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Infectious Episodes in Severely Granulocytopenic Patients

Summary: In a prospective study, 40 episodes of granulocytopenia (granulocytes $< 500/mm^3$) in 34 patients were analyzed. During 52.5% of these episodes there was proven infection; these infections were present for only 24.4% of the 1,435 granulocytopenic days. The risk of infection and mortality were closely linked with extreme granulocytopenia (granulocytes $< 100/mm^3$). Of the episodes with severe granulocytopenia (granulocytes 100–500/mm³) only a small number were associated with infections, and mortality was virtually absent in this category. These results implicate a restricted use of supportive measures (e. g. granulocyte transfusions) especially when granulocyte counts are higher than $100/mm^3$.

Zusammenfassung: Infektiöse Episoden bei schwer granulozytopenischen Patienten. In einer prospektiven Untersuchung wurden 40 granulozytopenischen Episoden (Granulozyten $< 500/mm^3$) bei 34 Patienten analysiert. Während 52,5% dieser Episoden wurden Infektionen nachgewiesen. Diese Infektionen waren nur während 24.2% von den 1435 granulozytopenischen Tagen vorhanden. Das Infektions- und Mortalitätsrisiko stand in enger Beziehung zu extremer Granulozytopenie (Granulozyten $< 100/mm^3$). Nur eine geringe Anzahl der Episoden mit schwerer Granulozytopenie (Granulozyten 100 bis $500/mm^3$) ging mit Infektionen einher, und Todesfälle kamen in dieser Gruppe nahezu nicht vor. Diese Resultate sprechen für eine beschränkte Anwendung von unterstützenden Maßnahmen (z. B. Granulozytentransfusionen), insbesondere wenn die Granulozytenzahl über $100/mm^3$ liegt.

Introduction

Bacterial infections constitute a serious problem in patients with granulocytopenia. Since 1966 a limited number of studies has shown the gradual but strong increase in the incidence of infections and mortality when granulocytes decrease from $1{,}000/mm^3$ to zero/mm^3 (1–3).

Many authors advocate aggressive therapeutic and preventive measures for granulocytopenic patients: e. g. prompt broad-spectrum therapy with two, three, or more antibiotics as soon as fever develops (4, 5); antibiotic prophylaxis on a large scale (6); supplementary treatment with granulocyte transfusions, either therapeutically (7, 8) or prophylactically (9). Over the past five years our policy for granulocytopenic patients has been less aggressive: no systemic antibiotics are given until bacterial infection is seriously suspected or proven (thus: fever *alone* is not taken as an indication to start antibiotic therapy) and granulocyte transfusions are only given to patients with absolute agranulocytosis and a proven bacterial infection that does not respond to appropriate antibiotic therapy (10). We favour such a less aggressive antibiotic therapy because this approach gives more time and possibilities for microbiological investigations and other diagnostic procedures, which means that bacterial infection may be excluded or more exactly diagnosed, the latter permitting better-adjusted antibiotic therapy. The restricted use of antibiotics also leads to less emergence of resistant microorganisms in the particular patient and in the hospital as well as to fewer side effects and costs.

Restricted use of granulocyte transfusion reduces costs, donor problems, and sensitization and other side effects. However, we questioned whether our less aggressive approach is detrimental for granulocytopenic patients in our hospital. The questions we asked ourselves were: (a) To what degree are granulocytopenia and infection related in our patients, i. e., during what percentage of granulocytopenic days is infection present? (b) How many patients die under our therapeutic approach? On this basis, must the indications for antibiotic therapy or granulocyte transfusions be reconsidered?

Materials and Methods

Patients

All patients (both in- and out-patients) in the Departments of Haematology and General Internal Medicine with granulocyte counts below $500/mm^3$ for at least three days were included in the study; no other selection was applied. The period of the study was the first six months of 1976. Cell counts were performed at least three times a week.

Classification

Infectious status: Proven bacterial and fungal infections (i. e., proven by biopsy or culture) were classified as either major (severe) infections or minor infections. Septicaemia or organ invasion (e. g. pneumonia, perirectal abscess, meningitis, endocarditis, arthritis, and osteomyelitis) were considered major infections; stomatitis, pharyngitis, skin abscess, and sinusitis were classified as minor infections. Episodes during which there were signs that could be attributed to infection (e. g. fever alone) but proof of infection could not be obtained were classified as doubtful infection. The duration of an infectious episode was defined as the number of days between the first day on which symptoms and signs attributable to infection appeared and the first day on which all signs of infections were gone.

