

# Mucocutaneous Findings in Febrile Neutropenic Children with Acute Leukemias

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*Febrile neutropenia is common in children with leukemia. Mucous membrane and skin are most common portals of entry for microorganisms in these patients. The aim of the present study was to find the prevalence of mucocutaneous findings in febrile neutropenic leukemic children. The authors prospectively examined children with fever with neutropenia in acute leukemia, aged 1-15 years, who were admitted to the Department of Pediatrics, King Chulalongkorn Memorial Hospital, between September 2000 and August 2001.*

*During the study period, 46 children had 116 admissions, 51 of which were due to febrile neutropenia. Their cancer diagnoses were ALL (76%) and ANLL (24%). The prevalence of mucocutaneous findings was 86% (61% were from infections, 22% from mucositis and 4% from chemical phlebitis). Other detected sites of infection were lower respiratory tract (36%), urinary tract (32%), upper respiratory tract (11%), septicemia (11%) and unidentified (35%). Thirty-four percent of the patients had more than one site of infection. Gram-negative septicemia was the most common infection (15 cases/71%) followed by gram positive (4 cases/19%) and candida (2 cases/10%). The prevalence of infection was found in severe neutropenia (absolute neutrophil count, ANC less than 500 cell/cu mm), moderate neutropenia (ANC, 500-1000 cell/cu mm) and mild neutropenia (ANC, 1001-1500 cell/cu mm) was 72%, 9% and 5%, respectively. Infection in patients in the severe neutropenia group was significantly more common than in moderate mild neutropenia groups ( $p < 0.01$ ). Seven patients (15%) died, all of them had severe and prolonged neutropenia, for more than 7 days. Daily physical examination of skin and mucous membrane are suggested for proper and prompt diagnosis and treatment of febrile neutropenic children with acute leukemia to reduce mortality and morbidity in these patients. A Guideline for the use of antimicrobial agents in neutropenic patients with acute leukemia is proposed.*

*In conclusion, infection was commonly found in severe neutropenia. Mucocutaneous infection was the most common site of infection in febrile neutropenia in children with leukemia.*

**Keywords:** Mucocutaneous findings, Febrile neutropenia, Acute lymphoblastic leukemic, Mucositis

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Leukemia is the most common childhood cancer, about one-third of pediatric malignancies<sup>(1)</sup>. Febrile neutropenia which commonly occurs in leukemia may be due to chemotherapy, radiation or the disease itself.

Neutropenia is the major risk factor of serious infections in cancer patients who are receiving chemo-

therapy<sup>(1)</sup>. Fever in neutropenic patients requires immediate diagnostic and therapeutic interventions. Although uncommon, neutropenia patients can have a serious infection in the absence of fever<sup>(2,3)</sup>. Identification of the source of infection and proper antibiotic therapy are essential steps to decrease mortality and morbidity. Patients with defined sites of infection also appear to benefit from continued broad-spectrum therapy or prolonged neutropenia. Mucosa and skin are common sites of infection in febrile neutropenic patients<sup>(3)</sup>. Mucocutaneous findings in febrile neutropenic children with leukemia may occur

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from adverse effects of chemotherapeutic drugs, infection resulting from immunosuppression, paraneoplastic syndromes, graft-versus-host disease (GVHD), nutritional deficiency and radiation reactions<sup>(4)</sup>. Mucosal damage allows invasion of opportunistic organisms<sup>(5)</sup>.

The purpose of the present study was to determine the mucocutaneous findings in febrile neutropenia in acute lymphoblastic leukemic patients that can be a source of infection. The authors excluded side effects of chemotherapeutic agents that are not portals of entry of microbial agents such as alopecia or hyperpigmentation.

