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TREATMENT OF VISCERAL LEISHMANIASIS WITH PENTAVALENT ANTIMONY AND INTERFERON GAMMA

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Abstract Acute visceral leishmaniasis is associated with an antigen-specific immunosuppression of mononuclear cells as evidenced by defective *in vitro* production of interferon gamma. We evaluated treatment with recombinant human interferon gamma in combination with conventional pentavalent antimony therapy in patients with visceral leishmaniasis.

Six of eight patients with visceral leishmaniasis (mean duration, 17 months) that had been unresponsive to multiple courses of pentavalent antimony responded to treatment with recombinant human interferon gamma (100 to 400 μ g per square meter of body-surface area per day) in addition to pentavalent antimony (20 mg per kilogram of body weight per day) for 10 to 40 days. The other two patients improved initially but then relapsed and required

treatment with amphotericin B. Eight of nine additional patients with previously untreated severe visceral leishmaniasis were also successfully treated with the combination of interferon gamma and pentavalent antimony. The 14 patients who responded to this regimen had marked improvement in symptoms and in measures of anemia and leukopenia, as well as weight gain, a decrease in spleen size, and an absence or reduction of leishmanias in splenic aspirates. These patients had no recurrence of illness after a mean (\pm SE) follow-up of 8 ± 1 months. Fever was the only major side effect of interferon gamma.

We conclude that the combination of interferon gamma and pentavalent antimony is effective in treating seriously ill patients with refractory or previously untreated visceral leishmaniasis. (*N Engl J Med* 1990; 322:16-21.)

VISCERAL leishmaniasis is caused by obligate intracellular protozoa of the genus *leishmania*. The disease is worldwide in distribution and occurs in parts of Africa, North and South America, eastern and southern Europe, and Asia.¹⁻³ Visceral leishmaniasis is characterized by fever, hepatosplenomegaly, anemia, and leukopenia. Pentavalent antimonial drugs have been the preferred therapy for more than 40 years. Antimonials are potentially toxic, however, and therapeutic failures occur in up to 15 percent of patients.^{1,4} Amphotericin B and pentamidine are alternative therapies but are also associated with toxicity.

In the present study, we used recombinant interferon gamma in combination with pentavalent antimony to treat patients with visceral leishmaniasis. The rationale for this regimen is based on the observation that during acute visceral leishmaniasis, peripheral-blood mononuclear cells fail to recognize leishmania antigen (as measured by T-cell blastogenesis

and the production of interleukin-2 and interferon gamma).⁵⁻⁷ T-cell recognition of mitogen and unrelated antigens is unaffected⁷; the antigen-specific immunosuppression is cell-mediated.⁸ Defects in the functioning of macrophages have been observed *in vitro*; they include decreased production of interleukin-1, decreased expression of major histocompatibility complex Class II molecules, and increased generation of prostaglandin E₂.⁹⁻¹³ Exogenously administered interferon gamma augments the capacity of macrophages to eliminate leishmania infection in *in vitro* models and acts synergistically with pentavalent antimony.¹⁴⁻¹⁷ Finally, the safety of parenteral recombinant human interferon gamma has been demonstrated in patients with leprosy, cancer, the acquired immunodeficiency syndrome, and chronic granulomatous disease.¹⁸⁻²¹

METHODS

The study population was made up of eight patients with visceral leishmaniasis that had been refractory to multiple courses of conventional therapy with pentavalent antimony (Group 1) and nine severely ill patients with previously untreated visceral leishmaniasis (Group 2). The patients' median age was 6 years (range, 2 to 23). The mean (\pm SD) duration of illness was 17 ± 9 months (range, 6 to 30) in Group 1 and 6 ± 6 months (range, 1 to 12) in Group 2. Thirteen patients were male and four female. All the patients were

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hospitalized at the Hospital Professor Edgard Santos in Salvador, Bahia, Brazil, during 1986 through 1988. Sixteen patients were from the state of Bahia and one patient was from the state of Sergipe. Informed consent was obtained from all patients or their guardians, and the study was approved by the committees on human rights of Cornell University Medical College and the University of Bahia.