Granulocytopenia: An episode of granulocytopenia was taken as the number of days during which a patient had less than 500 granulocytes/mm^3. A division according to the severity of the granulocytopenia was applied for the analysis of the re-

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sults, i. e., *severe* granulocytopenia (100–500 granulocytes/mm³) and *extreme* granulocytopenia (less than 100 granulocytes/mm³).

Haematological status: A patient was considered haematologically refractory when the short-term prognosis of the underlying disease was very poor due, for instance, to high numbers of circulating leukaemic cells unaffected by various chemotherapeutic agents, no recovery of the bone marrow in leukaemia, and leukaemic infiltrates at other sites resistant to chemotherapy.

Management of the Patients

Nursing: Admitted patients were nursed in reversed isolation in a conventional isolation room in a normal hospital ward. Patients selected for bone marrow transplantation were nursed in ultraclean rooms or down-flow isolators in the Isolation Pavillion and received partial antibiotic decontamination (PAD) (11).

Microbiology and antibiotic treatment: Bacterial examination and antibiotic treatment were performed as described elsewhere (10). In short: A bacteriological inventory was carried out on admission and repeated once a week. The patients were examined and treated for chronic asymptomatic infections (e. g. dental granuloma) and for carrier state of *Staphylococcus aureus* and *Candida* spp. No systemic antibiotic treatment was instituted until bacterial infection was seriously suspected or proven. Fever alone was not considered an indication for antibiotic treatment. The choice of the antibiotics was governed by the site of infection and the suspected causative micro-organism (based on gram-stained microscopical preparations, results of previous cultures, etc.). Initial therapy almost always consisted of a combination of two antibiotics given intravenously. When *Pseudomonas* infection was suspected, the initial therapy consisted of carbenicillin and gentamicin; when *Klebsiella* or *Escherichia coli* were suspected, cephalothin and gentamicin were the initial therapy; cloxacillin and gentamicin were given in cases of suspected staphylococcal infection. Whenever possible, antibiotic therapy was adjusted on the basis of the results of bacteriological investigations.

Transfusions: Granulocyte transfusions were only given to patients with agranulocytosis and proven serious infections not responding to proper antibiotic therapy within 24 hours. Granulocytes were harvested by collection of buffy coats from fresh units of heparin blood from random unpaid blood-bank donors. No premedication or sedimenting agents were used. All donors were negative for hepatitis-associated surface antigen and syphilis serology. Daily, $3.5-6 \times 10^9$ granulocytes were transfused. The leucocyte suspensions were irradiated with 1,500 rads to prevent accidental engraftment and possible subsequent graft versus host disease (12). Extremely leucocyte-poor red-cell suspensions for transfusion were prepared by the use of a cotton wool filter* (13). Platelet concentrates were made leucocyte-poor by an extra centrifugation step (14).

Statistical Analysis

Statistical comparisons were performed with the χ^2 test with the Yates correction (15).

Results

Thirty-four patients (20 males and 14 females) were studied. The diagnoses in these cases are given in Table 1. The average age was 41.8 years (range 13–71 years); 13 patients were over 50 years old. In this group there were

Table 1: *Underlying diagnoses in the present study.*

Diagnosis	No. of patients	No. of episodes
Acute myelocytic leukaemia	14	16
Acute monocytic leukaemia	3	4
Acute lymphocytic leukaemia	3	4
Acute undifferentiated leukaemia	2	2
Chronic myelocytic leukaemia	1	1
Hodgkin lymphoma + undifferentiated leukaemia	1	1
Lymphosarcoma	1	1
Unclassified myeloproliferative disease	2	2
Polycythaemia vera	1	1
Aplastic anaemia	4	6
Immunosuppressive treatment during rejection of renal transplant	1	1
Disseminated thyroid carcinoma	1	1
	34	40

40 episodes of granulocytopenia totalling 1,435 days, giving an average of 35.8 days per episode. Figure 1 shows the number and percentage of total episodes (a) and days (b) associated with major, minor, and doubtful infections. The occurrence and duration of proven infections in each granulocytopenic episode and the duration of that episode

* Produced by the Central Laboratory of the Netherlands' Red Cross Blood Transfusion Service, Amsterdam

