The oral and gastrointestinal mucosa acts as an important mechanical barrier that prevents local or systemic invasion by microorganisms. Cytotoxic chemotherapy-induced mucosal injury (MI) of oral cavity and intestinal epithelium occurs in many patients treated for malignancy. Compromise of the mucosal barrier can contribute to local invasion by colonizing microorganisms and, subsequently, to systemic infection. Historically, gram-negative bacteremia has been the most problematic bacterial infection in neutropenic patients, but its incidence has reduced over time because of the use of prophylactic antibiotics. There has been a shift in the type of infecting organisms responsible for bacteremia in these patients, from predominantly gram-negative organisms to gram-positive cocci. The viridans group of streptococci is composed of the most frequent bacterial pathogens associated with MI. When speciated, oral colonizers such as Streptococcus mitis, Streptococcus oralis, and Streptococcus sanguis II are the most frequently identified pathogens. Other systemic infections caused by vancomycin-resistant enterococci, Stenotrophomonas maltophilia, and Candida species have also been associated with MI after cancer treatment. Infection can also exacerbate MI after cancer treatment. The best recognized example is herpes simplex virus type 1 (HSV-1). Latent virus is frequently reactivated in HSV-seropositive patients; this reactivation leads to stomatitis, which can be indistinguishable from MI caused by cytoreductive therapies. Antiviral prophylaxis or treatment can control the virus-induced MI and bring about overall amelioration of MI. Recognition of this infectious cause of MI is important in order for clinicians to anticipate and minimize oral toxicity and to facilitate optimal delivery of the antineoplastic regimen. [J Natl Cancer Inst Monogr 2001;29:31–6]

Mucosal injury (MI) can lead to a variety of systemic consequences. These include impaired oral intake of fluid and nutrients, leading to dehydration and malnutrition; pain; nausea; vomiting; abdominal cramping; and diarrhea. The mucosa of the oral cavity and gastrointestinal (GI) tract also serves as an important mechanical barrier that helps to prevent a local or systemic invasion of various microbes and the absorption of microbial products that are normally present in the oral cavity and gastrointestinal (GI) lumen of the gut (1). Derangement in the barrier function of the GI tract plays a central role in the pathophysiology of systemic infection, shock, and sepsis syndrome. In this article, we will examine two propositions. The first is that MI is a major challenge to optimal management of the cancer patient. The second proposition examines the notion that certain microorganisms exacerbate MI, which, in turn, can increase the susceptibility for systemic infection from other commensal organisms. Infectious causes of MI are indistinguishable from cytotoxic drug-induced MI and can be confused with MI from the antineoplastic regimen. Infection-induced MI may necessitate dose reduction or modification of the antineoplastic regimen, which may compromise the ultimate benefits of the treatment regimen.

**Effects of Cancer Treatments on the Oral and GI Mucosa**

Cytotoxic chemotherapy is known to cause MI both in the oral cavity (2–6) and to mitotically active intestinal crypt cells (7). The manifestations of oral mucositis include erythema, ulcer formation, bleeding, and exudates. Methotrexate (7), 5-fluorouracil, cisplatin (8), cytarabine (9), etoposide, and radiation therapy (XRT) (10) have been shown to have mucosal-damaging effects. Most of the patients treated for head and neck cancer and almost half of the patients receiving chemotherapy for non-head and neck cancer develop oral complications (11).

The course of oral mucositis after standard- or high-dose chemotherapy parallels the neutropenia that occurs following such therapy. The onset of oral mucositis occurs near the nadir of neutrophil count, and its resolution parallels hematologic recovery (12).

Slavin et al. (9) described the natural history of cytotoxic therapy-induced intestinal damage. Initial injury began during the first week of cytotoxic therapy and was characterized by replacement of normal crypts of mucous-secreting cells by atypical undifferentiated cells. During subsequent weeks, the injury progressed to a second stage, which consisted of cellular necrosis, a lack of mitotic activity, disappearance of villous surface, and complications by various infections. Finally, the recovery phase was characterized by regeneration and differentiation of cells that covered the denuded surface.

