# Etiology and Outcome of Oral Mucosal Lesions in Children on Chemotherapy for Acute Lymphoblastic Leukemia

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## ABSTRACT

*Microbiological cultures were taken from oral cavity and blood in 100 mucositis episodes in 70 children with acute lymphoblastic leukemia (ALL). Oral mucositis was commonest in neutropenic children during induction chemotherapy. Fungal organisms (n=39) were commonest isolate from mucosa followed by bacteria (n=28). Isolation of organism from oral cavity had no association with those isolated from blood. Herpes serology was positive in 16% episodes compared to 2% of controls. Obtaining cultures from oral lesions is useful in appropriate management of lesions and thereby possibly preventing systemic spread.*

**Key words:** *Leukemia, Mucositis, Neutropenia, Sepsis.*

## INTRODUCTION

Chemotherapy affects cells with high mitotic index and children experience higher incidence of mucositis than adults(1). Considering the importance of oral mucositis in neutropenic patients and its potential role in sepsis, children on chemotherapy for acute lymphoblastic leukemia (ALL) presenting with oral complaints were studied to determine the etiology of oral mucositis and evaluate its potential role in causing systemic complications.

## METHODS

Children <15 years of age undergoing chemotherapy for ALL on MCP-841 protocol(2) who presented with mucositis, were enrolled between January 2003-August 2004. The chemotherapy schedule was induction, intensification phase followed by 18 months of maintenance phase. Data were collected with regard to chemotherapy; neutropenia [absolute neutrophils count (ANC) <500/mm$^3$] duration and severity [severe neutropenia was defined as ANC<100/mm$^3$]; and antibiotics/steroids usage in previous two weeks. Oral mucositis was graded according to WHO criteria(3).

In all subjects, scrapings from base of lesion and blood were taken during routine hospital hours and sent for fungal, aerobic and anerobic bacterial, herpes simplex virus (HSV) cultures and serology. Viral culture was sent in viral transport medium in icepacks. HSV serology was done by complement fixation test which, however, did not distinguish between HSV-1 and HSV-2. Urine was evaluated for presence of fungal elements.

Initial treatment of mucositis included topical analgesics, oral antifungals or acyclovir. Febrile neutropenic patients were treated with intravenous antibiotics. Amphotericin B was started if fever or mucositis persisted beyond 5 days of fluconazole or antibiotics.

## RESULTS

There were 70 eligible subjects with 100 episodes of mucositis. Median age of patients was 4.25 years (range: 6 months-15 years). There were 41, 39 and 20 episodes of mucositis during induction, intensification and maintenance phases of chemotherapy respectively. Ulcers were the commonest presentation (70%), followed by patches (18%) and vesicles (3%); 11% had both ulcer and patch. Grade

I mucositis was present in 37%, Grade II in 30%, Grade III in 23% and Grade IV in 10% episodes. Neutropenia was present in 64% episodes and was of prolonged duration (>1 week) in 33 of these episodes. No significant differences in risk factors were noted between mild and severe mucositis; presence of septic shock showed a trend towards significance in severe mucositis ($P = 0.07$) (***Table* I**).

Thirty-nine fungal organisms were isolated from the oral cavity in 38 episodes of fungal infections (***Table* II**). There were no significant predisposing factors for oral fungal colonization; however, there was a high association with steroid usage ($P = 0.07$) and presence of urine fungal hyphae ($P = 0.06$). Five of 6 patients with fungemia had prolonged severe neutropenia. Despite the use of amphotericin B, 3 patients died; two deaths were caused by *Candida tropicalis* and one by *Aspergillus niger*.

Swab cultures revealed 28 organisms from 23 mucositis episodes. Mixed infection was present in 5 episodes. There were four deaths in blood culture positive group; one patient had mixed infection due to both *Acinetobacter* and *Staphylococcus aureus*; the other three had bacterial sepsis due to *Escherichia coli, Klebsiella* and *Enterococci*. No culture proven case of septicemia demonstrated an oral source.

Elevation of HSV antibody titer (>1:8) was noted in 16 subjects; 7 of these patients (44%) developed recurrent oral ulcers compared to 31% (17/54) in HSV seronegative group ($P = 0.34$). Controls consisted of 50 children <15 years of age admitted for various illnesses in pediatric ward, of which one had significant HSV titer ($P = 0.001$). Although significant number of oral lesions were clinically compatible with Herpes infection and

**TABLE I** RISK FACTORS FOR MUCOSITIS AND COMPARISON BETWEEN MILD AND SEVERE MUCOSITIS

| Variable | Mild Mucositis (Grade I and II) ($n = 67$) | Severe Mucositis (Grade III and IV) ($n = 33$) |
|---|---|---|
| Sex (M: F) | 55 : 12 | 26 : 7 |
| Number with neutropenia | 41 (61.2%) | 23 (69.7%) |
| Prolonged neutropenia | 20 (29.8%) | 13 (39.4%) |
| Prior antibiotics | 20 (29.8%) | 17 (51.5%) |
| Steroid use | 42 (62.7%) | 26 (78.8%) |
| Fever | 53 (79.1%) | 27 (81.8%) |
| Oral organisms | | |
| Bacteria | 14 (20.8%) | 9 (27.3%) |
| Fungi | 26 (38.8%) | 12 (36.4%) |
| Viral | 0 (0%) | 1 (3%) |
| Sepsis | | |
| Bacterial | 9 (13.4%) | 5 (15.2%) |
| Fungal | 5 (7.4%) | 1 (3%) |
| Urine fungal hyphae | 15 (22.3%) | 7 (21.2%) |
| Comorbidities | | |
| Pneumonia | 15 (22.3%) | 12 (36.4%) |
| Shock | 7 (10.4%) | 8 (24.2%) |
| Diarrhea | 7 (10.4%) | 7 (21.2%) |
| Significant HSV titer | 12 (17.9%) | 4 (12.1%) |
| Mortality | 5 (7.4%) | 5 (15.1%) |

