Factors Influencing the Incidence of Infections in Felty's Syndrome

Ferdinand C. Breedveld, MD; Wim E. Fibbe, MD; Jo Hermans, PhD; Jos W. M. van der Meer, MD; Arnold Cats, MD

• To identify clinical and laboratory risk factors for the susceptibility to infections in Felty's syndrome, 46 patients were studied prospectively during a total number of 431 periods of three months ("patient-quarters"). The incidence of infections increased significantly with polymorphonuclear leukocyte (PMN) counts below $0.1 \times 10^3/mm^3$ ($<0.1 \times 10^9/L$). At PMN levels over $0.1 \times 10^3/mm^3$ ($>0.1 \times 10^9/L$), no association was found between PMN counts and the incidence of infections. Other factors found to be associated with an increased incidence of infections were severe disability, skin ulcers, glucocorticosteroid dose, monocyte counts, hypocomplementemia, and high levels of circulating immune complexes. The activity of the rheumatoid arthritis, erythrocyte sedimentation rate, hemoglobin concentrations, and lymphocyte counts were not associated with increased incidence of infections.

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I n 1924, Felty recognized the association of rheumatoid arthritis (RA) with leukopenia and splenomegaly.[1] Since then, the syndrome has been shown to be associated with a number of extra-articular manifestations of RA and recurrent infections.[2-4] Leukopenia in Felty's syndrome (FS) is primarily due to neutropenia. Several pathophysiologic mechanisms have been reported to explain the neutropenia, ie, insufficient granulopoiesis, reduced release of polymorphonuclear cells (PMNs) from the bone marrow, and shortened life span or excessive margination of the circulating PMNs.[3,5-17] Neutropenia is thought to be the main cause of the increased susceptibility to infections,[2,4,5,7,16,18-20] although other clinical factors have also been implicated, ie, hypocomplementemia,[21,22] defective function of PMNs,[22,23] severe disability,[24,25] skin ulcerations,[26] and corticosteroid therapy.[27]

Although the high risk of infection in FS has been recognized by many authors, the incidence of such infections has, to our knowledge, never been studied prospectively. Furthermore, most of the published studies have been restricted to the association between the incidence of infections and one particular parameter. We therefore undertook a prospective study on the relationship between

the incidence and type of infections in FS and multiple clinical factors. Disability, polyarthritis activity, skin ulcers, leukopenia, anemia, hypocomplementemia, levels of circulating immune complexes, and the dose of glucocorticosteroids were all considered as possible contributing factors to the incidence of infections.

PATIENTS AND METHODS
Patients

Patients referred to six hospitals, who had been registered by the National Committee for Research on Rheumatoid Diseases, the Netherlands, under the clinical diagnosis FS, were included in this study. For the diagnosis of FS, the patient had to have the combination of definite RA according to the American Rheumatism Association criteria, sustained neutropenia of under $2.0 \times 10^3/mm^3$ ($<2.0 \times 10^9/L$) lasting at least six months, and splenomegaly. Patients with drug-related marrow toxic reaction or myeloproliferative disorders were excluded. The patients were treated with a variety of medications, including nonsteroidal anti-inflammatory drugs and disease-modifying agents, such as gold salts, d-penicillamine, and chloroquine. These drugs were generally prescribed to treat the polyarthritis and not to increase the number of circulating PMNs. The neutropenia in FS was treated by splenectomy in four patients and by prednisone in nine patients. All patients with FS registered between June 1982 and June 1985 were enrolled. At the time of enrollment and at three-month intervals after that, the patients were examined by one of us and blood was collected for laboratory investigation. These three-month periods of follow-up will be called "patient-quarters." Only patients with at least one patient-quarter of follow-up were included in the study.

Clinical and Laboratory Data

Proved bacterial and fungal infections (ie, proved by culture of biopsy) were classified as either major (septicemia or organ infection, eg, pneumonia, septic arthritis, pyelonephritis) or minor (local infections, eg, stomatitis, bronchitis, skin abscesses, cystitis). Functional capacities were scored according to Steinbrocker et al.[28] Arthritis activity was scored according to the Ritchie articular index.[29] A score of 15 or less was considered as inactive RA and 16 or more as active RA. The dosages used for corticosteroid therapy were recorded as the highest dose given during the preceding patient-quarter. White blood cell counts were recorded at the baseline level (ie, in the absence of infection). Immune complexes (Icx) were measured by C1q binding assay[30]; the amount of Icx was expressed as microgram equivalents of a standard of aggregated IgG.[31] Complement activity was expressed as total hemolytic complement (CH_{50}) activity.[32] Where CH_{50} activity was decreased, the levels of C1q, C1 inhibitor, C3, and C4 were measured by radial immunodiffusion using monospecific antisera.[33] The C3 through C9

