due to targeted therapy have been reported to include OM or stomatitis, dysphagia, taste alterations and dysgeusia, xerostomia, lichenoid reactions, mucosal inflammation, and nonspecific mucosal sensitivity and pain [10]. These AEs can result in significant clinical impact affecting function and quality of life (QOL) and are consequently a negative impact on patient treatment adherence [243, 244]. In many cases, lesions are less severe than those induced by CT and radiotherapy; however, given the chronicity of treatment, the long-term impact of these oral complications warrants further investigation.

Clinical characteristics of targeted therapy-induced stomatitis are mainly reported in mTORI. Targeted therapy-induced mucosal lesions are characterized by repeated episodes of ulcerations [238]. The episode may include a single or multiple sites of mucosal ulcerations affecting primarily nonkeratinized oral tissues such as labial and buccal mucosa and the ventral surface of the tongue and floor of the mouth [10, 245].

Specifically, mTORI-associated stomatitis is classically characterized to be well-circumscribed single or multiple ovoid ulcerations less than 1 cm with central gray area surrounded by erythema [245–248] that closely resemble aphthous stomatitis [130, 246]. Mouth pain, dysgeusia, and dysphagia may be reported without clinical signs of ulceration [246], possibly indicative of early or low-grade mTORI-related stomatitis. The onset of mTORI-associated stomatitis usually occurs during the first 2 weeks of therapy with the majority of cases grades 1–2 in severity, with a median of 10 days (4–25 days) [246, 249].

Stomatitis secondary to mTORI usually resolves with dose reductions; however, recurrence of the oral ulcers has also been documented [247]. An observational study of mTORI in a variety of solid tumors noted that the majority of stomatitis cases resolved spontaneously without scarring in 4–5 days [245].

With the mTORI sirolimus, lesions are dose dependent and resolve following dose adjustment [130]. Generally, stomatitis is considered low-to-moderate grade and manageable with supportive therapy; however, optimal management remains unclear due to the lack of uniform measurement scales and terminology [125].

In a similarly undefined area, VEGFR multikinase inhibitors sunitinib and sorafenib had a median time to stomatitis of 1.1 months (range: 0.2–6.7 months) and 1.4 months (range: 0.2–15.7 months), respectively [135].

Cetuximab-associated mucositis appears to present with a general erythema and sensitivity of nonkeratinized mucosa that may be less ulcerative than typically seen with conventional cytotoxic CT and RT [250]. Combination therapy with cytotoxic agents may lead to combined presentation of more classical ulcerative mucositis. A small study of 13 patients under concurrent cetuximab and RT for HNC reported OM frequently involved areas that had received less than 10–15 Gy, most commonly the mucocutaneous junction of the lips [100]. It should be noted that, in these patients, HSV was not ruled out.

5.6 Clinical and Economic Consequences

The impact of OM extends far beyond the oral cavity, predisposing to systemic complications and impacting the delivery of optimal cancer therapy. In fact, several studies report that OM is associated with significantly worse outcomes in various patient populations. For example, in HSCT recipients, it was found that OM was associated with additional day with fever, increase in risk of significant infection, additional days of total parenteral nutrition (TPN), and additional days of injectable narcotic therapy [84, 251].

Similarly, the breakage of the mucosal barrier in neutropenic patients predisposes to septicemia or bacteremia, in particular viridans streptococci [252, 253]. A study reported a 47-fold increase in the incidence of these infections during a 17-year period and described a significant risk for septic shock (26% of cases with viridans streptococci septicemia vs. 4% of cases of septicemia involving other gram-positive bacteria) [253]. These complications can be life-threatening in many cases, particularly in immunocompromised patients. In fact, data indicate a significant increase in 100-day mortality risk in HSCT patients with OM. An increase of 3.9-fold in mortality rate was associated with each one-point increase in peak OMAS score [251].

OM may also predict the onset of hepatic veno-occlusive disease [254]. The sensitivity, specificity, and predictive value was high to suggest that in patients with hepatic abnormalities but without OM, other causes of the hepatic dysfunction should be investigated. It was suggested that this correlation reflects a similar cytotoxic-induced pathogenesis [254].