Diagnostic Criteria

All the patients had clinical manifestations of visceral leishmaniasis, including fever, hepatosplenomegaly, anemia, and leukopenia. Serologic tests for leishmania antibodies by enzyme-linked immunosorbent assay were positive, and leishmania amastigotes were demonstrated in Giemsa-stained direct smears of splenic aspirates from all patients.²² To obtain the size of the spleen, we measured the span below the left costal margin at the anterior axillary line. The splenic-aspiration procedure followed the protocol of Chulay and Bryceson.²³ A platelet count $\geq 80,000$ per cubic millimeter and prothrombin activity ≥ 60 percent of control were prerequisites for splenic aspiration. Leishmania amastigotes were measured in a splenic-aspirate smear over a period of 30 minutes by scanning 1000 oil-immersion fields ($\times 10$ eyepiece, $\times 100$ oil objective). The grading system (leishmania index) scored the smears logarithmically as follows: zero (indicating no parasites per 1000 fields), 1+ (1 to 10 parasites per 1000 fields), 2+ (1 to 10 parasites per 100 fields), 3+ (1 to 10 parasites per 10 fields), 4+ (1 to 10 parasites per field), 5+ (10 to 100 parasites per field), and 6+ (>100 parasites per field). Leishmanias were cultured, in Novy, McNeal, and Nicolle medium, from the splenic aspirates of 14 of the 17 patients.¹ The cultures of aspirates from the remaining three patients were contaminated.

A patient was considered to have visceral leishmaniasis refractory to antimony therapy if he or she had persistent clinical manifestations of visceral leishmaniasis and amastigotes in a splenic aspirate after receiving two or more documented courses of pentavalent antimony (20 to 30 mg per kilogram of body weight per day) totaling at least 20 days; such patients were assigned to Group 1. Patients with untreated leishmaniasis (Group 2) were severely ill, had hemorrhagic manifestations (epistaxis or petechiae), and had a leishmania index of at least 3+ on examination of their splenic aspirates.

Drugs and Therapy

Recombinant human interferon gamma (RU 42369, Roussel-UCLAF, Romainville, France) is produced from a strain of *Escherichia coli* transfected with a plasmid into which the gene coding for the synthesis of human interferon gamma has been inserted. The protein is nonglycosylated and contains 143 amino acids. The molecular weight is 17,000 by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and 34,000 by gel filtration in the native form. The specific activity is 2×10^7 U per milligram. The pentavalent antimony used was N-methylglucamine antimoniate sodium (Glucantime, Rhodia, São Paulo, Brazil) containing 85 mg of pentavalent antimony per milliliter.

The patients with refractory visceral leishmaniasis (Group 1) received daily intramuscular injections of interferon gamma (100 μ g per square meter of body-surface area) and intravenous infusions of pentavalent antimony (20 mg per kilogram per day) for 10 days. An exception was the first patient treated, who received interferon at a dose of 50 μ g per square meter per day. On the 10th day the patients were reevaluated and a second splenic aspirate was obtained. If the patient was clinically improved but the splenic aspirate remained positive for leishmanias, the combination therapy was continued at the same dosage for 10 more days (a total of 20 days). After 20 days, if the patient was clinically improved but the splenic aspirate was still positive, the interferon-antimony therapy was continued for 10 to 20 more days, with an increase in the dose of gamma interferon to 400 μ g per square meter per day (Patients 4 and 5). If the signs and symptoms of leishmaniasis persisted and the leishmania index in the splenic aspirate was 3+ or higher after 20 days or more, the interferon-antimony treatment was considered to have failed (Patients 6 and 7).

Patients in Group 2 received interferon (100 μ g per square meter per day) and pentavalent antimony (20 mg per kilogram per day) for 10 days. If the patient was afebrile (temperature $\leq 37.5^\circ\text{C}$ for 24

hours) and had no evidence of bleeding and the splenic aspirate was negative, both drugs were discontinued after 10 days (Patients 10 and 16). However, if the leishmania index in the splenic aspirate was 1+ or 2+, interferon was stopped and pentavalent antimony was continued (at a dose of 20 mg per kilogram per day) for 10 more days (Patients 11, 12, 13, 15, and 17). In two patients (Patients 9 and 14), who had clinical improvement but an index of 3+ in the splenic aspirate, interferon and antimony were both continued for an additional 10 days. Interferon was inadvertently discontinued on day 6 in Patient 12.

Clinical-Response Criteria

Clinical cure or successful therapy was defined by the maintenance of a temperature $< 37.5^\circ\text{C}$ for 24 hours or more, a decrease in the size of the spleen, the absence of bleeding, a leishmania index of zero to 1+ in the splenic aspirate, and at least one of the following: a white-cell count 4.0×10^6 per liter, hematocrit ≥ 30 percent, or a 10 percent weight gain. The absence of signs and symptoms of leishmaniasis for at least three months was also required after the criteria just described were met.

Laboratory Analysis

The laboratory tests performed routinely in our study were a white-cell count, differential white-cell count, hematocrit, hemoglobin measurement, biochemistry profile, and urinalysis; a chest x-ray film was also obtained. Electrocardiography was performed in all patients. Lymphocyte-blastogenesis assays were performed on mononuclear cells obtained from heparinized venous blood after Ficoll-Hypaque density-gradient centrifugation as previously described.⁷ The cells were stimulated with *Leishmania donovani chagasi* soluble antigen⁷ in a concentration of 1 μ g per milliliter of culture medium for five days. Uptake of [^3H]thymidine (New England Nuclear, Boston) was measured, and the results were expressed as a stimulation index (counts per minute of stimulated culture/counts per minute of unstimulated culture). A stimulation index ≥ 4 was considered positive for leishmanias.

