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## Prevention and management of oral infections in cancer patients

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**Abstract** The successful prevention and management of oral infections and infections from the oral cavity in cancer patients are based on identification of risk patients, selection of patients for prophylactic measures, diagnosis of infection and implementation of directed or empiric antimicrobial therapy. Identification of patients at risk for infection is based on each patient's type of oral microbial colonization and the presence of latent viral infections. Systemic and local resistance to infection will be decisive, and in many patients the risk can be estimated from the expected myelosuppressive effect of anti-cancer treatment. Diagnosis of infection is often based on clinical findings together with the results of microbiological investigations. Biopsies could be useful, but can seldom be obtained. Blood samples are mandatory for isolation of microorganisms involved in systemic infections in myelosuppressed patients. Prevention of infection requires both local and systemic measures. Elimination of the risk

of a breach in the first line of defence is urgent, and the maintenance of mucosal integrity is important. Monitoring microbial colonization is common, as is the institution of antiviral prophylaxis in patients with increased anti-HSV IgG (ELISA >10 000). Antifungal prophylaxis, to avoid colonization and superinfection, should be instituted in patients with low neutrophil counts. Gastrointestinal prophylaxis with quinolones is also commonly used in these patient groups. Treatment of oral infections in cancer patients should include systemic antimicrobial agents in most cases. Special attention should be directed to oral infections in neutropenic ( $<0.5 \times 10^9/l$ ) patients in whom oral microorganisms are the leading cause of bacteraemia. Invasive fungal infections of the oral cavity can be associated with systemic fungal infection and are indications for the use of liposomal amphotericin B.

**Key words** Infection · Viridans streptococci · Oral care · Cancer

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### Introduction

The oropharyngeal region comprises many ecologically different environments for the bacteria, and the oropharyngeal microflora is complex, consisting of more than 300 different bacterial species, 70% of which are

anaerobes, streptococci and Gram-negative anaerobic rods. Staphylococci and, especially, anaerobic Gram-negative rods, such as *Escherichia coli* and *Pseudomonas* species are less frequent. *Candida albicans* is isolated in 10–80% of normal healthy individuals, but usually in low numbers. Disease or antibiotic-induced ecological changes can lead to colonization with nonendogenous

microorganisms [13]. In healthy persons these colonizing microorganisms seldom cause problems, but in seriously diseased patients, such as those suffering from cancer, they may cause superinfection, local infections, such as stomatitis, or systemic infections, such as septicaemia. The patient's defence mechanisms may be impaired by cancer treatment or by the disease itself, leaving the patient susceptible to infection. In certain patients the deficiencies of the defence mechanisms are of a localized type, as seen in patients undergoing radiotherapy to the oral cavity and pharyngeal area. These patients generally suffer from problems related to an impaired function of the first line of defence. Thus, not only the break in the mucosal lining, but also the decreased amounts of saliva and secretory IgA make these patients more liable to bacterial and fungal localized infections. They generally have a normal function of the secondary line of defence, and the infection can consequently be limited to the oral cavity in most cases. On the other hand, in patients who have a significantly weakened second line of defence because of myelosuppression, localized infections may spread; translocation of microorganisms from the oral cavity into the circulation may ensue, with consequent septicaemia [3].

A cancer patient's risk of falling prey to a local or a systemic infection can often be estimated from knowledge of the patient's microbial status, the risk of damage to the first line of defence and the grade of expected myelosuppression.

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### **Colonization of the gastrointestinal tract**

The normal human gastrointestinal microflora is a remarkably stable ecosystem. With physiological, pathological or ecological disturbances of the oral cavity and the gastrointestinal tract, changes in the microflora can be found. The most common cause of disturbances is the administration of antibiotics. The microorganisms in the oral cavity, for example, can be influenced by antibiotics because of the direct effect during intake of peroral formulas, and because of secretion of antibiotics from the mucosal lining and gingival crevices or of secretion of an antibiotic in the saliva. The influence of antibiotics on the normal microflora cannot be estimated from pharmacokinetic data and knowledge of antimicrobial susceptibility alone, but must be studied under clinical circumstances. A number of studies on the effects of various antimicrobial agents have shown that the risk of a new colonization of the oral cavity is related to the effect of the antibiotic on the anaerobic microflora. Thus, agents that induce marked suppression of anaerobic microorganisms promote colonization of the oral cavity by Gram-negative enteric microorganisms as well as by fungal species, mainly *Candida* spp. [12]. Agents that induce colonization are second-

and third-generation cephalosporins, ampicillin in combination with beta lactamase inhibitors, clindamycin and erythromycin. Agents that have a less pronounced tendency to induce colonization are phenoxymethylpenicillin and metronidazole.

It is important to avoid oral colonization with enteric rods in cancer patients. Thus, antimicrobial agents should be chosen in such a way that the oral anaerobic flora is affected as little as possible, and agents that are known to induce colonization should be avoided.