In terms of economic outcomes, HSCT patients with OM had significantly longer hospital stays, and the hospital-associated expenses increased by US$ 25,405 for each one-point increase in peak OMAS score [251]. When comparing low-grade OM (no ulceration) to high-grade OM (ulcerations), the difference in mean hospital charges reached 42,749$ [251]. Importantly, these data are based on fee schedules in the early 2000s, and the absolute numbers are likely higher now. Furthermore, these figures did not adequately capture additional economic burdens including lost or lowered employment income and the use of complimentary medicines, and as such the economic burden associated with OM is expected to be much greater.

In patients with H&N cancer treated with RT, OM-associated pain is associated with weight loss or ≥5% and requires feeding tube insertion [255]. In patients with

H&N cancer treated with RT, the rate of hospitalization due to OM was 16% for all RT protocols and 32% for altered fractionation RT [28]. The functional status decreased by 33%, and QOL decreased by 20% by the sixth week of the RT [256], indicating that opioid analgesia provides inadequate relief. In 11% of patients, OM resulted in RT regimen interruption or medication [256], thus impacting on local tumor control and patient survival.

RT-related OM is also associated with increased utilization of resources, such as ED visits, admission, consultations with dietician, opioid analgesics, and gastrostomy. It results in an incremental cost of US$ 1700–6000, depending on the grade, as of cost data in 2006 [255].

Targeted therapy-induced OM has a relatively variable presentation and is a relatively new entity within the scope of OM. Nevertheless, reports consistently presented pain-associated functional limitations, such as limited diet, difficulty eating, difficulty swallowing, or difficulty speaking. These unsurprisingly predispose to dose reduction or discontinuation of the treatment, with an incidence of 47% in patients treated with mTORI [246].

5.6.1 Outcome Assessment Measures

OM assessment scales should be able to describe precisely, classify objectively, and measure reproducibly the severity of the mucosal damage [31]. Ideally, an OM scoring system should be validated and will require minimal training to produce systematic, accurate results characterized by intra-rater and inter-rater reliability. Unfortunately, no scale currently meets all these criteria or is accepted universally. As such, the assessment and clinical evaluation of OM still pose significant challenges in clinical practice and research [30, 31].

A number of instruments to evaluate the observable and functional dimensions of OM are available [31, 257, 258]. These OM scales range considerably in their complexity and have undergone varying degrees of validation. In addition, patient-reported outcome measures have been developed based on purely subjective criteria; however, they hold great importance in illustrating the impact of OM [69, 256, 259].

5.6.1.1 Clinician-Reported Outcome Measures

A series of scales have been developed by international societies and organizations for the assessment and diagnosis of OM (Table 5.5). These scales combine elements such as symptoms, signs, and function, usually comprising of four-point or five-point scales, that rate the overall status of oral mucosal, severity of oral pain, and, in some instances, the patient's functional capabilities relative to his or her oral status (e.g., the ability to swallow). Historically, many of these scales are based on the World Health Organization (WHO) developed in 1979 [260]. The National Cancer Institute published the fifth version for Common Toxicity Criteria (NCI-CTC) scales [261], and the Radiation Therapy Oncology Group (RTOG) scale is popular for assessment of RT-induced OM. These scales are used frequently by cooperative oncology groups and oncology researchers [262].

Table 5.5 OM scales assessing both objective and subjective variables: WHO, NCI-CTC, and RTOG

Scale	Cancer treatment	Grade 0	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)	Grade 5 (death)
WHO [260]	All types	None	Oral soreness, erythema	Oral erythema, ulcers, solid diet tolerated	Oral ulcers, liquid diet only	Oral alimentation impossible	N/A
NCI-CTC [261]	All types		Asymptomatic or mild symptoms; intervention not indicate	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death related to toxicity
RTOG [262]	Radiotherapy		Irritation/may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge/may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/may include severe pain requiring narcotic	Ulceration, hemorrhage, or necrosis	N/A