There are several studies (13) of D-xylose absorption tests that have been used as a measure of functional integrity of the intestinal mucosal barrier. Studies in patients with acute myeloid leukemia (AML) receiving remission induction therapy have shown malabsorption of D-xylose during weeks 2 and 3 after chemotherapy, secondary to gut epithelial damage (14,15). The magnitude of intestinal epithelial damage as measured by D-xylose malabsorption was strongly correlated with the induction regimen.

The effect of radiation therapy on oral cavity primarily results from local tissue changes. These changes are initiated by a reduction in the proliferation of basal epithelial cells, causing atrophy (11). The damage of connective tissue may lead to an increase in vascular permeability and tissue edema (10).

Oral complications of cancer chemotherapy may be direct somatotoxicity of chemotherapy against basal epithelium; indi-
rect somatotoxicity through the patient’s inability to contain local, minor oral disease during myelosuppression; or a combination of both (11). Local infection can produce inflammatory changes that further exacerbate MI.

The degree of MI is dependent on the dose intensity of the treatment regimen. Mucositis is particularly frequent in the bone marrow transplant (BMT) population because of the intensive conditioning regimen. Approximately 75% of patients develop some degree of mucositis after the conditioning regimen, which consists of high-dose chemotherapy or combined chemoradiation. Over two thirds of patients with leukemia and one third of those with non-Hodgkin’s lymphoma develop MI (11). Patients with solid tumors are at lower risk of developing MI (40%), except for patients with head and neck cancer who receive combined XRT and chemotherapy. Virtually all of these patients develop mucositis. The effects of XRT on the mouth primarily result from local changes. Consequently, the total dose of XRT to the oral cavity and dose rate are directly related to the extent of MI. The MI is noted at a level of 20 Gy when XRT is administered at a rate of 200 cGy daily (11).

MI of the oral cavity is frequently accompanied by oral infections. Viral, bacterial, and fungal infections are all common. In some clinical settings, systemic bacterial or fungal infections may be more common in patients with mucositis.

**MI AS CONTRIBUTORY FACTOR TO SYSTEMIC INFECTION**

**Bacterial Infections**

Bacteremia from gram-negative rods has been the most problematic bacterial infection in chemotherapy-induced neutropenia. The GI tract is a major source of bacteria in patients who develop MI as a result of chemotherapy (16). Between 25% and 50% of cases of septicemia in neutropenic cancer patients appear to originate from oral colonizing bacteria (17).

The incidence of gram-negative bacterial infections in neutropenic patients has decreased over time, perhaps because of both the prophylactic use of broad-spectrum antibiotics in neutropenic patients and the empiric use of systemic broad-spectrum antibiotics at first sign of fever in neutropenic patients (18) (Table 1). Nevertheless, studies (18–25) have shown that bacteremia caused by gram-positive organisms is becoming more common. At present, gram-positive bacteria represent the overwhelming majority of neutropenic systemic infections. Furthermore, substantial proportions of these gram-positive bacterial pathogens are viridans group streptococci.

Viridans streptococci are now the second most common genus of bacteria isolated from blood culture after coagulase-negative staphylococci. They can be responsible for up to 39% of bacteremia cases in neutropenic population (26). Several authors (27–29) have suggested that oropharyngeal lesions were the most probable portal of entry for viridans streptococci that caused bacteremia. Other investigators (30) have suggested that the rest of the digestive tract, particularly the stomach and lower respiratory tract, might also be portals of entry. In a recent review of literature on bacteremia caused by viridans streptococci in neutropenic patients (26), the most frequently isolated species in blood culture were *Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus sanguis II*. Various risk factors have been identified, and the presence of oropharyngeal mucositis was a statistically significant independent factor in most of these studies (26,32,35). Other risk factors included severe neutropenia, prophylactic antibiotic treatment with co-trimoxazole or quinolone, chemotherapy involving high doses of cytarabine, GI toxicity requiring antacids or H2 blockers, and heavy colonization by viridans streptococci (27–34). Bochud et al. (32) reviewed 26 episodes of viridans streptococcal bacteremia that occurred in 25 neutropenic patients undergoing intensive chemotherapy for hematologic malignancies. Multivariate analysis of predisposing factors showed that the presence of mucositis was an important independent risk factor for the development of viridans streptococcal bacteremia. Pharyngeal lesions were statistically significantly more frequent in case patients (85%) than in the control patients (55%) (P = .01). Multivariate analysis of risk factors showed that mucositis was among the three independent predictors for the development of viridans streptococcal bacteremia (P = .02).

