

# The Nature and Control of Infections in Patients with Acute Leukemia

EMIL FREI, III,<sup>1</sup> ROBERT H. LEVIN,<sup>2</sup> GERALD P. BODEY,<sup>3</sup> EDWARD E. MORSE,<sup>4</sup>  
AND EMIL J. FREIREICH

*National Cancer Institute, Bethesda, Maryland*

## SUMMARY

The spectrum of infections in patients with leukemia continues to change. During the past 8 years there has been a significant increase in infections due to fungi and other organisms with a lower order of pathogenicity and a natural resistance to commonly employed antibiotics. *Pseudomonas* infections constitute the most important bacterial problem. Serious staphylococcal infections have been markedly reduced by the synthetic, penicillinase-resistant penicillins. The reasons for the shifting patterns of infection are considered.

Several approaches to the treatment of the above infections through improving or replacing host defense mechanisms are considered. Granulocyte transfusions are effective in the management of *Pseudomonas* septicemia and significantly reduce the mortality of that disease. The host-defense deficits responsible for the frequency of fungus infections are considered. It is proposed that this deficit relates primarily to failure of lymphocyte function.

Infections cause many of the major complications and the majority of deaths in patients with acute leukemia (13). Most of the agents used in the treatment of acute leukemia depress granulocyte production and other facets of host response, and therefore increase the risk of infection. Thus, improved therapy of infections not only should prolong survival directly but should also allow for more intensive and therefore more effective anti-leukemic treatment. In this report the frequency and changing spectrum of infections in patients with acute leukemia will be presented and discussed. Selected approaches to the treatment of these infections will be considered.

## FREQUENCY AND SPECTRUM OF INFECTIONS

Autopsy protocols of the first 50 patients dying of acute leukemia at the Clinical Center, NIH, were examined for frequency and type of infection. These patients expired between 1953 and 1956. A similar study was made of the last 50 patients dying of acute leukemia in whom the autopsy protocols were complete (1962-63). These data are included in Tables 1 and 2. The 2 groups of patients were comparable in terms of age and type of leukemia. Of the 50 patients dying from 1953 to 1956, 44 had a major bacterial infection at autopsy, 34 of which were septicemic.

<sup>1</sup> Present address: University of Texas M. D. Anderson Tumor Institute, Houston, Texas.

<sup>2</sup> Deceased.

<sup>3</sup> Present address: University of Washington, Seattle, Washington.

<sup>4</sup> Present address: Johns Hopkins Hospital, Baltimore, Maryland.

The spectrum of bacteria is different from that which prevailed in the preantibiotic era, when Gram-positive organisms such as the pneumococcus and streptococcus predominated. In 1953-56, hemolytic *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections, usually septicemic, were most frequent (Table 1).

Bacterial infections remained a frequent problem in 1962-63, but an important shift in the spectrum occurred. Hemolytic *Staphylococcus aureus* infections were markedly and significantly reduced ( $P < 0.01$ ). A similar event followed the widespread use of penicillin in the late 1940's, but antibiotic-resistant staphylococcal infections subsequently increased and were a frequent and major problem in the 1953-56 era. The development and use of penicillins not inactivated by penicillinase, principally methicillin and oxacillin, is largely responsible for the decrease in staphylococcal infections between 1956 and 1960. *Pseudomonas* infections remain important and cause 50% of the major bacterial infections at the present time. The antibiotics polymyxin and colistimethate have not significantly altered the frequency or severity of such infections in patients with acute leukemia. Experimental approaches to the treatment of *Pseudomonas* infections will be considered below.

