

This Week's Citation Classic

Bodey G P, Buckley M, Sathe Y S & Freireich E J. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann. Intern. Med.* 64:328-40, 1966.
[Med. Branch, Leukemia Serv., and Math, and Statist, and Appl. Math. Sect., Natl. Cancer Inst., NIH, Bethesda, MD]

The frequency of infectious complications correlates inversely with the absolute number of neutrophils and lymphocytes circulating in the blood of leukemic patients. Both the degree and duration of neutropenia determine the risk of infection. Furthermore, recovery from infection in neutropenic patients depends upon whether or not the neutrophil count returns toward normal. [The SC[®] indicates that this paper has been cited over 365 times since 1966.]

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"The mid-1960s was an exciting period for those of us working on the Leukemia Service of the National Cancer Institute under the leadership of Emil J. Freireich. This is the second *Citation Classic* that was written during those years.¹ With the advent of effective treatment for childhood leukemia, attention was focused on complications which interfered with this therapy. Infection and hemorrhage were the most common causes of morbidity and mortality and the routine administration of platelet transfusions had reduced substantially the fatality rate from hemorrhage.

"Few physicians at that time were interested in the infectious problems of cancer patients, since a negative attitude prevailed regarding the treatment of patients with extensive malignant disease. The fact that neutropenic patients were especially susceptible to infection was universally recognized, but many infectious disease experts were of the opinion that therapy was ineffective in these patients.

"A previous study relating platelet count to hemorrhagic complications served as the model for this study of 54 consecutive leukemic patients.² All blood counts determined in these patients from diagnosis

until death (in some patients this represented more than one year) were included. Since absolute neutrophil and lymphocyte counts were not available, they had to be calculated from the total white blood count and differential percentages. Calculators were not nearly as sophisticated in those days and we had to share ours with other investigators! Most of the work was tedious and repetitious and became interesting only when all of the data had been tabulated. Because of the many numbers involved, calculations had to be checked and rechecked, a frustrating venture when errors were discovered. Finally, everything was in order and we consulted Y. Sathe and Marvin Zelen for a statistical analysis. We were somewhat surprised when they told us that statistical analyses were unnecessary because of the large number of observations and the magnitude of the differences—hence, no sacred p values!

"The information derived from this study has served as a reference for many subsequent investigations. The risk of infection was shown to increase only when the neutrophil count fell below 1,000/mm³. Hence, oncologists designing chemotherapeutic studies with myelosuppressive drugs select doses of such drugs that will not cause the neutrophil count to fall below this level for extended periods of time.

"During the last 15 years, we have studied new antibiotics and antibiotic regimens for the treatment of infection in cancer patients. The knowledge gained from this initial study led us to evaluate therapeutic efficacy related to the patients' initial neutrophil count and to changes in their neutrophil count during infection. We showed that aminoglycoside antibiotics were less effective in neutropenic patients and that response depended upon whether the neutrophil count increased or decreased during the infection.³ Subsequently, we found that this relationship between response and neutrophil count did not apply to all antibiotics—the antipseudomonal penicillins were effective even in persistently neutropenic patients.⁴ These observations have been confirmed by other investigators and cooperative groups."

1. **Hersh E M, Bodey G P, Nies B A & Freireich E J.** Causes of death in acute leukemia: a ten-year study of 414 patients from 1954-1963. *J Amer. Med. Assn.* 193:105-9, 1965. [Citation Classic. *Current Contents/Clinical Practice* 8(1): 10, 7 January 1980.]
2. **Gaydos L A, Freireich E J & Mantel N.** The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. *N. Engl. J. Med.* 266:905-9, 1962.
3. **Bodey G P, Middleman E, Umsawadi T & Rodriguez V.** Infections in cancer patients—results with gentamicin sulfate therapy. *Cancer* 29:1697-701, 1972.
4. **Bodey G P, Whitecar J P, Jr., Middleman E & Rodriguez V.** Carbenicillin therapy of *Pseudomonas* infections. *Amer. Med. Assn.* 218:62-6, 1971.