WHO World Health Organization, *NCI-CTC* National Cancer Institute-Common Toxicity Criteria, *RTOG* Radiation Therapy Oncology Group

Table 5.6 Selected OM scales assessing objective variables

Scale	Grade 0	Grade 1	Grade 2	Grade 3
WCCNR [266]	Lesions: none Color: pink Bleeding: none	Lesions: 1–4 Color: slight red Bleeding: N/A	Lesions: >4 Color: moderate red Bleeding: with eating and oral hygiene	Lesions: coalescing Color: very red Bleeding: spontaneous
OMI [264]	Included 34 items: various oral locations assessed for 11 atrophy items, 11 pseudomembrane items, ten erythema items, and two edema items; all are scored from 0 (normal) to 3 (severe), with overall scale ranging from 0 to 102			
20 item OMI [263]	Modified to include 20 items: Various oral locations assessed for nine erythema items, nine ulceration items, one atrophy item, and one edema item; all are scored from 0 (normal) to 3 (severe), summed for a total possible score of 0–60			
OMAS [265]	Nine oral locations assessed for erythema (0 = none, 2 = severe) and ulcers or pseudomembranes in the oral cavity (0 = no ulcer, 1 = <1 cm^2, 2 = 1–3 cm^2, 3 = >3 cm^2)			

WCCNR Western Consortium for Cancer Nursing Research, *OMI* Oral Mucositis Index, *OMAS* Oral Mucositis Assessment Scale

Additional OM scales have also been developed, and several examples are listed (Table 5.6). These scales use objective descriptors and apply them to specific anatomic areas, adding greater specificity with various aspects of oral function and subjective patient responses, and more accurately represent the anatomic severity of OM. These scales include, among others, Oral Mucositis Index (OMI) [263, 264], Oral Mucositis Assessment Scale (OMAS) [265], and Western Consortium for Cancer Nursing Research (WCCNR) [266]. The OMI and the OMAS have been found to correlate closely with OM pain scores [241, 264].

Another clinician-rated instrument is the Performance Status Scale for Head and Neck Cancer (PSS-HN) [267], which was designed to evaluate performance in areas of functioning most likely affected by HNC and its treatment. The PSS-HN is determined through the use of an unstructured interview with the patient. It consists of three subscales: normalcy of diet, understandability of speech, and eating in public. Each is rated from 0 to 100, with higher scores indicating better performance. The PSS-HN has been shown to have adequate inter-rater reliability and to be sensitive to differences in performance and change over time [268–270].

In addition to these commonly used approaches, there are a number of detailed objective and combined scoring scales, which are designed for clinical and research purposes, as well as various study-specific scales, such as Oral Assessment Guide [271], Southwest Oncology Group Criteria [272], Eastern Cooperative Oncology Group Scale [273], Spijkervet Radiation Mucositis Scale [274], Walsh Quantitative Scoring System for Oral Mucositis [275], Tardieu Quantitative Scale of Oral Mucositis for HSCT [276], Daily Mucositis Scale for HSCT [277], MacDibbs Mouth Assessment [278], and more.

The most relevant scales for routine clinical management, which are also most widely used, appear to be those based on NCI (43–63%) or WHO (31–38%) design [31, 38, 215]. Briefly, the WHO scale measures anatomical, symptomatic, and

functional components of OM. The severity of the condition is graded by a scale from 0 (no OM) to 4 (patient requiring TPN). The NCI-CTC scale also combines variables of symptoms, signs, and function. Severity is graded from 0 (no OM) to 5 (death related to toxicity). It is noteworthy to mention that NCI-CTC v3 scored separately clinical and functional variables. This was merged into one scale in the NCI-CTC v4 and stayed this way for the NCI-CTC v5. RTOG scale to address OM due to radiotherapy, graded 0 (no change over baseline) to 4 (ulceration, hemorrhage, or necrosis).