A major shift in the frequency and type of fungus, virus, and other infections has occurred (Table 2). Fungus infections were considered to be present only when tissue invasion and reaction could be demonstrated. Oral moniliasis and superficial fungus invasion of the esophagus were not included. A significant increase in fungus infections has occurred, particularly fungus infections involving mul-

TABLE 1  
CHANGING SPECTRUM OF INFECTIONS OBSERVED AT AUTOPSY IN PATIENTS  
WITH ACUTE LEUKEMIA: BACTERIAL INFECTIONS

Time period	No. of patients	Total bacterial infection	Hemolytic <i>Staphylococcus aureus</i>	<i>Pseudomonas aeruginosa</i>	<i>Escherichia coli</i>	Proteus	Klebsiella	<i>Clostridium perfringens</i>	$\alpha$ -Hemolytic streptococcus	Severe pneumonia (unspecified)
1953-56	50	44 (34) <sup>a</sup>	15 (12)	9 (8)	6 (6)	2 (2)	1 (1)	3 (3)	2 (2)	6
1962-63	50	30 (20)	2 (1)	15 (11)	4 (3)	3 (3)	2 (2)	0	0	2

<sup>a</sup> Numbers in parentheses indicate number with septicemia.

TABLE 2  
CHANGING SPECTRUM OF INFECTIONS OBSERVED AT AUTOPSY IN PATIENTS WITH ACUTE  
LEUKEMIA: MYCOTIC, VIRUS, AND EXOTIC INFECTIONS

Time period	No. of patients	Total fungus infections	Candidiasis	Aspergillosis	Cryptococcosis	Mucormycosis	Tuberculosis	Other
1953-56	50	13 (2) <sup>a</sup>	10 (2)	3 (0)	0	0	2	Herpes zoster, generalized, 1 Cytomegalic inclusion disease, 5; Pneumocystes, 1; <i>Listerella monocytogenes</i> , 1; herpes simplex, disseminated, 1; <i>Bacteroides</i> , 1; Toxoplasma, 1.
1962-63	50	32 (17)	17 (13)	11 (3)	2 (1)	2 (0)	1	

<sup>a</sup> Numbers in parentheses indicate the number of infections in which more than 1 organ was involved.

tiple organs ( $P < 0.01$ ). *Candida* and *Aspergillus* have been the major problem. In addition, there has been a significant increase in virus and other infections ( $P = 0.05$ ).

A number of factors contribute to this increase in frequency and severity of fungus infections. Progress in the treatment of acute leukemia has resulted from and has attended the increased use of anti-leukemic agents, all of which suppress various facets of immune response, including normal lymphocyte and granulocyte production. This, plus the increased survival of children with acute leukemia, has resulted in increasing patient time spent at more depressed levels of immune response. Thus, an ideal circumstance is created for invasion with organisms of low-order pathogenicity such as fungi and cytomegalic inclusion virus. Use of broad-spectrum antibiotics results in the ascendancy of fungi in carrier sites such as the mouth, gastrointestinal tract, and skin. Finally, the injury and ulceration that the anti-metabolites frequently inflict on the oral and intestinal mucosa constitutes an excellent portal of entry for these microorganisms.

Amphotericin B constitutes a major advance in the antibiotic treatment of fungus infections. Both *Candida* and *Aspergillus* species are sensitive to amphotericin B *in vitro*, and there is some evidence for clinical efficacy. Until the present time, however, this agent has not made major inroads on the frequency and severity of opportunistic fungus infections in patients with neoplastic disease primarily because of the difficulty in diagnosing such infections in patients with advanced, complicated acute leukemia (1). Amphotericin B, because of its toxicity, should not be used in the absence of an established diagnosis of fungus infection.

It is concluded that antibacterial antibiotics along with

a number of other factors have altered and continue to change the spectrum and frequency of microbial infections in patients with acute leukemia. Further progress with antibiotic therapy, particularly with respect to the treatment of *Pseudomonas* and fungus infections, may be anticipated. Such progress, however important, is likely to be attended by a further shift of infecting agents to those with drug resistance and low-order pathogenicity. Thus, the antibiotic approach may in the future be attended by diminishing returns. Since a deficit in host defenses, as a result of the disease or its treatment, has been and increasingly will be responsible for infections by microbial agents, particularly those with low orders of pathogenicity, it is pertinent to consider approaches to treatment which involve improving or replacing "natural" defense mechanisms.

