[17] Cordis Corporation, *Technical Memorandim*, PVI, 25th July 1973.
[18] Green, G. D., *Chemistry and Industry*, 1974, In press.
[19] Furman, S., *Annals of Thoracic Surgery*, 1972, 14, 328.
[20] Bonchek, L. I., *Annals of Surgery*, 1972, 176, 686.
[21] Dieter, R. A., *et al.*, *Geriatrics*, 1973, 28, 78.
[22] Green, G. D., *et al.*, *British Heart Journal*, 1969, 31, 707.
[23] Thalen, H. J. T., *et al.*, *Annals of the New York Academy of Sciences*, 1969, 167, 515.
[24] Parsonett, V., *et al.*, *American Journal of Cardiology*, 1970, 25, 311.
[25] Edhag, O., *et al.*, *British Heart Journal*, 1971, 33, 185.
[26] Eraut, C. D., Evans, R. C., and Shaw, D. B., *British Heart Journal*, 1973 35, 557.
[27] Karlof, I., and Lagergren, H., in *Cardiac Pacing. Proceedings of the 4th International Symposium*,1974, ed. J. Thalen, p. 84, Van Gorcum.
[28] Sykosch, H. J., *Cardiac Pacing*. Proceedings of the 4th International Symposium, Groningen. 1974, ed. J. Thalen, p. 95. Van Gorcum.
[29] Besse, P., and Lardeau, P., in *Cardiac Pacing. Proceedings of the 4th International Symposium*,1974, ed. J. Thalen, p. 90, Van Gorcum.
[30] Sowton, E., in *Cardiac Pacing, Proceedings of the 4th International Symposium*,1974, ed. J. Thalen, p. 109, Van Gorcum.

Hospital Topics

Fever in the Neutropenic Patient

K. ATKINSON, H. E. M. KAY, T. J. McELWAIN

British Medical Journal, 1974, 3, 160-161

Summary

A total of 100 consecutive episodes of fever of 101° F (38·3°C) or above in 56 neutropenic patients have been investigated. All the patients had either acute leukaemia or aplastic anaemia. A cause for the fever was found in 68 of these episodes, in 87% of which it was due to infection. The commonest single finding was septicaemia (30 episodes). Only two episodes of fever could be ascribed solely to the underlying malignant disease.

Infection should be assumed to be present and the cause of fever in neutropenic patients until proved otherwise.

Introduction

As a result of the increasing use of cytotoxic chemotherapy and radiotherapy for malignant disease neutropenia is common. Fever in the neutropenic patient is a difficult problem. In a group of 56 patients with a neutropenia of 1,000/mm³ or less we have investigated 100 consecutive episodes of fever of 101° F (38·3° C) or more to determine the cause.

Patients and Methods

The patients had either acute leukaemia or aplastic anaemia (table I) and were nursed in the reverse barrier unit at this hospital during their illness. All had a neutropenia of 1,000/mm³ or less, and in most cases the count was less than 100/mm³. Any patient was investigated whose temperature reached 101° F (38·3° C) at two consecutive four-hourly intervals or 101° F twice in 48 hours or 102° F (38·3° C) or above on one occasion. The routine procedure was: careful physical examination, the performance of two or three sets of blood cultures (5 ml blood in 50 ml glucose broth, 3 ml in 20 ml broth in a Castaneda's medium bottle, and 1 ml in 10 ml Robertson's meat broth), examination of a midstream specimen of urine, and chest *x*-ray examination. If the fever did not settle after four days (with or without the use of antibiotics) the blood was examined for the presence of atypical "viral" lymphocytes and the urine for cytomegalovirus cells. In addition viral serological tests with paired serum were done.

TABLE I—*Underlying Disease in 100 Consecutive Febrile Episodes*

	No. of Episodes
Acute myeloblastic leukaemia	46
Acute lymphoblastic leukaemia	18
Acute undifferentiated leukaemia	14
Blast transformation of chronic myeloid leukaemia	8
Lymphosarcoma cell leukaemia	5
Aplastic anaemia	9

Results

A cause of the fever was determined in 68 episodes (table II). There was a definite cause in 66 and a probable cause in two. Though the largest single group was one in which no cause was found (32 episodes) the commonest single cause (30 episodes) was septicaemia with a positive culture. (Gram-negative bacteria in 17, Gram-positive bacteria in 12, and a fungus in 1). The second commonest cause was pneumonia (11 episodes), followed by blood transfusion (6) and urinary tract infection (5). One of the two perioral infections started as a pustule growing *Staphylococcus aureus*, while the other started as a typical herpes simplex vesicle. In spite of appropriate treatment both went on to cause extensive perioral and perinasal crusting with severe tissue necrosis. There was one episode of fever in which no abnormality other than severe aphthous-like mouth ulcers was present; these grew no abnormal organisms.