Ruescher et al. (35) reported on 24 patients who were treated with high-dose chemotherapy and an autologous BMT for hematologic malignancies and who had developed bacteremia with α-hemolytic streptococci. Of these 24 patients with bacteremia, 14 (62%) had ulcerative mucositis, compared with 16 (36%) of 45 patients in the control population (P<.05). Patients with ulcerative mucositis were found to be three times as likely to develop α-hemolytic streptococcal bacteremia as those without ulcerative mucositis (odds ratio = 3.02).

Streptococcal organisms are the most frequent bacterial pathogens associated with MI. However, systemic infections by other bacteria and fungi have also been implicated as sequelae of MI.

Vancomycin-resistant enterococci (VRE) are rapidly increasing causes of infection in hospitalized patients and are associated with considerable morbidity (36). Mucositis has been implicated as a possible contributory factor associated with invasive VRE infection. In one study reported by Kuehnert et al. (37), 738 cancer patients admitted into the hospital had at least one stool specimen obtained for VRE. Nineteen cases of VRE bacteremia were identified. When case patients were compared with control patients, the presence of mucositis, among other factors, was statistically significantly associated with VRE bloodstream infection (P<.01) in univariate analysis. When the independent importance of various risk factors identified in univariate analyses was tested in multivariate analysis using logistic regression models, only mucositis remained statistically significantly associated with VRE bacteremia. Furthermore, when the severity of mucositis was assessed quantitatively, the risk of VRE bacteremia increased with increasingly severe mucositis (P<.003); this finding remained valid after adjusting for severity.

**Table 1. Infectious pathogens encountered in cytotoxic-induced myelosuppression†**

<table>
<thead>
<tr>
<th>Systemic pathogen</th>
<th>Relative frequency</th>
<th>Relative severity</th>
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<tbody>
<tr>
<td>GNR</td>
<td>+</td>
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<tr>
<td>GPC</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Candida</td>
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<tr>
<td>Aspergillus</td>
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<td>+++</td>
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<td>HSV</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>CMV</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
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*GNR = gram-negative rods; GPC = gram-positive cocci; HSV = herpes simplex virus; CMV = cytomegalovirus.

†+, less frequent; ++, frequent; ++++, more frequent.
of illness and degree of neutropenia. Kuehnert et al. hypothesized that the association of mucositis with VRE bacteremia may be due to diffuse GI mucosal breakdown, which promotes bloodstream entry by gut-colonizing VRE.

In recent years, the emergence of increasing bloodstream anaerobic infections in neutropenic patients, formerly rare, has been described. Most of these patients have oral mucositis or periodontal disease (38).

Labarca et al. (39) reported Stenotrophomonas maltophilia bacteremia in a cluster of eight allogeneic BMT patients. In addition to other associated factors identified when infected patients were compared with control patients, severe mucositis was identified as one of the risk factors (P = .028).

**Fungal Infection**

Invasive fungal infections are frequent in patients undergoing cancer chemotherapy that results in prolonged neutropenia and after a BMT (40). As many as 40% of patients undergoing BMT develop invasive fungal infection when neutropenia persists for more than 20 days (41).

*Candida* and *Aspergillus* sp. are the most frequent causes of fungal infection in leukemia patients undergoing chemotherapy and in BMT patients. Invasive fungal disease in these patients is associated with a high mortality rate (approximately 50%–90%) (42,43). *Candida* species are commensal organisms that reside normally on the oral mucosa and in the lumen of the GI tract. They not only can cause local infection of the oral mucosa, which is painful, but also can result in esophageal candidiasis or in systemic dissemination. Systemic fungal infections are difficult to recognize and respond poorly to treatment (44). The intact mucosa is an important host defense against systemic *Candida* infection in neutropenic patients (14).