#### GRANULOCYTE TRANSFUSIONS

It is emphasized that qualitative differences exist in host-defense deficits depending on the type of neoplastic disease (7). Thus, in chronic lymphocytic leukemia, the frequency of infections relates primarily to deficient circulating  $\gamma$ -globulin and antibody production (10). In Hodgkin's disease, delayed skin sensitivity and homograft response are impaired (5, 9), which probably explains the susceptibility of patients with this disease to granulomatous infections (7). In acute leukemia, however, the most important factor predisposing to bacterial infections is severe granulocytopenia. The median circulating granulocyte count at the onset of 41 consecutive episodes of *Pseudomonas* septicemia at the Clinical Center was 100/cu mm (Table 4). Circulating antibody response to secondary antigenic stimulation and serum  $\gamma$ -globulin is normal in patients with acute leukemia (12).

Replacement therapy involving the transfusions of granulocytes obtained by leukopheresis of donors with chronic myelogenous leukemia has been employed at the Clinical Center during the past 3 years (8). Donors not in blastic crisis with peripheral white counts in excess of 100,000/cu mm have been employed. Leukopheresis of 2 units from such donors frequently produces a white cell yield of greater than  $10^{11}$ . Pilot studies indicated that such transfusions may be effective in raising the absolute granulocyte count in the recipient and in controlling serious infection (Chart 1). Granulocyte transfusions have been given to 60 recipients during the past 3 years, primarily to children with acute leukemia with granulocytopenia and severe bacterial infection. There is a linear relationship between the number of transfused cells and the posttransfusion increment in the recipient. The median increment after a transfusion of  $10^{11}$  cells is 1000/cu mm. Survival of such granulocytes in the circulation is curvilinear with a median of 24 hr (3). The effect of such transfusions in patients with *Pseudomonas* septicemia will be considered in some detail (Tables 3, 4).

Forty-one episodes of septicemia due to *Pseudomonas*

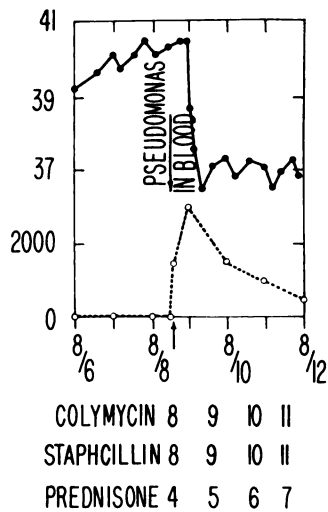


CHART 1.—This 8-year-old boy with advanced acute leukemia and severe granulocytopenia (*interrupted line*) developed *Pseudomonas* septicemia. The patient had not responded after 8 days of Colymycin and Staphicillin treatment. On the morning of August 8 (8/8),  $2 \times 10^{11}$  granulocytes were transfused (*vertical arrow*). An abrupt increase in circulating granulocytes occurred, associated with defervescence.

*aeruginosa* occurred in patients with leukemia at the Clinical Center between January 1962 and December 1963. Nineteen of these were treated with granulocyte transfusion. The patients were not randomly allocated to the 2 groups. The presence of an available donor rather than any clinical characteristics of the recipient determined whether a granulocyte transfusion was given. Various prognostic factors for the 2 groups were comparable (Table 3). The extremely low granulocyte count on the day of positive culture should be reemphasized.