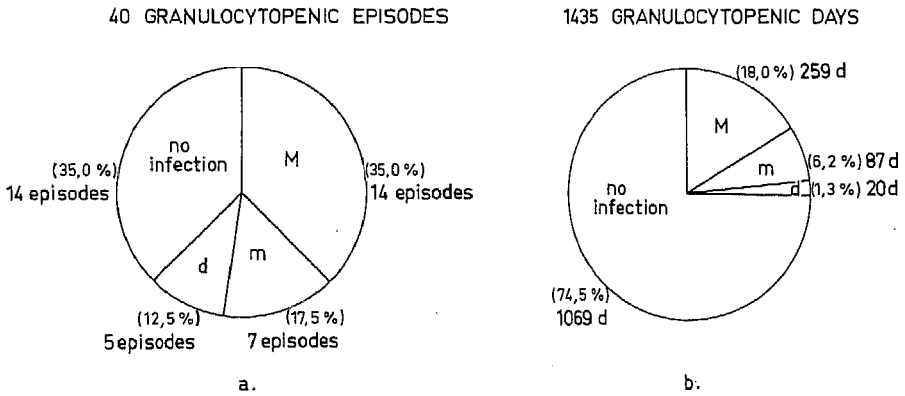
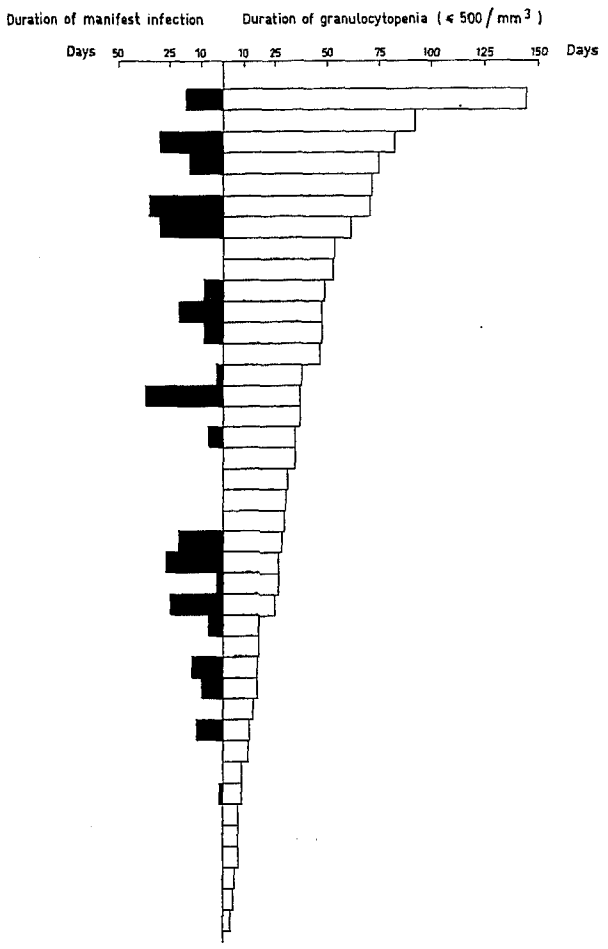


Figure 1: *Number of episodes (a) and days (b) of granulocytopenia and proportion of infections. M = major infection, m = minor infection, d = doubtful infection.*



is given in Figure 2 a. The same data for episodes of extreme granulocytopenia only are given in Figure 2 b.

The incidence of infection during severe and extreme granulocytopenia is given in Table 2. During severely granulocytopenic episodes the incidence (4 out of 15 episodes) is significantly lower (χ^2: 4.87, $p < 0.027$) than during extremely granulocytopenic episodes). If only major infections are considered, this difference is significant at $p < 0.010$ (1 in 15 vs 13 in 25; χ^2: 6.59).

Table 2: *Incidence of infection during granulocytopenic episodes.*

	Severe granulocytopenia (100–500/mm³)		Extreme granulocytopenia (< 100/mm³)	
Proven infection	4		17	
major		1		13
minor		3		4
No/doubtful infection	11		8	
Total	15		25	

The nature of the infections in the various episodes and the mortality involved is given in Table 3. Of the 34 patients in this series, 12 died during an episode of granulocytopenia. Table 4 shows the mortality according to cause of death and severity of the granulocytopenia. One out of 15 episodes of severe granulocytopenia and 11 out of 25 episodes of extreme granulocytopenia ended in death. This difference is significant (χ^2: 4.57, $p < 0.032$). The only fatality in the severely granulocytopenic episodes was caused by myocardial infarction, whereas eight out of 11 deaths during extreme granulocytopenia were due to an infection. The other two causes of death in this last group were leukaemic pulmonary infiltration and adrenal haemorrhage, and in one patient the cause of death was unknown. These data link mortality due to infection and extreme granulocytopenia closely (χ^2: 4.17, $p < 0.041$). Of the eight patients who died due to infection under extreme granulocytopenia, seven were classified as haematologically refractory. The only patient in this group who died in spite of a good short-term prognosis was a 62 year-old man suffering from a pulmonary infiltrate without septicaemia during cytostatic treatment for acute lymphocytic leukaemia.