Table 1.—Leukocyte Distribution and Occurrence of Infections in 46 Patients With Felty's Syndrome*						
			Major Infections		All Infections	
Cells × 10³/mm³ (× 10⁹/L)	No. of Patients	No. of Patient-Quarters	Patient-Quarters With Infection, %†	Incidence‡	Patient-Quarters With Infection, %†	Incidence‡
PMNs						
<0.1	7	18	28	28	61	111
0.1-0.5	15	48	0	0	8	15
0.5-1.0	19	48	6	6	20	25
1.0-2.0	40	203	4	5	23	31
>2.0	24	114	2	2	11	11
Lymphocytes						
<0.1	0	0	. . .	. . .	. . .	. . .
0.1-0.5	8	34	9	9	38	47
0.5-1.0	30	150	5	6	18	27
1.0-2.0	33	162	3	3	23	29
>2.0	16	85	3	3	11	13
Monocytes						
<0.1	12	55	5	5	40	49
0.1-0.2	34	190	7	8	20	31
0.2-1.0	28	185	1	1	15	16
>1.0-2.0	1	1	. . .	. . .	. . .	. . .

*PMN indicates polymorphonuclear leukocyte. Normal values are as follows: PMNs, 2.5 to 7.0 × 10³/mm³ (2.5 to 7.0 × 10⁹/L); lymphocytes, 1.0 to 4.0 × 10³/mm³ (1.0 to 4.0 × 10⁹/L); monocytes, 0.2 to 1.0 × 10³/mm³ (0.2 to 1.0 × 10⁹/L).
†Percentage of patient-quarters with at least one documented infection.
‡Number of observed infections per 100 patient-quarters of follow-up.

levels were determined hemolytically.[34] Functional activity of C1 inhibitor[35] and C2[36] was assessed with the appropriate hemolytic assay.

Infections occurring in one patient-quarter were related to clinical and laboratory data documented at the beginning of that interval to avoid an influence of infection on these factors. Because the individual factors may vary between the various intervals, any given patient could have been classified in different subsets of that factor, which means that the sum of the number of patients in the subsets may exceed the number of patients studied (Table 1).

Statistical Analysis

For evaluation of the contribution made by the clinical factors under study to the occurrence of infection, clinical data were recorded before each patient-quarter and related to the occurrence of infections in the following three months. However, it should be noted that the patient-quarters were not all independent, since the 431 quarters were studied in 46 patients.

The relation between the number of infections per patient-quarter and the peripheral blood cell count was investigated by linear regression. With the regression equation for PMNs and monocytes, expected values of the numbers of major as well as of major and minor infections were computed for the patient-quarters of all patients with various subsets of PMN and monocyte counts. Next, the ratios of observed-to-expected numbers of infections (based on PMN and monocyte counts) were recorded for the specific conditions (hypocomplementemia, skin ulcers, etc) being evaluated. Observed-to-expected ratios lower than 1 indicate fewer infections than would occur by chance, whereas values higher than 1 indicate an increased incidence of infections. To test for an association between clinical factors and the occurrence of infections, 2 × 2 tables were used, ie, percentages of patient-quarters with or without infections were compared with percentages of patient-quarters with or without the factors. We considered P values lower than .05 statistically significant.

RESULTS
Patients

From June 1982 to June 1985, 46 patients with FS were studied for a mean follow-up period of 9.4 patient-quarters (range, one to 12), resulting in a cumulative number of 431 patient-quarters. The mean duration of the neutropenia at the time of entry to the study was four years (range, 0.5 to 16 years). The mean duration of RA before the recognition of the neutropenia was 15 years (range, 0 to 46 years). In most of the patients, the splenomegaly was documented shortly after the discovery of the neutropenia by palpation (26 patients) or radioisotope scanning (20 patients). All patients had symptoms of arthritis. At the end of the study, the patients were classified functionally according to Steinbrocker et al,[28] which gave the following results: grade I, ten patients; grade II, 12 patients; grade III, 12 patients; and grade IV, 12 patients. The rheumatoid arthritis was active in 28% of the patient-quarters (Table 2).