The most noticeable drawbacks of the OM scales include the fact that assessment potentially is confounded by a combination of symptoms, signs, and functional changes. Scoring of functional variables may not be correlated directly with oral mucosal events. For example, OM assessed with a scale such as the NCI-CTC scale may be rated grade 4, which describes the patient as requiring "parenteral or enteral nutrition or support." However, in the HSCT setting, many patients are placed on TPN because of intestinal toxicity. Moreover, the symptoms that the WHO scale measures may not be due to OM at all but to local infection, hemorrhage, or the presence of an underlying malignancy. The WHO scale can be assigned without even examining the patient and thus can potentially reflect etiologies other than clinical OM. Despite these drawbacks, the WHO scale is considered most accurate in measuring the clinical consequences of OM (i.e., pain and the requirement of parenteral medication and nutrition).

A major disadvantage of the more detailed and complex clinician-reported scales (Table 5.6) is that they are best delivered and performed by an experienced/trained examiner and are often more laborious. Furthermore, only some have been validated for their accuracy with many only validated in narrow clinical cohorts. The OMAS scale is the most technically challenging as it measures lesion size and erythema at nine different sites in the oral cavity. Obviously, this scale is very difficult to use in patients with severe pain who are unable to open their mouths for an adequate oral examination. Similar challenges are also faced in children affected by cancer, in which communication and cooperation may be difficult.

The frequency with which the scales are applied relates to the objective of the examination. Whereas daily evaluations are of value for a nursing care plan, an intense, twice-weekly examination may be effective for an interventional study [31].

The sensitivity and accuracy of each scale are often a function of the conditions under which the examination takes place, including adequate illumination and inspection of oral tissues, depending on the place where the patient is being evaluated—a hospital bed, dental chair, etc. Regardless of the scale used, increasing evidence confirms the importance of training and standardization in improving the accuracy and consistency of OM assessment [31].

5.6.1.2 Patient-Related Outcome Measures

Quality-of-life instruments are needed in order to estimate OM severity and patients' experiences during therapy, thus guiding patient care and assessing the efficacy of

therapeutic interventions targeted against OM. These patient-related outcome measures are used in clinical investigations and research settings.

The OM Daily Questionnaire (OMDQ) [69, 279] contains ten items and was developed originally for use of palifermin in HSCT patients' clinical trials. Items included questions regarding degree of mouth soreness and degree of limitation of functioning (swallowing, eating, drinking, talking, and sleeping) due to mouth soreness. Mouth and throat soreness (MTS) scores were highly correlated with functioning limitation items and also with the WHO scale. Interestingly, patients reported changes 1–3 days earlier than clinicians [69, 279].

The OMDQ has also been used and validated in HNC patients undergoing radiotherapy, with or without CT [256]. Mean QOL scores decreased significantly during RT, corresponding with the peak of OM severity. Symptomatic management of OM was insufficient to avoid negative patient-reported outcomes.

The Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) is another validated, reliable, and feasible patient-reported outcome instrument for assessing the impact of OM [259]. It consists of 12 items that assess patient well-being and function. The time frame for reference is the past week. The first two questions assess overall health and QOL, rated on a seven-point scale. The third question quantifies MTS the patient is experiencing on a five-point scale. The remaining three questions assess the degree of mouth, throat, and overall mouth and throat pain and soreness using an 11-point scale [259].

The Functional Assessment of Cancer Therapy-Head and Neck Cancer (FACT-HN) includes the FACT-General (FACT-G) and an HNC-specific additional-concerns subscale (HNCS) [280]. The FACT-G is a general cancer QOL scale for evaluating patients receiving cancer treatment [281]. The FACT-G can be supplemented by site- and/or treatment-specific subscales, including HNCS. The FACT-G has four subscales: physical well-being (PWB) (seven items), social/family well-being (SWB) (seven items), emotional well-being (EWB) (six items), and functional well-being (FWB) (seven items). The HNCS has additional 9–12 HNC specific items, each rated on a 1 to 4 Likert-type response format (ranging from 0 [not at all] to 4 [very much]). Items are then combined to describe patient functioning in these six areas. Higher subscale scores represent better QOL. The FACT-HN was found to be reliable and valid when applied to HNC patients [269, 270, 280].