All infections were treated with systemic antibiotics and for five infections in five patients granulocyte transfusions were added to the regimen on the indications mentioned above. Two of these five patients were classified as hae-

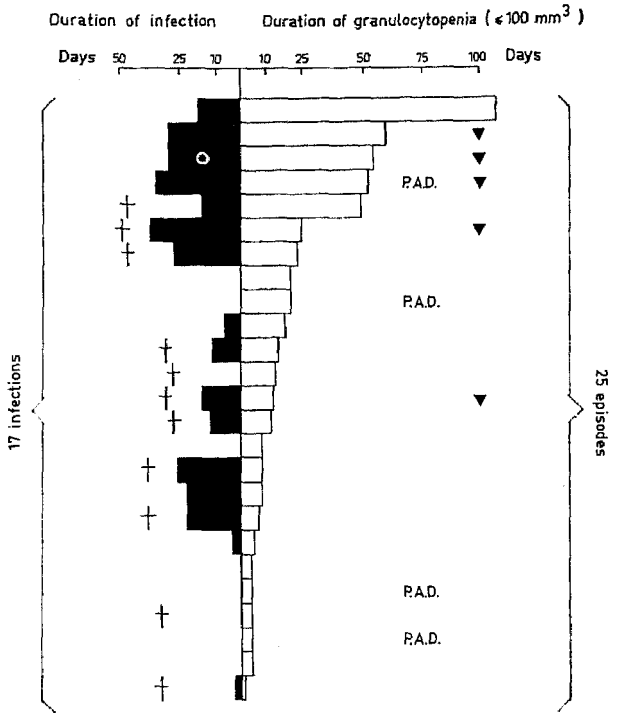


Figure 2: *Patterns of duration of proven infection and of granulocytopenia grouped according to length of the granulocytopenic period. One horizontal bar represents one episode.*
a: all episodes of granulocytopenia (< 500/mm³);
b: episodes of extreme granulocytopenia (≤ 100/mm³).
▼ *granulocyte transfusions*
* *two separate infections during one period of granulocytopenia*
PAD *partial antibiotic decontamination*
† *died during granulocytopenia*

Table 3: *Nature of infections during granulocytopenic episodes (< 500/mm³).*

Infection	Number of episodes	Number of deaths
Major infection		
Septicemia due to a gram-negative species*	5	3
Septicemia due to a gram-positive species*	2	0
Septicemia due to both gram-positive and gram-negative species*	1	0
Septicemia & pneumonia	2	2
Pneumonia (blood cultures negative)	1	1
Perirectal abscess	2	1
Disseminated fungus infection	1	1
Total	14	8
Minor infection		
Stomatitis	4	1
Sinusitis	1	0
Conjunctivitis	1	0
Leg ulcer	1	0
Total	7	1

* No signs of pneumonia.

Table 4: *Mortality during granulocytopenic episodes.*

	Severe granulocytopenia (100–500/mm³)		Extreme granulocytopenia (< 100/mm³)	
Death	1		11	
due to infection		0		8
due to other causes		1		3
Survival	14		14	
Total	15		25	

matologically refractory and died due to infection despite treatment; the other three survived.

Of the 34 patients with granulocytopenia, three were nursed in strict isolation and received PAD during four extremely granulocytopenic episodes. In three of these episodes no infection was seen; in the fourth episode, anaerobic septicaemia developed after sigmoidoscopy in a 23 year-old male with aplastic anaemia. Since the treatment given during these episodes differed, these cases were excluded in a recalculation of the incidence of infection in severe and extreme granulocytopenia (Table 5).

Table 5: *Incidence of infection during granulocytopenic episodes (episodes during partial antibiotic decontamination excluded).*

	Severe granulocytopenia (100–500/mm³)	Extreme granulocytopenia (< 100/mm³)
Proven infection	4	16
No/doubtful infection	11	5
Total	15	21

The difference between the severely and extremely granulocytopenic episodes is now significant at $p < 0.005$ (χ^2: 6.80).