Hematologic Data

The leukocyte distribution of the patients during the 431 patient-quarters is given in Table 1. There was a weak correlation between the peripheral blood counts of PMNs, lymphocytes, and monocytes ($r \approx .20$). The PMN counts were over $2.0 \times 10^3/mm^3$ ($>2.0 \times 10^9/L$) in 26% of the patient-quarters, and the numbers of lymphocytes and monocytes were normal in 57% and 43%, respectively. Severe neutropenia occurred more frequently than severe lymphocytopenia (Table 1). Anemia was present in 65% of the patient-quarters (Table 2), and platelet counts were below the normal range in 19% of the patient-quarters. The erythrocyte sedimentation rate was above 100 mm/h in 27% and below 50 mm/h in 20% of the patient-quarters (Table 2).

Serologic Data

Serum rheumatoid factor was present in all patients. Forty-five patients had antinuclear antibodies as well. Circulating Icx were demonstrated in 80% of the 204 patient-quarters in which patient serum samples were investigated for Icx. Hypocomplementemia, defined as depressed CH_{50} activity, was present in 30% of the 201 patient-quarters investigated. Among the hypocomplementemic serum samples, C4 activity was lower than normal in 92%, C2 in 81%, and C3 in 56%. The level of C1q was normal in 68%, and C1 inhibitor and the C3-9 complex were

Table 2.—Association of Clinical Factors With the Occurrence of Infections in Felty's Syndrome*

		Major Infections			All Infections		
	No. of Patient-Quarters	Patient-Quarters With Infection, %†	Observed Incidence‡	Observed-to-Expected Ratio§	Patient-Quarters With Infection, %†	Observed Incidence‡	Observed-to-Expected Ratio§
Arthritis activity							
Active	121	2	3	0.8	25	29	1.1
Inactive	310	5	5	1.1	21	27	1.0
Functional class							
Grade I	107	2	2	0.2	10	19	0.5
Grade II	138	2	2	0.4	25	31	1.1
Grade III	108	5	5	0.5	19	20	1.0
Grade IV	78	11	13	2.2	25	37	1.5
Ulcers							
Present	80	13	14	2.6	35	53	1.7
Absent	332	2	3	0.3	17	21	0.8
Prednisone dose, mg							
0	353	4	5	0.8	19	24	1.0
1-20	66	5	5	0.8	21	29	0.9
>20	12	8	8	1.6	42	88	1.8
Westergren ESR, mm/h							
<50	86	5	5	0.9	22	34	0.9
50-100	230	4	4	1.1	21	25	1.0
>100	115	5	6	1.0	20	24	1.1
Hemoglobin, g/dL (g/L)							
<8 (<80)	5	0	0	0	20	20	1.2
8-12 (80-120)	275	5	5	0.9	21	23	0.9
>12 (>120)	151	4	4	1.2	30	32	1.1
CH$_{50}$ activity							
Decreased	60	17	18	3.2	40	58	1.7
Normal	141	4	4	0.5	23	31	1.1
Immune complexes, µg Eq/mL							
<10	40	0	0	0	10	10	0.5
10-1000	130	8	9	1.8	26	38	1.3
>1000	34	18	18	2.2	60	91	2.2

*ESR indicates erythrocyte sedimentation rate; CH$_{50}$, total hemolytic complement.
†Percentage of patient-quarters with at least one documented infection.
‡Calculated number of infections per 100 patient-quarters.
§Quotient of observed number of infections and expected number of infections based on polymorphonuclear leukocyte and monocyte counts.

normal in all patients. A pattern of decreased C4 and C2 concentrations with normal amounts of the C3-9 complex implies complement activation via the classic pathway. The presence of hypocomplementemia was significantly correlated with the presence of Icx levels above 1000 µg Eq/mL ($P<.001$). Hypocomplementemia was not observed in patient-quarters in which no circulating Icx could be detected.