### Material and Method

All consecutive leukemic patients who had fever and neutropenia, admitted to the Department of Pediatrics, King Chulalongkorn Memorial Hospital between September 2000 and August 2001, were prospectively recruited. Neutropenia was defined as absolute neutrophil count (ANC) of less than 1500 cell/cu mm and categorized into three gradations: mild (ANC 1001-1500 cell/cu mm), moderate (ANC 500-1000) cell/cu mm and severe (ANC less than 500 cell/cu mm). Fever was defined as a single oral temperature  $\geq 38.3^{\circ}\text{C}$  or a temperature of  $\geq 38.0^{\circ}\text{C}$  more than 1 hour<sup>(5)</sup>.

Complete physical examination was done including oral and perianal area to find the source of infection. Complete blood count, urine analysis and hemoculture were done in every patient. KOH and swab culture were done at all mouth lesions. Tzanck smear and culture for HSV were done in suspected cases of HSV infection. Aspiration and swab culture were performed for gram staining and cultures in suspected cases of skin infection. Other investigations and/or cultures were done according to clinical suspicion of infection.

### Results

There were 46 patients with 51 episodes of fever and neutropenia from a total of 116 admissions. Thirty-five patients (76%) had acute lymphoblastic leukemia and 11 patients (24%) had acute non lymphoblastic leukemia. The mean patients age was 9.2 years (ranged, 1-15 years) and the male: female ratio was 1.04:1.

The prevalence of mucocutaneous findings in febrile neutropenic children with acute leukemia was 86%, (61% of which were from infection, 22% from mucositis, and 4% from chemical phlebitis). Four patients had more than one mucocutaneous manifestation. The prevalence of infection was found in severe neutropenia (absolute neutrophil count, ANC less than 500 cell/cu mm), moderate neutropenia (ANC, 500-1000 cell/cu mm) and mild neutropenia (ANC, 1001-1500 cell/cu mm) was 72%, 9% and 5%, respectively. Infection in the patients in the severe neutropenia group was significantly more common than in the moderate and mild neutropenia groups ( $p < 0.01$ ). Table 1 shows the sites of infection in 46 febrile neutropenic children with acute leukemias. Sixteen patients (34%) had more than one site of infection. The most common site was mucocutaneous infection (61%), followed by urinary tract (37%), lower respiratory tract (33%), upper respiratory tract (11%), septicemia (11%) and unidentified (35%). Hemocultures were positive in 21 patients (46%) Gram-negative septicemia was the most common infection (15 cases/71%), followed by gram positive (4 cases/19%) and candida (2 cases/10%). The details of isolated organisms are shown in Table 2.

Table 3 shows the mucocutaneous findings in febrile neutropenia and the microbial isolations from cultures of the patients. Seven patients died during the study period; 4 had pneumonia that progressed to respiratory failure and 3 had perianal cellulitis.

**Table 1.** Site of infections found in 46 febrile neutropenic acute leukemic children

Site of infection	Severe neutropenia	Moderate neutropenia	Mild neutropenia	Total (%) n = 46
Mucocutaneous infection	20	5	4	28 (61%)
Lower respiratory tract	12	4	1	17 (37%)
Urinary tract	13	2	0	15 (33%)
Upper respiratory tract	4	0	1	5 (11%)
Septicemia	4	0	1	5 (11%)
Unidentified	11	3	2	16 (35%)

Severe (ANC < 500/mm<sup>3</sup>), moderate(ANC = 500-1000/mm<sup>3</sup>), mild(ANC >1001 -1500/mm<sup>3</sup>)  
Sixteen patients (34%) had more than one sites of infection

**Table 2.** Organisms causing bacteremia/fungemia from hemoculture in febrile neutropenic acute leukemia patients

Microorganisms	Episodes (%)
Gram negative bacilli	15 (71%)
<i>Klebsiella pneumoniae</i>	9
<i>Enterobacter spp.</i>	2
<i>Escherichia coli</i>	1
<i>Pseudomonas aeruginosa</i>	3
Gram positive cocci	4 (19%)
<i>Staphylococcus aureus</i>	2
Coagulase negative <i>staphylococci</i>	2
Candida (not albicans)	2 (10%)
Total	21

litiis and abscess prior to sepsis and death. All seven had fever and prolonged neutropenia more than 7 days (range 7-28 days).