*P* value >0.05 for all variables.

responded to oral acyclovir therapy, only one had HSV-1 isolated in culture.

## DISCUSSION

Fungal organisms were the commonest isolates from oral mucosal lesions followed by bacterial infections in this study. In a study of 1000 hospitalized patients on chemotherapy, 51.5% of orofacial infections were fungal, 33.1% bacterial and 15.1% viral; 19.1% were polymicrobial infections(4).

Oral cavity has been shown to be a source of both bacterial and fungal septicemia in various studies(5). Two out of six cases of fungemia (*Candida tropicalis* and *Rhodotorula*) had the same organism isolated from oral mucosal lesion thereby suggesting that oral colonization with those fungi resulted in fungemia. Interestingly *Candida albicans,* a common colonizer of mucosal surfaces had not caused systemic candidemia in any patient here. This is consistent with previous studies which have shown that *Candida albicans* is a non-invasive colonizer(6,7), and that colonization with *Candida tropicalis,* a more aggressive fungus, should generate a high index of suspicion of systemic dissemination in neutropenic patients(8). In our study, one-fifth of patients with *Candida tropicalis*

**TABLE II** ISOLATION OF FUNGI AND BACTERIA FROM ORAL CAVITY AND BLOOD CULTURES

| Organism | Oral lesion culture | Blood culture |
|---|---|---|
| **Fungal** | (*n* = 39) | (*n* = 6) |
| *Candida albicans* | 24 (61.5%) | 0 (0%) |
| *Candida tropicalis* | 5 (12.8%) | 2 (33.3%) |
| *Candida parasilosis* | 2 (5.1%) | 1 (16.6%) |
| *Candida glabarata* | 1 (2.6%) | 0 (0%) |
| *Candida krusei* | 1 (2.6%) | 0 (0%) |
| *Trichosporon* | 1 (2.6%) | 0 (0%) |
| *Aspergillus* | 4 (10.2%) | 2 (33.3%) |
| *Rhodotorula* | 1 (2.6%) | 1 (16.6%) |
| **Bacterial** | (*n* = 28) | (*n* = 14) |
| Enterococcus | 1 (3.6%) | 4 (28.5%) |
| *Staph.epidermidis* | 1 (3.6%) | 0 (0%) |
| *Streptococcus viridans* | 4 (14.2%) | 0 (0%) |
| Group b Streptococcus | 1 (3.6%) | 0 (0%) |
| *Staphylococcus aureus* | 4 (14.2%) | 1 (7.1%) |
| Coagulase Neg. Staph. | 3 (10.7%) | 2 (14.2%) |
| *Escherichia coli* | 3 (10.7%) | 2 (14.2%) |
| *Klebsiella* | 3 (10.7%) | 2 (14.2%) |
| *Pseudomonas aeruginosa* | 3 (10.7%) | 2 (14.2%) |
| *Acinetobacter* | 0 (0%) | 1 (7.1%) |
| Anerobes | | |
| *Veillonella* | 3 (10.7%) | 0 (0%) |
| *Peptostreptococcus* | 1 (3.6%) | 0 (0%) |
| *Lactococcus* | 1 (3.6%) | 0 (0%) |

**WHAT THIS STUDY ADDS?**

- Oral mucositis is common in neutropenic children during induction phase of chemotherapy for ALL with fungal organisms being the commonest isolates.

isolated from oral lesion developed fungemia; further, two patients who had fungemia due to *Candida tropicalis* died suggesting its invasive nature. Sanford, *et al.*(9) reported that 8.3% neutropenic patients with acute leukemia on chemotherapy and Aspergillus stomatitis developed invasive Aspergillosis. We had isolated *Aspergillus* from oral cavity in 4 patients; none had fungemia and all responded to antifungals. The role of oral cavity in causing systemic bacterial sepsis was not directly demonstrated in this study. Severe oral mucositis was found to be significantly more common in neutropenic cancer patients with *Staphylococcus aureus* bacteremia than gram-negative bacteremia(10).

There was a significantly higher prevalence of HSV serology in children on chemotherapy. The occurrence of recurrent oral ulcers in patients with a positive titer was however not statistically significant ($P = 0.34$). Previous studies have shown that HSV in patients on chemotherapy are reactivated ulcers rather than primary infection(11). Thus herpes serology is useful in predicting recurrent oral lesions with HSV in patients on chemotherapy. HSV-1 was isolated in culture in only 1% episodes which was lower as compared to 15-60% isolation in previous studies(4,12-16); this could be due to inadequate epithelial cells in the collected specimen. Further, Tzanck smears could have potentially identified more HSV cases.

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