Infections

A total of 115 infections (20 major, 95 minor) were diagnosed during the study, resulting in an overall infection rate of 27 per 100 patient-quarters. These infections occurred in 22% of the patient-quarters. The major infections were observed in only 14 patients. These patients were studied for a mean of 8.4 patient-quarters (range, three to 12). The 95 minor infections were distributed over 34 patients studied during a mean of 9.7 patient-quarters (range, two to 12). Infecting organisms and isolation sites are given in Table 3. Staphylococcus aureus was the most commonly isolated organism, occurring in 50% of the major and 32% of the minor infections. Pseudomonas aeruginosa, Escherichia coli, and other Enterobacteriaceae together accounted for 43% of the isolations from patients with major

infections and 45% with minor infections. There were four infections with Candida albicans. Disseminated or deep-tissue fungal infections, severe viral infections, and infections caused by intracellular bacteria (eg, mycobacteria) were not observed. Bacteremia occurred in ten patients in association with major organ infection and in four patients without a major organ infection (Table 3). Four patients died of major organ infection and sepsis during the study.

Leukocytes and Infection

The percentage of patient-quarters with documented major or all (major and minor) infections increased significantly when PMN counts were under 0.1×10^3/mm^3 ($<0.1 \times 10^9$/L), ($P<.001$, PMNs$<0.1 \times 10^3$/mm^3 vs PMNs $>0.1 \times 10^3$/mm^3 [PMNs$<0.1 \times 10^9$/L vs PMNs$>0.1 \times 10^9$/L]) (Table 1). The incidence of major infections rose strongly from fewer than six infections per 100 patient-quarters at PMN counts over 0.1×10^3/mm^3 ($>0.1 \times 10^9$/L) to 28 when PMN counts were under 0.1×10^3/mm^3 ($<0.1 \times 10^9$/L) (Table 1). For all infections, these figures were fewer than 31 infections per 100 patient-quarters with over 0.1×10^3/mm^3 ($>0.1 \times 10^9$/L) and 111 per 100 patient-quarters with under

Table 3.—Types of Infection and Causative Organisms in 46 Patients With Felty's Syndrome				
Type of Infection	Gram-Positive Cocci	Gram-Negative Rods	Mixed	*Candida*
Major				
Septic arthritis	2	0	...	...
Osteomyelitis	2	0	...	...
Muscle abscess	2	0	...	...
Pneumonia	3	0	...	...
Septic pericarditis	1	0	...	...
Pyelonephritis	0	2	...	...
Diverticulitis	0	2	...	...
Meningitis	1	0	...	...
Ecthyma gangrenosum	0	1	...	...
Bacteremia without other types of major infection	3	1	...	...
Total	14	6	...	...
Minor				
Conjunctivitis	1	1	0	0
Stomatitis	1	0	1	1
Pharyngitis	5	0	1	0
Sinusitis	2	2	2	0
Otitis media	1	1	0	0
Esophagitis	0	0	0	3
Bronchitis	0	11	4	0
Cystitis	0	26	0	0
Skin abscess	12	0	12	0
Cellulitis	6	0	2	0
Total	28	41	22	4

$0.1 \times 10^3/mm^3$ ($<0.1 \times 10^9/L$). Individual patients with highly variable PMN counts during the study period also developed infections more frequently at PMN counts under $0.1 \times 10^3/mm^3$ ($<0.1 \times 10^9/L$).

In the presence of lymphocytopenia and monocytopenia, the percentage of patient-quarters with at least one documented major or minor infection was also increased (Table 1). Multiple regression analysis showed the PMN counts under $0.1 \times 10^3/mm^3$ ($<0.1 \times 10^9/L$) to be the most important determinative factor for the increased incidence of infection; the influence of monocyte counts under $0.1 \times 10^3/mm^3$ ($<0.1 \times 10^9/L$) on all infections was small ($P<.05$ vs monocytes counts over $0.1 \times 10^3/mm^3$ [$>0.1 \times 10^9/L$]; not significant for major infections) and lymphocyte counts did not make an independent contribution apart from the PMN and monocyte counts.

Role of Arthritis Activity, Disability, Skin Ulceration, and Glucocorticosteroid Therapy

Patients with active and inactive polyarthritis had similar rates of infection, being two and five per 100 patient-quarters, respectively, for major infections. For all infections, 25 per 100 patient-quarters were associated with infection when the arthritis was active, against 21 per 100 patient-quarters when the arthritis was inactive (Table 2).

Next, the role of disability was investigated. The percentage of patient-quarters with documented infections was significantly higher ($P<.01$ for major and for all infections) in patients incapable of any self-care (grade IV) than in patients capable of all daily activities (grade I; Table 2). The influence of disability alone was assessed by calculating the expected number of infections on the basis of the PMN and monocyte counts documented in the patient-quarters with

different functional grades. The observed-to-expected ratio for major infections in patient-quarters with functional grade IV was 2.2 vs 0.2 in patient-quarters with functional grade I. For all infections, these ratios were 1.5 and 0.5. Patient-quarters with functional grades II and III were associated with a higher incidence of all infections compared with patient-quarters with functional grade I, although for major infections alone, no difference was found.