### Discussion

Neutropenia is a common side effect in leukemic patients undergoing chemotherapy. Fever is the most common sign of infection. Delay in starting appropriate antibiotics in febrile neutropenic patients often leads to higher morbidity and mortality. There are many guidelines<sup>(5-8,9)</sup> for the use of antimicrobial agents in neutropenic patients but the guidelines are generalized and have to be applied to variations in

individual patients and types of infections, settings in which patients are treated and antimicrobial susceptibility patterns<sup>(5)</sup>.

The differential diagnosis of mouth lesions in febrile neutropenic patients includes trauma, side effect of chemotherapeutic agents and infection. Normal defense mechanism of oral cavity includes intact mucous membranes, mucosal renewal, epithelial desquamation, saliva production and the presence of specific host factors such as secreting immunoglobulin and oral flora<sup>(9)</sup>. Chemotherapeutic agents inhibit the growth of rapidly dividing cells including oral epithelial which have a high mitotic index with a renewal occurring every 7 to 14 days<sup>(4)</sup>.

Mucositis can be a portal of entry for bacteria and fungi. Opportunistic pathogens causing bacteremia in neutropenic patients often originate in the oral cavity<sup>(10)</sup>. Several antimicrobial agents have been investigated for their efficacy in preventing and treating oral mucositis but so far they have yielded no consistent benefit<sup>(8)</sup>. Systemic fungal infections are a major cause of morbidity and mortality among patients with hematological malignancies and neutropenia. Up to one-third of febrile neutropenic patients who do not responded to a 1-week course of antibiotic therapy have systemic fungal infection<sup>(11)</sup>. The predisposing factors of fungal infection are neutropenia, broad spectrum antibiotic exposure, use of corticosteroid,

**Table 3.** Mucocutaneous findings in 51 episodes of febrile neutropenia

Mucocutaneous findings	No of case (%)	Microbial isolation (number)
Infection	31 (59.6%)	
Mucous membrane		
Oral	17 (32.7%)	
Candidiasis	7	<i>Candida albican</i> (3), <i>Candida spp.</i> (5), no growth (2)
Bacteria	8	<i>Acinetobacter baumannii</i> (3), <i>Acinetobacter spp.</i> (1), <i>Enterobacter spp.</i> (1), <i>Pseudomonas spp.</i> (1), <i>Streptococcus viridians</i> (1)
Herpes simplex virus	3	<i>Herpes simplex virus</i> (3)
Perianal	4 (7.7%)	
Candidiasis	1	<i>Candida spp</i> (1)
Cellulites	2	<i>Enterobacter spp.</i> (1), <i>Klebsiella pneumoniae</i> (1)
Abscess	1	<i>Enterobacter spp.</i> (1)
Skin	10 (19.2%)	
Cellulitis	5	<i>Klebsiella spp.</i> (2), <i>Pseudomonas aeruginosa</i> (1), <i>Staphylococcal aureus</i> (1), no growth (1)
Abscess	4	<i>Klebsiella spp.</i> (2), <i>Pseudomonas aeruginosa</i> (1), <i>Staphylococcal aureus</i> (1)
Infected port	1	<i>Spingobacterium multivorum</i> (1)
Non infection	13 (25%)	
Oral mucositis	11	
Phlebitis	2	
Total	44 (84.6%)	

Four patients had more than one mucocutaneous findings

mucositis and intravascular device<sup>(12,13)</sup>. In the present study, candida was found in 41% in the case of oral mucosal infection and 14% from hemoculture. The use of fluconazole at the initiation of chemotherapy<sup>(14)</sup> or oral itraconazole solution in neutropenic patients with hematologic malignancy<sup>(15)</sup> helps to prevent invasive fungal infection in neutropenic patients from hematological malignancy.