The therapeutic effect of such transfusions on *Pseudomonas* septicemia is presented in Table 4. Before the use of granulocyte transfusions, *Pseudomonas* septicemia was almost uniformly fatal complication of leukemia. Thus, of 23 consecutive episodes of *Pseudomonas* septicemia reported in 1958, 22 were fatal and only 2 patients lived more than 7 days from the 1st positive blood culture (2). The situation is similar today for patients not receiving granulocyte transfusions in that the median survival from the 1st positive blood culture was only 2 days and 18 of the patients died within 7 days (Table 4). Defervescence occurred significantly more frequently and promptly in patients receiving granulocyte transfusions. The median survival was also significantly better in the patients receiving granulocyte transfusions. Previous and present experience indicates that if a patient survives more than 7 days he is cured of that episode of *Pseudomonas* septicemia. Eighteen of 22 patients not receiving granulocytes died within 7 days, 17 of whom had *Pseudomonas aeruginosa* in the heart blood culture. Only 9 of 19 patients receiving such transfusions died within 1 week, and in 4 of these *Pseudomonas* was eliminated from the blood. Ten of the transfused patients survived beyond 7 days, and *Pseudomonas* septicemia recurred in 2 of these patients.

It is concluded that granulocyte transfusions are effective in *Pseudomonas* septicemia as well as in other bacterial infections (3). The development of methods for the more effective acquisition and preservation of granulocytes must precede the widespread use of this form of therapy.

Transfusion of granulocytes obtained from patients with chronic myelogenous leukemia may have a sustained as well as an immediate beneficial effect on host defense, i.e., granulocyte number in the recipient. Twelve of our 60 recipients have had persistence of donor cell mitotic activity in the recipients marrow and/or peripheral blood for up to 80 days after the transfusion (6). The major and

TABLE 3  
TREATMENT OF PSEUDOMONAS SEPTICEMIA WITH GRANULOCYTE TRANSFUSIONS:  
COMPARABILITY OF GROUPS

GROUPS	NO. OF EPISODES OF PSEUDOMONAS SEPTICEMIA	AGE		DURATION FROM ONSET OF FEVER TO POSITIVE CULTURE (days)		ABSOLUTE GRANULOCYTE COUNT ON DAY OF POSITIVE CULTURE		START OF ANTIBIOTIC TREATMENT WITH RELATION TO POSITIVE CULTURE		
		Median	No. <15 years	Median	Range	Median	Range	Prior	Immediate	After
Granulocyte transfusion(s) given	19	19	9	8	0-30	100	<50-800	12	5	2
Granulocyte transfusion not given	22	11	13	5	0-30	100	<50-2500	16	4	2

TABLE 4  
EFFECT OF GRANULOCYTE TRANSFUSIONS IN PATIENTS WITH PSEUDOMONAS SEPTICEMIA

GROUPS	NO. OF EPISODES OF PSEUDOMONAS SEPTICEMIA	DEFERVESCENCE <sup>a</sup>			SURVIVAL FROM POSITIVE CULTURE (days)				
		No.	Days to defervescence		Median	Survival <7 days		Survival >7 days	
			From culture	From transfusion		No.	Pseudomonas present in heart blood	No.	Pseudomonas present in heart blood
Granulocyte transfusion(s) given	19	10	3	1	8	9	5	10	2
Granulocyte transfusion not given	22	4	8+		2	18	17	4	2
		$P = <0.05$			$P = 0.01$ (rank test)			$P = <0.05$	

<sup>a</sup> Fall in temperature to less than 37.6°C; persistence of afebrile state for 72 hr.