The FACT-HN Symptom Index (FHNSI) is comprised of ten items from the FACT-HN that have been selected by expert clinicians from 17 National Comprehensive Cancer Network (NCCN) institutions, as the most important symptom targets when treating patients with advanced HNC [282].

Another questionnaire developed to assess the QOL of cancer patients is the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) [283]. The questionnaire is composed of five multi-item scales (physical, role, social, emotional, and cognitive functioning) and nine single items (pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhea, constipation, sleep disturbance, and QOL). It is supplemented by disease-specific modules, e.g., HN. It includes 28 questions rated on a Likert-type scale (1–4) and other two questions rated on a 1–7 scale, regarding overall health and

QOL. All items relate to the past week. The QLQ-C30 is a well-validated instrument providing a broad view of the patients' QOL [284, 285]. This has evolved into the EORTC H&N35 module—a lengthy but well-validated questionnaire—general to all HNCs and all modalities of treatment, assessing seven scales: pain, swallowing, senses, speech, social eating, social contact, and sexuality [286].

Other patient-reported outcome measures exist and are beyond the scope of this section.

5.7 Treatment and Prevention

There is extensive literature about the management of OM, which indicates the great need for an effective treatment. However, as of today, there is only a single drug that the FDA has cleared for the prevention of OM. This fact represents the numerous challenges in identifying an effective and safe treatment and to successfully complete the regulatory phases.

In attempt to identify the interventions for OM which have the strongest evidence, the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) conduct periodically a systematic review. The results of the systematic review are presented as three types of guidelines: recommendation, suggestion, and no guideline possible (NGP). Additionally, the guidelines specify the aim of the intervention: prevention, treatment, or management of OM-associated pain [287].

The current version of the MASCC/ISOO clinical practice guidelines for the management of OM was published in 2019–2020 (Tables 5.7 and 5.8). The details of the systematic review appear in the set of guideline publications [288–295] and are summarized in formal guidelines summary paper [296]. Guidelines for the management of gastrointestinal mucositis were developed as well (Table 5.9) [291].

Targeted therapy-related mucositis requires a dedicated clinical approach as the pathogenesis of this oral lesions is different than the pathogenesis of the conventional OM. Furthermore, from the current data, it seems that steroids, which are effective for targeted therapy-related mucositis, are reported to be ineffective for conventional OM. A key element in the management of targeted therapy-related mucositis is the dose reduction of the drug [246]. Dose reduction reduces the severity and frequency of the oral eruptions; however, this approach clearly compromises the efficacy of cancer therapy and thus affects prognosis. Among the interventions studied for targeted therapy-related mucositis are topical steroids, such as clobetasol gel 0.05% and dexamethasone solution 0.01% [246]. Systemic steroids were also reported to be effective, for example, intralesional injections of triamcinolone 40 mg/mL or prednisone 5 mg/day [246, 297]. Interestingly, a case report of steroid-resistant temsirolimus mucositis suggested that colchicine may be effective in healing of existing lesions and reduce frequency of new lesions [298]. These therapeutic interventions are enhanced by palliative treatments with local anesthetics or topical antihistamines [297].

Table 5.7 MASCC/ISOO clinical practice guidelines for the management of oral mucositis [288–290, 292–296]