Herpes simplex virus (HSV) in immunocompromised patients is usually more severe and more extensive. Oropharyngeal HSV in immunocompromised patients can present with widespread involvement of the mucosa similar to the mucositis caused by cytotoxic agents (Fig. 1, 2). The lesions can spread locally to cause esophagitis, tracheobronchitis and pneumonitis<sup>(16)</sup>. Intravenous acyclovir is effective in the treatment and prevention of dissemination of mucocutaneous HSV infection<sup>(17)</sup>. Acyclovir prophylaxis in immunocompromised patients, especially



**Fig. 1** Group of vesicles at lower lip from reactivation of herpes simplex virus during febrile neutropenia



**Fig. 2** Diffuse mucositis during febrile neutropenia in a T-cell leukemia after having vincristine, metrotrexate, doxyrubicin and 6 MP

in those having chemotherapy reduces the rate of symptomatic HSV infection.

Extravasation of chemotherapeutic agent can cause inflammatory reaction, aching, phlebitis in the irritant group and cause severe tissue injury including necrosis of the affected area depending on the property of the cytotoxic agent which can be classified as either irritants or vesicants<sup>(4)</sup>. If the extravasation is significant, necrosis, eschar formation, ulceration may appear over several weeks<sup>(18)</sup> and then become portals of entry to microbial agents.