Wingard et al. (44) reported on 89 consecutive patients treated intensively for leukemia or undergoing BMT for a 12-month period. They observed 18 episodes of *Candida* sepsis in 17 patients (19%). Three (5%) of 60 patients colonized by *Candida albicans* in their mucosa became infected, while 14 (56%) of 25 patients colonized by *C. tropicalis* became infected (P<.001). These data suggest that *C. tropicalis* is a more virulent systemic pathogen than *C. albicans* in neutropenic cancer patients, despite being a less frequent colonizer of mucosal surface (45). When examined in animal models of *Candida* virulence, no difference in virulence was noted between *C. albicans* and *C. tropicalis* when the organisms were given intravenously. However, after the organisms were inoculated into the esophagus in mice given chemotherapy that induced damage of the gut mucosa (Fig. 1) and neutropenia, *C. tropicalis* isolates were substantially more virulent than *C. albicans* isolates. In dose–response assays, systemic invasive infection occurred at inoculation doses more than 100-fold less with *C. tropicalis* isolates than with *C. albicans* isolates (46,47).

Bow et al. (14) studied the relationship of cytotoxic regimen with intestinal mucosal damage and fungal colonization in the pathogenesis of invasive fungal disease in 138 patients undergoing induction therapy for untreated AML. They used weekly D-xylose absorption tests (13) for evaluation of the functional integrity of the upper GI tract and to measure small intestinal epithelial damage. Their results suggested that pathogenesis of invasive fungal disease is linked to cytotoxic therapy-related gut epithelial damage in the setting of fungal colonization of the gut. Patients in whom invasive fungal disease developed had lower serum D-xylose levels (indicative of greater intestinal epithelial damage), with the maximal difference noted at weeks 2 (P = .0288) and 3 (P = .0019) of chemotherapy, than did uninfected patients. Bow et al. speculated that damaged mucosal surface may facilitate infection by promoting adherence, local proliferation, and translocation of microorganisms colonizing these surfaces. In this study, gut epithelial damage was maximal during weeks 2 and 3 of induction therapy, which was coincident with the neutrophil nadir. In another report (13), neutropenic colitis and hepatosplenic fungal infection were also correlated with the D-xylose malabsorption. The mean serum D-xylose levels during week 2 of chemotherapy in AML patients were lower among subjects who developed neutropenic enterocolitis (P = .002) and hepatosplenic candidiasis (P = .002) (15). Neutropenic enterocolitis was strongly correlated with the development of candidemia (P = .005).

Various other reports have identified mucositis as a risk factor for fungemia among the patients receiving antineoplastic therapy. In one report (48) of 41 episodes of breakthrough fungemia occurring in cancer patients receiving antifungal prophylaxis, mucositis was identified as one of the risk factors for breakthrough fungemia (34.2% versus 13.1%; P<.05).

While each of these studies had methodological differences, each supports the concept that MI offers a portal of entry into the systemic circulation for commensal oral and GI bacteria. Thus, the ability to treat and prevent the severe MI would be an important tool to decrease the rate of bacterial infections in this patient population.

These studies in aggregate suggest that systemic infections resulting from MI occur in more intensively treated patients.
(acute leukemia, induction therapy, and BMT) or are more prevalent in regimens that cause greater degrees of MI and that children are as vulnerable as adults. The reasons are not clear: Oral commensal organisms appear to be more frequent systemic pathogens than GI-colonizing organisms, despite the fact that there is a substantially greater burden of gut-colonizing organisms compared with oral colonizers and the fact that there is a much greater surface area of gut mucosa compared with oral mucosa.

**Infection Contributing to MI**

Herpes simplex virus type 1 (HSV-1) causes the most common symptomatic oral viral infection. HSV seropositivity is an indicator for latent or persistent infection, which may reactivate from a variety of stimuli such as chemotherapy or radiotherapy. This risk for reactivation correlates with the dose intensity of antineoplastic therapy. Reactivation occurs in up to 70%–80% of seropositive BMT and acute leukemic patients (49,50). Reactivation rates are lower in less intensely treated patient groups. HSV reactivation occurs in 38%–60% of non-Hodgkin’s lymphoma patients under treatment and in 15%–20% of patients receiving chemotherapy or radiotherapy for head and neck cancer (51–62). The frequency of HSV reactivation in various antineoplastic treatment settings, especially solid tumor treatment regimens, is not well established. In many patients who are seropositive for HSV, the virus is reactivated after the chemotherapy (63). Resultant HSV-induced mucositis may be difficult to differentiate from MI from direct damage caused by chemotherapy, since the telltale labial blister, the pathogenomonic feature of reactivation of HSV, may not be present. Deep and extensive oral ulcerations may occur because of HSV-1 (Fig. 2). In patients treated with high-dose chemotherapy with BMT or after intensive chemotherapy for leukemia, HSV-1 mucosal infection can also spread contiguously along the mucosal surface, resulting in esophagitis, tracheitis, or pneumonitis.