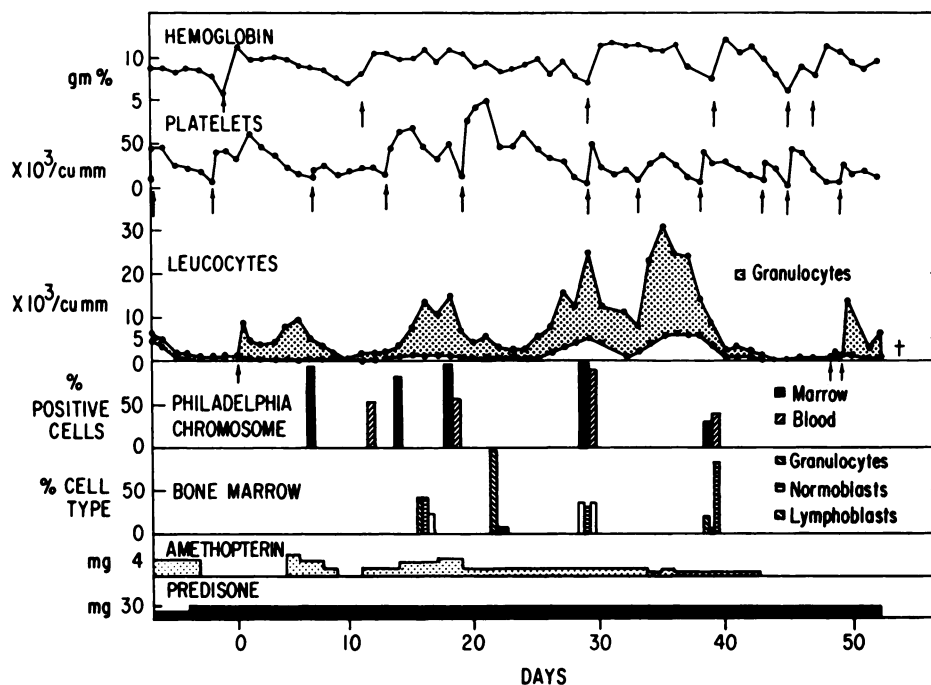


CHART 2.—This 8-year-old boy with acute lymphocytic leukemia received  $1.8 \times 10^{11}$  granulocytes from a donor with chronic myelogenous leukemia on day 0. An abrupt increase in circulating granulocytes followed (shaded area under leukocytes) and persisted for 40 days with white cell counts ranging up to 29,000/cu mm. Granulocytopoiesis was prominent in the bone marrow, and the Ph<sup>1</sup> chromosome (donor cells) was present in the majority of metaphases in the bone marrow and cultured peripheral blood.

conclusive evidence for such homografts is the presence of metaphases containing the Ph<sup>1</sup> chromosome in direct preparations of marrow. Not only can these homologous cells persist and replicate in the marrow, but they may mature and be released into the peripheral blood in some recipients (Chart 2).

The control of mycotic infection is a major problem at present and will become increasingly important in the future. Improved antibiotic treatment will be sought, but approaches involving the enhancement of host response should be considered. The facets of host defense impor-

tant in combating fungi have been reviewed and are not well defined (11). Although humoral antifungal substances, presumably antibodies, have been demonstrated, their importance in controlling such infections is doubtful. Antibody response to booster antigenic stimulus and serum  $\gamma$ -globulin remained normal in patients with acute leukemia in spite of the frequency of systemic fungus infections (12). Also, fungus infections are not particularly frequent in patients with agammaglobulinemia (4). Granulocytes are probably not of major importance, except during the initial reaction to fungus invasion (11). Most of the evi-

dence suggests that failure of lymphocyte function predisposes to systemic fungus infection. Thus, the change of a local fungus infection to a systemic one is often associated with conversion of the delayed skin sensitivity test from positive to negative. Delayed skin sensitivity is mediated by lymphocytes. Systemic fungus infections occur very frequently in the rare disease essential lymphocytophthisis and are also frequent in other situations probably associated with defective lymphocyte function such as runt disease, secondary disease, and Hodgkin's disease (7). Patients with advanced leukemia have almost invariably received prolonged and intensive treatment with lympholytic agents and perhaps as a result of this have frequent systemic fungus infections. The transfusion of immunologically competent cells might be difficult to justify because of the risk of secondary disease. However, such transfusions are being employed experimentally and clinically in an effort to improve host defense against leukemic cells. If these transfusions prove effective in controlling fungus infections in these patients, the use of such treatment in selected patients with progressive systemic mycotic infections should be considered.

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