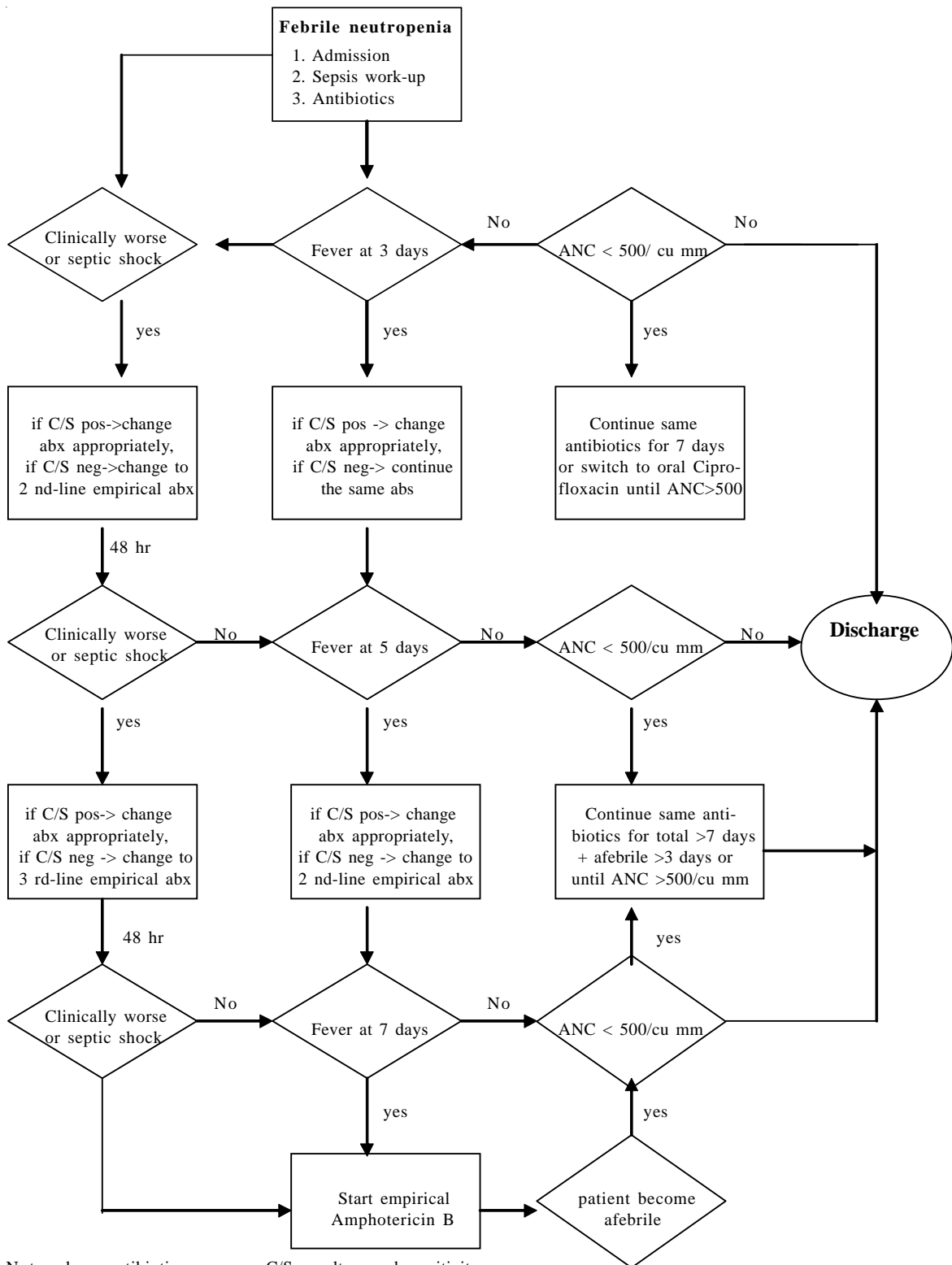
Perianal area is another important portal of entry for organisms that should be carefully looked for whenever the patient had febrile neutropenia. Three patients in the present study had diarrhea prior to perianal cellulites and febrile and severe protracted neutropenia (range, 19-24 days) before they developed septic shock and died. The result of the present study confirmed previous studies in Thailand<sup>(19-21)</sup> that gram-negative infections are more common than gram-positive bacteria in febrile neutropenic patients. The prevalence of gram-positive organism in European countries have increased since the use of intravascular devices<sup>(22-24)</sup>. Daily physical examination of skin and oral mucosa are suggested for proper and prompt diagnosis and treatment of febrile neutropenic children with acute leukemia to reduce and decrease mortality and morbidity of the patients. From the result of the present study, the authors suggest a guideline for the use of antimicrobial agents in neutropenic patients with acute leukemia as in Chart 1.