During patient-quarters in which skin ulcers were observed, the percentage of intervals with documented major infections was 13% compared with 2% in intervals without ulcers ($P<.01$). For all infections, 35% of the intervals were associated with infection when ulcers were present as against 17% in the absence of ulcers ($P<.01$). The observed-to-expected ratio for major infections in patient-quarters with ulcerations was 2.6 vs 0.3 in patient-quarters without ulcerations. For all infections, this ratio was 1.7 with ulcers vs 0.8 in their absence (Table 2). Patient-quarters during which prednisone was given in a daily dose of less than 20 mg were associated with frequencies of infection similar to those for quarters without glucocorticosteroid therapy. Patient-quarters during which patients received more than 20 mg of prednisone per day had a higher incidence of infection and an observed-to-expected ratio for infection higher than 1 (Table 2). However, this association was not statistically significant.

Role of Hematologic and Serologic Factors

When patient-quarters were grouped according to the Westergren erythrocyte sedimentation rate in subsets of under 50, 50 to 100, and over 100 mm/h, no difference was found in the association with either major infections or all infections (Table 2). Patient-quarters grouped according to hemoglobin concentrations in subsets of under 8, 8 to 12, and over 12 g/dL (<80, 80 to 120, > 80 g/L) also showed no difference in the association with major or all infections (Table 2).

The percentage of patient-quarters with documented infections was significantly higher in the presence than in the absence of hypocomplementemia (Table 2, $P<.01$ for major, $P = .03$ for all infections). The difference persisted after calculation of the observed-to-expected ratio for major and for all infections.

Three of the four patients who died of an infection during the study suffered from recurrent *S aureus* septicemia probably arising from skin ulcers. The serum samples of these patients differed from the other hypocomplementemic serum by the absence of CH_{50} activity, which diminished suddenly in the presence of high levels of Icx before the manifestation of the infections.

A progressive increase in the percentage of patient-quarters with at least one documented infection became evident when patient-quarters were grouped according to levels of circulating Icx: under 10, 10 to 100, or over 1000 μg Eq/mL (values in healthy controls, <10 μg Eq/mL). This increase was significant at the $P<.01$ level for major and for all infections when patient-quarters with Icx under 10 μg Eq/mL were compared with those with over 1000 μg Eq/mL. The association between infection incidence and Icx persisted after calculation of the observed-to-expected ratio for major and for all infections (Table 2).

No correlation was found between the presence of hypocomplementemia or Icx levels and the presence of skin ulcers, particular functional grades, or glucocorticosteroid therapy. Multiple regression analysis revealed that not only neutropenia and monocytopenia but also hypocomplementemia with high Icx levels, skin ulcers, and severe disability contributed independently to the incidence of infection in FS.

Felty's Syndrome—Breedveld et al

COMMENT

The data obtained in this study indicate that an increased risk of infections in FS is primarily related to peripheral blood PMN counts lower than $0.1 \times 10^3/mm^3$ ($<0.1 \times 10^9/L$). Other factors of importance are the presence of severe disability, skin ulcers, glucocorticosteroid therapy, monocytopenia, hypocomplementemia, and circulating Icx. Infections in FS are caused almost exclusively by pyogenic and enteric bacteria, whereas serious viral, fungal, or intracellular bacterial infections, such as tuberculosis, were absent. These data are compatible with an intact immune system and indicate a primary defect in number or function of PMNs.