Section	Intervention		LoE	Category	Guideline statement
Guidelines that were determined in 2019–2020 based on new evidence					
BOC	Multi-agent combination	1	III	Suggestion	The panel suggests that implementation of **multi-agent combination** oral care protocols is beneficial for the prevention of OM during CT
		2	III	Suggestion	The panel suggests that implementation of **multi-agent combination** oral care protocols is beneficial for the prevention of OM during H&N RT
		3	III	Suggestion	The panel suggests that implementation of **multi-agent combination** oral care protocols is beneficial for the prevention of OM during HSCT
	Professional oral care	4	III	NGP/expert opinion	No guideline was possible regarding the use of **professional oral care** for the prevention of OM for patients with hematologic, solid, or H&N cancers due to limited and inconsistent data An expert opinion complements this guideline. Although there was insufficient evidence to support the use of professional oral care for OM prevention, the panel is of the opinion that dental evaluation and treatment as indicated prior to cancer therapy is desirable to reduce risk for local and systemic infections from odontogenic sources
	Patient education	5	III	NGP/expert opinion	No guideline was possible regarding the use of **patient education** for the prevention of OM in hematologic cancer patients during HSCT or CT due to limited and inconsistent data An expert opinion complements this guideline. The panel is of the opinion that educating patients about the benefits of BOC strategies is still appropriate as this may improve self-management and adherence to the recommended oral care protocol during cancer treatment
	Saline or sodium bicarbonate	6	III	NGP/expert opinion	No guideline was possible regarding the use **of saline or sodium bicarbonate** rinses in the prevention or treatment of OM in patients undergoing cancer therapy due to limited data An expert opinion complements this guideline. Despite the limited data available for both saline and sodium bicarbonate, the panel recognizes that these are inert bland rinses that increase oral clearance which may be helpful for maintaining oral hygiene and improving patient comfort
	CHX	7	III	Suggestion against	The panel suggests that **CHX** not be used in the prevention of OM in patients undergoing H&N RT
Anti-inflammatory agents	Benzydamine	8	I	Recommendation	The panel recommends **benzydamine** mouthwash for the prevention of OM in patients with H&N cancer receiving a moderate-dose RT (<50 Gy)
		9	II	Suggestion	The panel suggests the use of **benzydamine** mouthwash for the prevention of OM in patients with H&N cancer receiving RT-CT

(continued)

Table 5.7 (continued)

Section	Intervention		LoE	Category	Guideline statement
PBM (laser/ light therapy)	PBM	10	I	Recommendation	The panel recommends the use of intraoral **PBM** therapy using low-level laser therapy for the prevention of OM in adult patients receiving HSCT conditioned with high-dose CT, with or without total body irradiation using one of the selected protocols[a]; it is recommended that the specific PTPs of the selected protocol will be followed for optimal therapy
		11	II	Recommendation	The panel recommends the use of intraoral **PBM** therapy using low-level laser therapy for prevention of OM in adults receiving RT to the H&N (without CT)[a]; the specific PTPs of the selected protocol should be followed for optimal therapy Safety considerations unique to patients with oral cancer should be considered
		12	I	Recommendation	The panel recommends the use of intraoral **PBM** therapy using low-level laser therapy for the prevention of OM in adults receiving RT-CT for H&N cancer (LoE I)[a]; the specific PTPs of the selected protocol should be followed for optimal therapy Safety considerations unique to patients with oral cancer should be considered
Cryotherapy	Cryotherapy	13	II	Recommendation	The panel recommends using oral **cryotherapy** to prevent oral mucositis in patients undergoing autologous HSCT when the conditioning includes high-dose melphalan
		14	II	Recommendation	The panel recommends using 30 min of oral **cryotherapy** to prevent oral mucositis in patients receiving bolus 5-FU CT during the infusion of the CT
Antimicrobials, coating agents, anesthetics, analgesics	Morphine rinse	15	III	Suggestion	Topical **morphine** 0.2% mouthwash is suggested for the treatment of OM-associated pain in H&N cancer patients treated with RT-CT
	Sucralfate	16	II	Recommendation against	**Sucralfate** (combined topical and systemic) is not recommended for the prevention of OM-associated pain in H&N cancer patients treated with RT
		17	II	Recommendation against	**Sucralfate** (combined topical and systemic) is not recommended for the treatment of OM-associated pain in H&N cancer patients treated with RT
		18	II	Recommendation against	**Sucralfate** (combined topical and systemic) is not recommended for the treatment of OM-associated pain in solid cancer patients treated with CT
Growth factors and cytokines	KGF-1	19	I	Recommendation	The use of **KGF-1** intravenously is recommended for prevention of OM in patients with hematological cancer undergoing autologous HSCT with a conditioning regimen that includes high-dose chemotherapy and TBI
	GM-CSF	20	II	Suggestion against	The evidence suggests that topical **GM-CSF** should not be used for the prevention of OM in patients undergoing HSCT