Antiseptic solutions for suppression of the oral microflora have been extensively investigated. Most interest has been directed to studies on the effect of chlorhexidine. It is still controversial whether routine chlorhexidine rinses have a place in the care of cancer patients. It is an excellent agent for control of dental plaque accumulation, but a number of studies have failed to show any positive effect on mucositis or infection [18]. Chlorhexidine has a relatively weak antifungal effect, but promotes colonization with Gram-negative enteric rods.

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### **Herpes simplex virus infection**

Infections with herpesvirus are common causes of morbidity and also mortality in cancer patients with myelosuppression. Herpes simplex virus type 1 (HSV) infections are rarely life threatening, but may cause severe oral ulcerations and significant breakdown in the first line of defence. In BMT patients with serological evidence of an earlier HSV infection, up to 80% are likely to have an HSV-reactivated infection if prophylaxis is not instituted [10]. If viral prophylaxis is instituted with acyclovir (for example), reactivation can be avoided in most cases. The risk of reactivation is highest in patients with an HSV IgG titre of >10,000 (ELISA) [6]. Prophylaxis can in many cases be limited to this high-risk group. Prevention of reactivation of HSV will also decrease the risk of a break in the first line of defence and may thus, also decrease the risk of bacterial translocation from the oral cavity and the subsequent risk of viridans streptococcal septicaemia [14].

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### **Disruption of the first line of defence**

Cancer patients are subject to various situations that can disrupt the continuity of the oral mucous membranes. Radiotherapy of the oral cavity severely damages the oral mucosa, as do many cytotoxic anticancer drugs with direct stomatotoxicity, such as methotrexate, 5-fluorouracil, bleomycin and cytosine arabinoside. Indirect effects of anticancer drugs are observed mainly in patients with myelosuppression and low numbers of platelets.

Submucosal bleedings when platelet counts are less than  $20 \times 10^9/l$  are likely to cause mucosal disruption. Chronic periodontal disease and partially erupted teeth are potential sources of oral infection. Sharp teeth and removable prostheses further increase the risk of decubital ulcers and subsequent infection. In the group of patients that are severely myelosuppressed reactivation of HSV is a common finding and one of the most frequent reasons for disruption of the oral mucosa. In patients treated with allogeneic BMT, graft-versus-host disease of the oral mucosa is an important cause of mucosal damage. In BMT patients the frequency of oral ulcerations is also related to the marrow cell dose infused [8].

### Oral infections in myelosuppressed patients

In patients myelosuppressed by disease or anticancer treatment, infections of the oral cavity or systemic infections emerging from the oral cavity, are increasing problems. The risk of infection is depending on the number of neutrophilic leucocytes (PMN cells) in blood. If PMN cells are less than  $0.5 \times 10^9/l$  the risk of infection is clearly increased and when the number is less than  $0.1 \times 10^9/l$  the risk rises dramatically. In selected patient groups with pronounced myelosuppression, such as BMT patients, viridans streptococci from the oral cavity are the leading cause of bacteraemia [17]. In 500 allogeneic BMT patients at Huddinge University Hospital, 164 patients had at least one positive blood culture. In the vast majority of them Gram-positive organisms were recovered (89%), while Gram-negative organisms were only present in 4%. Gram-negative bacteraemia was more dangerous: 3 of 7 patients affected died as a direct consequence of this, while 8 of 164 died of bacteraemia caused by Gram-positive microorganisms. The most common bacterial species were viridans streptococci and coagulase-negative staphylococci (CNS). The viridans streptococci have their normal habitat in the oral cavity, while CNS reside on the skin. Viridans streptococci enter the circulation through disruption of the oral mucosal membrane, while CNS usually enters along indwelling catheters penetrating the skin. In both these cases a break in the first line of defence is obviously a prerequisite for infection. A prolonged aplastic period increases the risk of infection. The use of granulocyte colony-stimulating factors (G-CSF) shortens the aplastic period and may decrease the risk of septicaemia [17].

### Oral infections secondary to radiotherapy of the head and neck

Radiotherapy of the head and neck induces physiological changes in the oral cavity in relation to the radiation

dose given. Thus, low doses of 10–30 Gy are usually tolerated, while higher doses rapidly increase the oral problems. Low salivary flow and radiation-induced mucositis develop and exert a dramatic influence on the microbial ecosystem. The most significant change is a pronounced increase in the number of colonizing *Candida* organisms [7]. There is also often an increased number of Gram-negative enteric rods. The relationship between increased *Candida* colonization and superficial infection of the oral mucous membranes is obvious. The importance of Gram-negative colonization is less understood.

A number of different therapeutic and prophylactic modalities that aim at reducing the microbial burden on the mucosal membranes have been studied. Oral rinses with antiseptic solution, systemic administration of immunoglobulin and local administration of G-CSF have all been tried, with promising results [4, 11]. Similar results have been observed when cytoprotection of the oral mucosa has been applied [2].