The role played by PMNs in host defense is important for eliminating facultative extracellular microorganisms, and it is generally accepted that neutropenia predisposes to infection, although the level at which low PMN counts put the patient at risk of infection differs according to the underlying disease. Patients with a myelodysplastic syndrome or acute leukemia show an increased incidence of infections when PMN counts drop below $1.5 \times 10^3/mm^3$ ($<1.5 \times 10^9/L$), the effect becoming more prominent at PMN counts between 0.1 and $0.5 \times 10^3/mm^3$ (between 0.1 and $0.5 \times 10^9/L$). At PMN counts below $0.1 \times 10^3/mm^3$ ($<0.1 \times 10^9/L$), there is a striking increase of severe infections.[37-39] In idiopathic neutropenia, the correlation between an increased incidence of infections accompanied by PMN counts below $0.5 \times 10^3/mm^3$ ($<0.5 \times 10^9/L$) has been reported to be both present and absent, but the incidence and the severity of the infections was considerably lower than in patients with myelodysplasia with similar neutrophil counts.[40-42] In eight series of patients with FS, 122 of 192 patients had a history of infections.[2,4,7,13,16,18-20] In two studies on the relation between PMN counts and the occurrence of infections, PMN counts did not identify patients with FS at high risk of infection. However, these data are difficult to interpret since no details as to the number and type of the infection were given.[2,18] The present findings in patients with FS reveal a significant correlation between the incidence of infections and neutrophil counts below $0.1 \times 10^3/mm^3$ ($<0.1 \times 10^9/L$). At PMN counts over $0.1 \times 10^3/mm^3$ ($>0.1 \times 10^9/L$), no influence of PMN counts on the incidence of infections was found in this study either.

In addition to neutropenia, we found other factors that were also related to the increased risk of infections. Earlier reports of infection in the rheumatoid patient stated that RA itself predisposes to infection.[5,15] Since the present study did not include control groups of patients with RA and normal subjects, this question was not addressed directly. The relevant question for the treatment of patients with FS is to identify factors that are associated with an increased incidence of infection. Skin ulcers have been reported to occur in 19% to 50% of patients with FS[2,13,18,19] and are thought to be related to vasculitis, neuropathy, hypostatic edema, or perforation of rheumatoid nodules.[13] In the present study, the higher incidence of infections in the presence of skin ulcers was due not only to the occurrence of infections at the site of the ulcer, but also to the presence of major infectious diseases such as bacteremia, osteomyelitis, and septic arthritis, in which the skin ulcers functioned as port of entry for the microorganisms. Previous studies reported that bedridden patients with RA are at greater risk of infections of the skin, joints, and respiratory tract.[24-27] In accordance with these findings, the severely debilitated patients studied herein were also found to be at greater risk of infection compared with those still capable of normal daily activities. Numerous authors have reported an association between glucocorticosteroid therapy and an increased incidence of infections.[43] In the present study, a distinct influence on the incidence of infections by glucocorticosteroid treatment was only seen at doses higher than 20 mg of prednisone daily and not at lower doses. The latter might be explained by the very low doses with which these patients were generally treated. These results suggest that prednisone therapy in doses higher than 20 mg daily are not useful to treat neutropenia in patients with FS.

The present results confirm that hypocomplementemia and high levels of circulating Icx predispose to infection, as described by others in selected patients with RA.[21] In an earlier study, we found that the capacity of PMNs from patients with FS to ingest S aureus in the presence of serum containing Icx as well as decreased complement activities to be lower than this capacity of PMNs from healthy controls.[22] This finding suggests that the combined presence of circulating Icx and hypocomplementemia leads to impaired host resistance to infection by hampering phagocytosis of bacteria by patient PMNs.

A uniformly effective treatment for neutropenia in FS is not available. Since the first report in 1932,[44] many authors have recommended splenectomy for patients with FS with recurrent infections[7,20] or for prophylactic purposes when PMN counts fall below 0.5 to $1.0 \times 10^3/mm^3$ (<0.5 to $1.0 \times 10^9/L$).[4] In 1968, Sandusky et al[45] reviewed 104 cases of FS and found that, after splenectomy, PMN counts returned to normal in 60% of the cases. In recent studies, neutropenia recurred in 38 of 114 patients following splenectomy,[2,4,8,13,15,18-20,46] and, despite this operation, several patients with increased PMN counts still suffered from recurrent infections.[2,18,20] These reports indicate that splenectomy is still a controversial procedure. Treatment of neutropenia in FS with other regimens such as glucocorticosteroids,[2,18] cytostatic drugs,[47] lithium carbonate,[48] d-penicillamine,[49] or gold compounds[50] have met with variable degrees of success and should, like splenectomy, be studied prospectively and on a larger scale to establish the benefits and risks of treatments. Treatment of neutropenia appears to be indicated only in cases where the condition is severe, ie, PMN count under $0.1 \times 10^3/mm^3$ ($<0.1 \times 10^9/L$) with recurrent major infections. Because most of the patients with FS with less severe neutropenia have a relatively low risk of developing major infections, we believe that these patients should not be routinely subjected to the potentially toxic side effects of any treatment if such treatment is intended solely to achieve an increase in the number of circulating PMNs.

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