It is frequently difficult to distinguish between infectious and noninfectious oral mucositis caused by chemotherapy or irradiation. For example, when phase I dose escalation studies were performed for etoposide in a stem cell rescue setting, severe mucositis was reported to be the dose-limiting toxic effect (64). When phase I dose-escalation studies of etoposide were repeated with acyclovir prophylaxis to prevent HSV reactivation, the maximally tolerated dose of etoposide, evaluated at 50% higher doses (65,66), was not achieved, clearly indicating that much of the formerly described MI attributed to etoposide-direct cytotoxicity was instead caused by reactivation of HSV. Ulcerative mucositis is still seen after administration of etoposide with acyclovir prophylaxis, especially at the high doses used in conditioning regimens in the BMT setting, but it is less severe.

Acyclovir, a nucleoside analogue, which is selectively phosphorylated by a virus-specified thymidine kinase targeting the viral DNA polymerase, is highly effective in preventing MI from HSV-1 and has been shown to be effective prophylactically in prospective randomized trials (51,54,66,67). Before acyclovir’s prophylactic use, HSV-infected patients had mortality rates from HSV-1 infection as high as 5%–10% after BMT (68). Acyclovir prophylaxis can have secondary benefits in the reduction of the risk for systemic infection from streptococcal bacteria colonizing the mucosa. This was amply illustrated in 60 consecutive BMT patients in which the risk for streptococcal bacteremia was 25% in 30 patients not treated with acyclovir prophylaxis but 0% in 30 consecutive patients in which acyclovir prophylaxis was given (69).

Oral cytomegalovirus (CMV)-associated infection of the lip, labial mucosa, tongue, and pharynx has rarely been described in immunocompromised patients (70,71) and can be an infrequent infectious cause of MI. Some reports have described CMV infection of the tongue following BMT (72). CMV esophagitis and gastritis, while more common in acquired immune deficiency syndrome, are less frequently seen after BMT. Few case reports have described CMV esophagitis or gastritis either accompanying the more commonly seen CMV pneumonitis or coinciding with HSV in patients receiving immunosuppressive therapy for treatment of graft-versus-host disease (73–75). CMV infection is an infrequent cause of colitis in BMT patients (76).

**Conclusions and Recommendations for Future Research**

We conclude that the intact mucosa is an important host defense against systemic infection in neutropenic patients. MI is an important and identifiable risk factor for various bacterial and fungal infections, including viridans streptococcal, enterococcal, anaerobic bacteria, and certain gram-negative bacteria, in patients receiving cytotoxic chemoradiotherapy for the treatment of various malignancies. Moreover, the risk of invasive fungal disease is linked to cytotoxicity-related oral and gut epithelial damage in the setting of fungal colonization of the oral cavity and the gut.

The distinction between an infectious etiology of MI as opposed to regimen-related tissue damage is crucial to the optimal delivery of the antineoplastic regimen. Direct cytotoxicity during the course of repeated cycles of chemotherapy may necessitate dose reduction in subsequent courses of treatment. Such dose reductions may compromise the ultimate therapeutic control of the underlying neoplasm, since dose intensity has been shown in a number of studies (77–80) of certain neoplasms to affect not only remission rates but also survival. If an infectious etiology for MI were the case, then treatment of the infection during that given course would be appropriate, and subsequent secondary prophylaxis during subsequent courses of treatment to suppress further reactivation and MI would be appropriate to facilitate the delivery of the entire treatment dose. Moreover, amelioration of MI would make the antineoplastic regimen more
palatable to the patient and facilitate better compliance. At present, no specific therapies are proven to be effective to either treat or prevent MI secondary to cytotoxic chemoradiotherapy. Thus, new modalities to treat and prevent severe MI and the ability to understand the early steps in pathogenesis of infections at the mucosal barrier would improve the outcome of these groups of patients, reducing the treatment-related morbidity and mortality.

REFERENCES


**Note**

*Editor’s note:* J. R. Wingard is a consultant for Intrabiotics and Amgen and is an investigator in a clinical trial by Intrabiotics to test a product that may be used in the prevention of mucositis.