Natural and misc.	Glutamine	21	I	Recommendation against	The panel recommends against the use of **glutamine** (parenteral) for the prevention of OM in patients undergoing HSCT
		22	II	Suggestion	The panel suggests **glutamine** (per os) for the prevention of OM in patients with H&N cancer receiving RT-CT The suggestion is with caution due to the higher mortality rate seen in HSCT patients treated with parenteral glutamine
	Honey	23	II	Suggestion	**Honey** is suggested for the prevention of OM in H&N cancer patients treated with either RT or RT-CT
	Chewing gum	24	III	Suggestion against	**Chewing gum** is not suggested for the prevention of OM in pediatric patients with hematological or solid cancer treated with CT
Guidelines that were determined in 2014 and no new evidence for these agents was published since					
Antimicrobials, coating agents, anesthetics, analgesics	Patient-controlled analgesia with morphine	1	II	Recommendation	The panel recommends that **patient-controlled analgesia with morphine** be used to treat pain due to oral mucositis in patients undergoing HSCT
	PTA or BCoG	2	III	Recommendation against	The panel recommends that **PTA** and **BCoG** antimicrobial lozenges and PTA paste not be used to prevent OM in patients receiving RT for H&N cancer
	Iseganan	3	II	Recommendation against	The panel recommends that **iseganan** antimicrobial mouthwash not be used to prevent OM in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT
		4	II	Recommendation against	The panel recommends that **iseganan** antimicrobial mouthwash not be used to prevent OM in patients receiving RT or RT-CT for H&N cancer
	Pentoxifylline	5	III	Suggestion against	The panel suggests that **systemic pentoxifylline**, administered orally, not be used to prevent OM in patients undergoing bone marrow transplantation
Natural and miscellaneous	Pilocarpine	6	III	Suggestion against	The panel suggests that **systemic pilocarpine**, administered orally, not be used to prevent OM in patients receiving RT for H&N cancer
		7	II	Suggestion against	The panel suggests that **systemic pilocarpine**, administered orally, not be used to prevent OM in patients receiving high-dose CT, with or without total body irradiation, for HSCT

[a]These guidelines refer to specific PBM protocols. For the detailed protocols, see the full text in the 2019 guidelines paper [288]
OM oral mucositis, *BOC* basic oral care, *NPG* no guideline possible, *CHX* chlorhexidine, *PBM* photobiomodulation, *PTP* physical therapy parameters, *KGF-1* keratinocyte growth factor 1, *GM-CSF* granulocyte macrophage colony-stimulating factor, *PTA* polymyxin, tobramycin, and amphotericin B (as a lozenge or a paste), *BCoG* bacitracin, clotrimazole, and gentamicin (as a lozenge), *HSCT* hematopoietic stem cell transplantation, *CT* chemotherapy, *RT* radiotherapy, *RT-CT* radiochemotherapy, *H&N* head and neck, *TBI* total body irradiation

Table 5.8 Recommended intraoral photobiomodulation therapy protocols for the prevention of oral mucositis (details in Zadik 2019) [288]

Cancer treatment modality	Wavelength (nm)	Power density (irradiance; mW/cm^2)	Time per spot (s)	Energy density (fluence; J/cm^2)	Spot size (cm^2)	Number of sites	Duration
HSCT	632.8	31.25	40	1.0	0.8	18	From day after cessation of conditioning for 5 days
	650	1000[a]	2	2.0	0.04	54–70	From the first day of conditioning till day +2 post-HSCT (for 7–13 days)
RT	632.8	24	125	3.0	1	12	Entire RT course
RT-CT	660	417[a]	10	4.2	0.24	72	Entire RT course
	660	625[a]	10	6.2	0.04	69	Entire RT course

[a]Potential thermal effect; the clinician is advised to pay attention to the combination of specific parameters

CT chemotherapy, *HSCT* hematopoietic stem cell transplantation, *IO* intraoral, *NR* not reported, *PBM* photobiomodulation, *RT* radiotherapy, *wk* week

Patient education is also an important, yet commonly overlooked, part of the overall supportive treatment approach. Although there is currently no proof that patient-targeted education leads to significantly reduced OM prevalence, it is assumed that patient education encourages the patient to maintain adequate oral hygiene, which in turn reduces the risk for oral infections and systemic spread of the infections through the ulcerated oral mucosa.