Only two episodes of fever could be attributed with certainty to the underlying malignant disease rather than to any asso-

TABLE II—*Cause in 100 Consecutive Febrile Episodes*

	No. of Episodes		No. of Episodes
No cause found	32	Active malignant disease	2
Septicaemia	30	Pelvic abcess	1
Pneumonia	11	Bartholin's abcess	1
Blood transfusion	6	Cellulitis	1
Urinary tract infection	5	Boils	1
Cytomegalovirus infection	3	Candida oesophagitis	1
Intravenous infusion site infection	3	Mouth ulcers	1
Perioral infection	2		

Leukaemia Unit, Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey
K. ATKINSON, M.B., M.R.C.P., Lecturer in Medicine
H. E. M. KAY, M.D., F.R.C.PATH., Consultant Clinical Pathologist
T. J. McELWAIN, M.B., M.R.C.P., Consultant Physician

ciated infection. Both were in patients with blastic transformation of chronic myeloid leukaemia and are of interest in that each was associated with the rapid development of severe lymphadenopathy. All bacteriological, virological, and protozoological investigations produced negative results, and lymph node biopsy in one case showed infiltration with immature white cells. In both cases the lymphadenopathy and fever responded to cytotoxic chemotherapy with prednisone, vincristine, and colaspase (asparaginase).

Of the 32 episodes in which no cause could be determined 21 were treated empirically with antibiotics. In 16 cases the temperature resolved, 15 within four days (table III). In our experience four days is the usual time taken for fever to respond to antibiotics in patients with proved infection, particularly septicaemia. The decision to administer antibiotics in the absence of a known cause, however, was based entirely on the clinical state of the patients. If they seemed ill antibiotics were administered; if not, antibiotics were usually withheld. In 11 episodes they were withheld (table III). Again most resolved within four days, and objective conclusions are impossible to draw.

TABLE III—*Outcome in 32 Patients with Fever of Unknown Cause*

	Treatment with Antibiotics	No Treatment
Resolution within 4 days	15	7
Resolution within 10 days	1	2
No or equivocal response	5	2

Discussion

The major lesson from this study is that in neutropenic patients most fevers whose cause can be determined are due to infection. In 68 cases a cause was determined, and in 58 of these (85%) the cause was an infection of some sort. For practical purposes infection should be assumed to be present until proved otherwise. Our findings are closely similar to those of Raab *et al.*,[1] who found a cause in 74% of 149 febrile episodes in patients with acute leukaemia, 68% due to infection and 6% due to cerebral haemorrhage. No cause was determined in 26%. As in their study most febrile episodes in patients with acute leukaemia occurred when the disease was in relapse; out of 91 episodes in patients with acute leukaemia in our series only four occurred when the disease was in remission, all in adult cases of acute lymphoblastic leukaemia just before or during prophylactic cranial irradiation.

Neutropenia alters the normal clinical response in infected patients. Boils, infections at the sites of intravenous infusions, and the Bartholin's abscess presented as firm, red, relatively non-tender lumps owing to the absence of pus. Irrigation of such lesions with 0·1 ml saline through a fine-gauge needle, with reaspiration of the saline and culture of the whole needle in a blood culture bottle is recommended for such lesions. Similarly pyuria is often absent in the midstream urine specimen and copious sputum is not produced in chest infections. Physical signs in the chest are often minimal and the chest *x*-ray findings are of paramount importance. The physical examination must include careful scrutiny of the perianal area; not only are perianal lesions relatively common in leukaemia[2] but pseudomonal septicaemia in such patients is sometimes accompanied by a purplish necrotic skin lesion—ecthyma gangrenosum—especially in the perinanal area.[3]

The patients with cytomegalovirus infection posed difficult problems in that they all suffered from severe malaise but had no abnormal physical signs apart from high fever and tachycardia. They showed, of course, no response to antibiotic therapy. When suspicion of a viral infection is aroused by such a lack of response it may be strengthened by the finding of atypical "viral" lymphocytes in the blood and sometimes typical desquamated epithelial cells in the urine.[4] When the large number of blood and platelet transfusions given on an acute leukaemia ward are considered the few episodes caused by such transfusions is perhaps surprising. This is almost certainly due, however, to the routine administration on this unit of chlorpheniramine and hydrocortisone before such transfusions. Surprisingly no febrile episodes in this series could be ascribed to drugs, though undoubtedly colaspase can cause fever,[5] and daunorubicin and cytorabine, the agents used on this unit for acute myeloblastic leukaemia, probably can.

The similarity in outcome in the two groups of patients with fever of undetermined cause treated with and without antibiotics is important in that it emphasizes the need to consider only proved infections when assessing the effectiveness of any given antibiotic combination.

References

1 Raab, S. O., Hoeprich, P. D., Wintrobe, M. M., and Cartwright, G. E., *Blood*, 1960, **16**, 1609.
2 Seal, S. H., and Stearns, M. W., *Cancer (Philadelphia)*, 1973, **31**, 149.
3 Givler, R. L., *Diseases of the Colon and Rectum*, 1969, **12**, 438.
4 Chang, S. C., *Acta Cytologica*, 1970, **14**, 338.
5 Oettgen, H. F., *et al.*, *Recent Results in Cancer Research*, 1970, **33**, 219.