In conclusion, infection was commonly found in severe neutropenia. Mucocutaneous infection was the most common site of infections in febrile neutropenia in children with acute leukemia.

## References

1. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. *NEJM* 1993; 328: 1323-32.
2. Chanock SJ, Pizzo PA. Fever in the neutropenic host. *Infectious Dis Clin North Am* 1996; 10: 777-97.
3. Lucas KG, Brown AE, Armstrong D, Chapman D, Heller G. The identification of febrile, neutropenic children with neoplastic disease at low risk for bacteremia and complications of sepsis. *Cancer* 1996; 77: 791-8.
4. Susser WS, Whitaker-Worth, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. *J Am Acad Dermatol* 1999; 40: 367-98.
5. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with

**Chart 1.** Guideline for the use of antimicrobial in febrile neutropenic children with acute leukemia



Note abx = antibiotics  
pos = culture positive  
C/S = culture and sensitivity  
neg = culture negative

- cancer. *Clin Infect Dis* 2002; 34: 730-51.
6. Link H, Bohme A, Cornely OA, Hoffken K, Kellner O, Kern WV, et al. Antimicrobial therapy of unexplained fever in neutropenic patients. Guideline of the Infection diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), Study Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft supportiv-massnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society). *Ann Hematol* 2003; 82: S105-17.
  7. Buchheidt D, Bohme A, Cornely OA, Fatkenheuer G, Fuhr H, Heussel G, et al. Diagnosis and treatment of documented infections in neutropenic patients. Recommendations of the Infections Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol* 2003; 82: S127-32.
  8. Donowitz GR, Maki DG, Crnich CJ, Pappas PG, Rolston KV. Infections in the neutropenic patient. New views of an old problem. *Hematology* 2001; 113-39.
  9. Donnelly JP, Bellm LA, Epstein JB, Sonis ST, Symonds RP. Antimicrobial therapy to prevent or treat oral mucositis. *Lancet Infect Dis* 2003; 3: 405-12.
  10. Bergmann OJ. Oral infections and septicemia in immunocompromised patients with hematologic malignancies. *J Clin Microbiol* 1988; 26: 2105-9.
  11. Empiric antifungal therapy in febrile granulocytopenic patients. EORTC International Antimicrobial Therapy Cooperative Group. *Am J Med* 1989; 86: 668-72.
  12. Meunier F, Aoun M, Bitar N. Candidemia in immunocompromised patients. *Clin Infect Dis* 1992; 14: S49-53.
  13. Baddley JW, Stroud TP, Salzman D, Pappas PG. Invasive mold infections in allogeneic bone marrow transplant recipients. *Clin Infect Dis* 2001; 32: 1319-24.
  14. Winston DJ, Chandrasekar PH, Lazarus HM, Goodman JL, Silber JL, Horowitz H, et al. Fluconazole prophylaxis of fungal infection in patients with acute leukemia. Results of a randomized placebo-controlled, double, multicenter trial. *Ann Intern Med* 1993; 118: 495-503.
  15. Glasmacher A, Prentice A, Gorschloer M, Engelkert S, Hahn C, Djulbegovic B, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. *J Clin Oncol* 2003; 21: 4615-26.
  16. Marques AR, Straus SE. Herpes simplex. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, eds. *Fitzpatrick's Dermatology in general medicine*, 6<sup>th</sup> ed. New York: Mc Graw-Hill 2003: 2059-70.
  17. Whitley RJ, Roizman B. Herpes simplex virus infection. *Lancet* 2001; 357: 1513-8.
  18. Bauerjee A, Brotherston T, Lamberty B, Campbell R. Cancer chemotherapy agent-induced perivenous extravasation injuries. *Postgrad Med J* 1987; 63: 5-9.
  19. Punpanich W, Sawadichai K, Pratuangtham S, Hathirat P. Trends in bacterial infection in febrile neutropenic children: Ramathibodi Hospital. *Thai J Pediatr* 1999; 38: 9-16.
  20. Chuvate A. Infection in febrile neutropenic children in acute leukemia in Chulalongkorn University Hospital [Thesis for the diploma of Thai board of Pediatrics of the Medical Council]. Chulalongkorn University 1998.
  21. Anunnatsiri S, Chansung K, Chetchotisakol P, Sirijerachai C. Febrile Neutropenia: A retrospective study in Srinagarind Hospital. *Srinagarind Med J* 1997; 12: S26-7.
  22. Glauser M. Empiric therapy of bacterial infections in patients with severe neutropenia. *Diagn Microbiol Infect Dis* 1998; 31: 467-72.
  23. Oppenheim BA. The changing pattern of infection in neutropenic patients. *J Antimicrob Chemother* 1998; 41: 7-11.
  24. Gonzalez-Barca E, Fernandez-Sevilla A, Carratala J, Granena A, Gudiol F. Prospective study of 288 episodes of bacteremia in neutropenic cancer patients in a single institution. *Eur J Clin Microbiol Infect Dis* 1996; 15: 291-6.