Lastly, OM should be differentiated from oral infections that often develop while patient is administered the anticancer therapy and may coincide with OM. These infections are typically bacterial, viral, or fungal. While the symptoms may be similar (e.g., OM and candidiasis may cause burning pain), or the signs may be similar (e.g., OM, bacterial infection, and HSV reactivation during neutropenia may cause oral ulcerations on nonkeratinized mucosa), the coinfection amplifies the clinical presentation and hinders the diagnosis of OM. The clinical presentation and laboratory tests are critical in confirming a diagnosis. Empiric antimicrobial treatment may be initiated based on the clinical presentation but must then be reevaluated once laboratory results are available.

5.8 Summary

OM is a clinical entity with a significant impact on the patient, clinicians, and health-care system. The understanding of the pathogenesis has improved markedly over the last few decades; however, this has not yet led to universally adopted

Table 5.9 MASCC/ISOO clinical practice guidelines for the management of gastrointestinal mucositis [291]

Intervention		LoE	Guideline category	Guideline statement
Guidelines that were determined in 2019–2020 based on new evidence				
Probiotics	1	II	Suggestion	The panel suggests that **probiotics containing *Lactobacillus*** spp. may be beneficial for prevention of RT or RT-CT-induced diarrhea in patients with pelvic malignancy
HBO	2	II	Suggestion	The panel suggests that **hyperbaric oxygen** is an effective way to treat RT-induced proctitis in patients with pelvic malignancy
Guidelines that were determined in 2014 and no new evidence for these agents was published since				
Amifostine	1	II	Recommendation	The panel recommends that intravenous **amifostine** be used, at a dose of ≥340 mg/m^2, to prevent radiation proctitis in patients receiving RT
	2	III	Suggestion	The panel suggests that intravenous **amifostine** be used to prevent esophagitis induced by RT-CT in patients with non-small cell lung carcinoma
Octreotide	3	II	Recommendation	The panel recommends that **octreotide**, at a dose of ≥100 μg subcutaneously twice daily, be used to treat diarrhea induced by standard- or high-dose CT associated with HSCT, if loperamide is ineffective
Sucralfate	4	III	Suggestion	The panel suggests that **sucralfate** enemas be used to treat chronic radiation-induced proctitis in patients with rectal bleeding
	5	I	Recommendation against	The panel recommends that systemic **sucralfate**, administered orally, not be used to treat gastrointestinal mucositis in patients receiving RT for a solid tumor
Sulfasalazine	6	II	Suggestion	The panel suggests that systemic **sulfasalazine**, at a dose of 500 mg administered orally twice a day, be used to prevent radiation-induced enteropathy in patients receiving RT to the pelvis
ASA, mesalazine, olsalazine	7	I	Recommendation against	The panel recommends that **ASA, and the related compounds mesalazine and olsalazine**, administered orally, not be used to prevent acute radiation-induced diarrhea in patients receiving RT for a pelvic malignancy
Misoprostol	8	I	Recommendation against	The panel recommends that **misoprostol** suppositories not be used to prevent acute radiation-induced proctitis in patients receiving RT for prostate cancer

OM oral mucositis, *GM-CSF* granulocyte macrophage colony-stimulating factor, *PTA* polymyxin, tobramycin, and amphotericin B (as a lozenge or a paste), *CT* chemotherapy, *RT* radiotherapy, *RT-CT* radiochemotherapy, *HBO* hyperbaric oxygen, *ASA* 5-acetylsalicylic acid

preventative or therapeutic approaches. As such, there remains a great need for effective prophylactic therapies to mitigate OM prevalence and severity without compromising treatment efficacy. The clinical practice guidelines for the management of OM provide the current evidence-based summary of the best practice for OM.

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