### Identification of patients at risk for oral infections

In many cases, patients at risk of local and systemic infections from the oral cavity can be identified even before anticancer therapy is instituted.

Risk of local infections is observed in patients with dental infections, sharp teeth and, especially, advanced periodontitis and partially impacted wisdom teeth. Dental infections predispose these patients to oral infection if radiotherapy of more than 40–50 Gy is administered to larger parts of the oral cavity. Involvement of both parotid glands further increases the risk of infectious complications, as does concomitant administration of anticancer agents with stomatotoxicity.

Low numbers of PMN cells and a high tendency to reactivation of latent HSV infection further add to the risk of local infection in myelosuppressed patients with high HSV titres.

Systemic infection from the oral cavity should be expected mainly in patients with pronounced myelosuppression as a consequence of treatment or disease. Since the first line of defence is the main barrier against infection in these patients, oral ulcerations will further increase the risk of systemic infection. A prolonged aplastic period and low platelet counts additionally compromise the patient. The use of G-CSF may shorten the aplastic period and decrease the risk of infection.

### Prevention of infection

Prevention of oral infection should be directed against colonization of the oral microflora with nonendoge-

nous microorganisms and the maintenance of a well functioning mucosal first line of defence. Consequently, antibiotics that promote new colonization because of suppression of the normal anaerobic flora should, if possible, be avoided. Antifungal prophylaxis is indicated in patients with pronounced myelosuppression. Non absorbable antifungal agents, such as nystatin, are commonly used. Some centres have reported a reduced incidence of fungal infection when fluconazole has been used for fungal prophylaxis during the aplastic period in BMT patients [16]. However, fluconazole prophylaxis may lead to selection of resistant *Candida krusei* or *Candida glabrata*. Oral prophylaxis with antiseptics or topical antibiotics has not been shown to have any advantage over saline rinses and washing. Contaminated food and beverages should be avoided. All oral and dental infections should be eliminated before cancer treatment is instituted. Risk of decubital ulcers should be minimized, and the patients should be instructed to avoid hot drinks and food in order to escape burns and further stress to the mucous membranes. Several local regimens to prevent mucositis have been suggested, but no particular programme is commonly accepted.

HSV reactivation should be prevented, especially in myelosuppressed patients, and antiviral prophylaxis can be used in HSV seropositive patients. Prophylaxis can, however, be limited to those with high titres of anti-HSV antibodies in many cases.

Gastrointestinal decontamination with quinolones is extensively used, but is associated with an increased risk of bacteraemia with oral viridans streptococci, which in some cases are also penicillin resistant [9].

### Management of oral infections

Conventional surgical treatment of acute localized oral infections should be instituted if possible. In many patients it is not possible to perform dental extractions or biopsies, for example, because of low numbers of platelets or PMN cells. Therapy is thus limited to antimicrobial treatment in many patients, which is based on clinical findings and microbiological analyses if present. Dental infections should be treated with intravenous penicillin or aminopenicillins. Combinations with metronidazole ensure an effect against penicillin-resistant anaerobes also. During recent years it has been ob-

served that viridans streptococci can become highly resistant to penicillins. In bacteraemic neutropenic patients the rate of highly resistant streptococci (MIC > 4 mg/l) increased from zero in 1987 to 17 episodes per 1000 admissions 5 years later [1]. Macrolides are generally unsuitable alternatives to penicillin. Vancomycin, ofloxacin and teicoplanin are generally active against penicillin-resistant viridans streptococci [5].

Fungal infection in the oral cavity is a common finding in cancer patients. The diagnosis is made from the clinical findings together with results of microbiological investigations. In the treatment of localized infections in immunocompetent patients fluconazole is generally the drug of choice for therapy. In the myelosuppressed patient, in contrast, invasive oral fungal infections may cause dissemination of microorganisms, with subsequent systemic infection. The diagnosis of invasive fungal infections is difficult, since blood cultures and antigen and serological tests are usually negative or have a low specificity. In transplant recipients treated with cyclosporin, which has a synergistic nephrotoxic effect with amphotericin B [15], even low doses of amphotericin B can induce acute toxic side effects. In these patients liposomal amphotericin B should be considered, since the toxicity is considerably lower [19].

### Conclusions

Prevention and management of oral infections in cancer patients are based on:

- Maintenance of a normal oral microflora to avoid colonization with nonendogenous potential pathogenic microorganisms
- Maintenance of the first line of defence and prevention of disruption of the mucosal barrier
- Identification of patients at risk and institution of proper antimicrobial prophylaxis when needed
- Continuous monitoring of oral status together with microbiological specimens from infected sites
- Institution of systemic antimicrobial therapy when infection is diagnosed (empiric therapy is often necessary in myelosuppressed patients pending results from the microbiological laboratory)
- Ability to cope with emergence of resistance among oral viridans streptococci, which is an increasing problem in myelosuppressed cancer patients

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