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## อาการแสดงทางผิวหนังและเยื่อในผู้ป่วยมะเร็งเม็ดเลือดขาวเฉียบพลันที่มีเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำ

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ภาวะไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำ พบได้บ่อยในเด็กที่เป็นมะเร็งเม็ดเลือดขาว เยื่อและผิวหนังเป็นทางให้เชื้อโรคเข้าสู่ร่างกายที่สำคัญ การศึกษานี้เป็นการเก็บรวบรวมข้อมูลแบบไปข้างหน้าในผู้ป่วยเด็กที่เป็นมะเร็งเม็ดเลือดขาวมีไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำอายุตั้งแต่แรกเกิดจนถึง 15 ปี ที่เข้ารับการรักษาในหอผู้ป่วยเด็กโรงพยาบาลจุฬาลงกรณ์ ระหว่าง 1 กันยายน พ.ศ. 2543 ถึง 30 สิงหาคม พ.ศ. 2544 เป็นเวลา 1 ปี ผู้ป่วยที่ศึกษาทั้งหมด 46 ราย เข้ารับการรักษาในโรงพยาบาลทั้งหมด 116 ครั้ง มีไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำ 51 ครั้ง ผู้ป่วยเป็นมะเร็งชนิด ALL ร้อยละ 76 และ ANLL ร้อยละ 24 ผลการศึกษาพบว่ามีการแสดงของผิวหนังและเยื่อ ร้อยละ 86 (เป็นการติดเชื้อร้อยละ 61 เยื่อผิวอักเสบร้อยละ 22 และเส้นเลือดอักเสบจากการให้เคมีบำบัดร้อยละ 4) ส่วนการติดเชื้อที่อื่นที่พบคือ ที่ทางเดินหายใจส่วนล่างร้อยละ 36 การติดเชื้อทางเดินปัสสาวะร้อยละ 32 การติดเชื้อทางเดินหายใจส่วนบนร้อยละ 11 การติดเชื้อในกระแสเลือดร้อยละ 11 และไม่พบสาเหตุร้อยละ 35 โดยมีผู้ป่วยร้อยละ 34 ที่พบการติดเชื้อมากกว่า 1 แห่ง การติดเชื้อในกระแสเลือดพบว่าเชื้อกรัมลบเป็นสาเหตุที่พบบ่อยที่สุด (ร้อยละ 71) รองลงมาคือ เชื้อกรัมบวก (ร้อยละ 19) และเชื้อ candida (ร้อยละ 10) อุบัติการณ์ของการติดเชื้อในผู้ป่วยที่มีไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำมาก (< 500 เซลล์ต่อ ลบ.มม.) ต่ำปานกลาง (500-1,000 เซลล์ต่อ ลบ.มม.) และต่ำเล็กน้อย (1,001-1,500 เซลล์ต่อ ลบ.มม.) พบร้อยละ 72, 9 และ 5 ตามลำดับ อุบัติการณ์ของการติดเชื้อในผู้ป่วยที่มีไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำมากกว่ากลุ่มที่มีเม็ดเลือดขาวนิวโทรฟิลต่ำปานกลางและต่ำเล็กน้อยอย่างมีนัยสำคัญทางสถิติ ( $p < 0.01$ ) มีผู้เสียชีวิตทั้งหมด 7 ราย ซึ่งทุกรายมีเม็ดเลือดขาวนิวโทรฟิลต่ำนานกว่า 7 วัน ควรทำการตรวจผิวหนังและเยื่อต่าง ๆ ทุกวัน เพื่อหาสาเหตุและการรักษาในผู้ป่วยเหล่านี้เพื่อลดอัตราการพิการและการตาย ได้นำเสนอแนวทางการให้ยาต้านจุลชีพในผู้ป่วยที่มีไข้ร่วมกับเม็ดเลือดขาวนิวโทรฟิลต่ำในผู้ป่วยที่เป็นมะเร็งเม็ดเลือดขาวแบบเฉียบพลัน

โดยสรุป ภาวะติดเชื้อพบได้บ่อยในผู้ป่วยที่มีเม็ดเลือดขาวนิวโทรฟิลต่ำมาก การติดเชื้อที่ผิวหนังและเยื่อเป็นการติดเชื้อที่พบได้บ่อยที่สุดในผู้ป่วยมะเร็งเม็ดเลือดขาวที่มีไข้ร่วมกับเม็ดเลือดขาวต่ำ

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