Discussion

Infection is the main hazard in the neutropenic patient (1). This is reflected in our study, where the majority of the granulocytopenic episodes were associated with infection. We found the risk of infection greatly increased in patients in whom the granulocyte count fell below 100/mm³, and all deaths due to infection occurred in relation to these extremely granulocytopenic episodes. Of the episodes with severe granulocytopenia (100–500 granulocytes/mm³), only a small number were associated with infections and mortality was virtually absent in this category. The need for a more aggressive antibiotic therapy and for such treatment as prophylactic antibiotics and prophylactic granulocyte transfusions is therefore questionable. It is interesting, although difficult, to compare our results with the data of some well-known reports in the literature. Since many infectious episodes in extremely granulocytopenic patients end in death, it is of limited value to compare the average duration of infection with the average duration of granulocytopenia. Under this restriction, and excluding episodes with PAD and strict isolation, analysis shows that proven infection was present during 53% of the days of extreme granulocytopenia, whereas this percentage is 9.3 for the days of severe granulocytopenia. If only major infections are taken into account, these percentages are 40 in extreme and 6.3 in severe granulocytopenia. Remarkably, *Bodey* et al. (1) also reported that 53% of days with less than 100 granulocytes/mm³ were days with proven infection. At levels between 100 and 500 granulocytes/mm³, they found 35%. The latter percentage is probably really different from our findings. The divergence might be due to the composition of *Bodey*'s patient material (all patients with acute leukaemia) or nursing methods. In their study, *Levine* et al. (2) considered only days of severe infection, probably comparable to major infections in our study. These authors found infection in 40% of the days with levels between 100 and 500/mm³ in a patient group given conventional ward care. The results in these two studies are very similar to ours with respect to extremely neutropenic episodes. The possible differences in the severely neutropenic episodes might be explained by the conventional isolation of our patients in single rooms as opposed to conventional ward care. This kind of isolation might provide a limited advantage that is lost in the extremely neutropenic episodes, which might require strict isolation. In many of the infections seen during our study a cure was not achieved either with antibiotics alone or after the addition of supportive granulocyte transfusions. This high proportion of failure of the therapy and the associated mortality must be considered in the light of the short-term prognosis of the haematological status. The total outcome of infection in the patients classified as haemato-

logically refractory may be partially attributable to the underlying disease, but in addition the diagnostic and therapeutic approach to the infection may be less active. This last consideration is often disregarded in clinical reports on neutropenic patients. If these cases are excluded, the mortality due to infection is much lower. A more aggressive form of antibiotic therapy does not seem to improve these results.

Recently, some controlled studies (7, 8) have indicated a beneficial effect of therapeutic granulocyte transfusions during infectious episodes in granulocytopenic patients. It is a pity that the authors do not discuss the results of the granulocyte transfusions in relation to the number of circulating granulocytes prior to transfusion. Since the number of granulocytes that can be transfused is relatively small compared to the amount required in bacterial infections (16), it is questionable whether granulocyte transfusions are of benefit as long as circulating granulocytes are present.

Most patients with granulocytopenia need frequent red cell and platelet transfusions. Successful long-term suppletion with blood components can only be achieved if the development of anti-HLA antibodies is prevented. It is now possible to postpone immunization via white blood cell-antigens by the use of extremely leucocyte-poor red cell suspensions (13) and platelet concentrates (14) from random blood donors. However, granulocyte transfusions originating from random donors nullify the efforts to avoid antibody development and may make time-consuming and expensive leucocyte and platelet cross-matching necessary.

In this study mortality proved to be linked to infection, and fatal infections linked to episodes of extreme granulocytopenia. Although the number of episodes is rather small and the patient group heterogeneous, we feel that the results support our views favouring restricted use of granulocyte transfusions. We have doubts about the efficacy of transfused granulocytes in patients with more than 100 circulating granulocytes/mm^3, and we are well aware of the transfusion problem due to immunization with white blood cells. Therefore we do not favour the use of prophylactic granulocyte transfusions and we are now inclined to administer granulocyte transfusions only to patients with *extreme* granulocytopenia (less than 100/mm^3) who have a proven major infection and do not respond promptly to appropriate antibiotic therapy.

Only a small number of patients in the present series were treated in strict isolation and received PAD. Whether fewer infections were acquired during extreme granulocytopenia under these conditions cannot be concluded from this series. However, further investigations have shown the benefit of this form of treatment (17, 18).

Acknowledgements

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