Historical Controls

A total of 101 patients with a diagnosis of visceral leishmaniasis were hospitalized at the Hospital Professor Edgard Santos during the decade before the study (1976 through 1985). Fourteen patients were excluded because they either received fewer than 10 days of antimony therapy or did not have diagnostic results on bone marrow aspiration. Splenic aspirations were not performed in Bahia until 1986. The charts of 87 patients were reviewed for age, duration of illness, history of antimony therapy, and therapeutic response. Of these 87 patients, 55 were selected by a random-table method for a more detailed analysis of clinical characteristics before and after antimony therapy.

Statistical Analysis

The difference in response rates was compared by the two-tailed chi-square test. Differences in other variables were compared by Student's t-test.

RESULTS

The first patient to receive interferon gamma and antimony had refractory visceral leishmaniasis and had received seven courses of antimony (totaling 90 days) during the previous 20 months (Table 1). Despite therapy, she had persistent fever, abdominal swelling, weight loss, pancytopenia, and epistaxis. Examination of a splenic aspirate showed a leishmania index of 5+. She underwent 10 days of treatment with interferon gamma (50 μ g per square meter per day, given intramuscularly) and pentavalent antimony (20 mg per kilogram per day, given intravenously). One day after the completion of therapy, a splenic aspirate was negative for leishmanias. On the basis of this dra-

Table 1. Patient Characteristics and Results of Treatment with Interferon Gamma and Antimony in Patients with Refractory Visceral Leishmaniasis (Group 1) or Previously Untreated Visceral Leishmaniasis (Group 2).*

PATIENT NO.	AGE (YR)	DURATION OF ILLNESS (MO)	PREVIOUS ANTIMONY TREATMENT			STUDY TREATMENT		
			NO. OF COURSES	DOSE (mg/kg/day)	TOTAL NO. OF DAYS	INTERFERON GAMMA		ANTIMONY (20 mg/kg/day)
						dose (μg/day)	no. of days	no. of days
Refractory disease (Group 1)								
1	8	24	7	20	90	35	10	10
2	3	15	6	16	40	50	20	20
3	2	10	3	30	20	50	20	20
4	11	18	3	16	40	125	20	40
						500	20	
5	6	24	6	24	60	50	20	30
						200	10	
6	12	30	3	18	40	125	40	60
						500	20	
7	5	9	3	16	40	100	20	20
8	5	6	2	20	40	60	20	20
Mean	6.5	17	4.1	20	46	109	28	28
Previously untreated disease (Group 2)								
9	7	3	—	—	—	100	20	20
10	2	1	—	—	—	35	10	10
11	13	6	—	—	—	100	10	20
12	23	12	—	—	—	125	6	20
13	3	6	—	—	—	55	10	20
14	6	12	—	—	—	70	20	20
15	12	7	—	—	—	100	10	20
16	17	2	—	—	—	125	10	10
17	6	Unknown	—	—	—	50	10	20
Mean	9.8	6	—	—	—	84	12	18
LABORATORY AND CLINICAL INDEXES								
						FOLLOW-UP (MO)		
WHITE-CELL COUNT (×10 ⁶ /liter)		HEMATOCRIT (%)	SIZE OF SPLEEN (cm)	WEIGHT (kg)	LEISHMANIA INDEX	LYMPHOCYTE SI		
value before treatment/value after treatment								
Refractory disease (Group 1)								
1	2/6	29/35	12/4	17/19	5+/0	1/13	17	
2	3/6	12/37†	13/7	12/14	6+/0	1/18	13	
3	4/6	22/26	14/10	10/12	5+/0	2/4	10	
4	5/6	31/38	11/6	22/24	6+/1+	1/1	7	
5	3/5	21/20	13/8	15/16	6+/1+	2/9	4	
6	2/5	29/25	20/16	34/36	6+/4+	3/2	11	
7	2/5	17/39†	18/14	16/16	6+/3+	2/7	16	
8	4/6	20/34	9/6	17/17	4+/0	No data	3	
Mean	3.1/5.6	23/32	14/9	18/19	5.5+/1.1+	1.7/7.7	10.1	
Previously untreated disease (Group 2)								
9	3/8	28/34	12/4	23/25	4+/0	<1/8	8	
10	4/6	28/36	6/1	12/13	3+/0	1/4	7	
11	2/1	29/32	10/7	28/31	5+/0	2/36	7	
12	3/2	27/29	11/4	56/61	4+/0	4/78	10	
13	3/5	25/33	16/10	13/14	4+/0	8/74	5	
14	4/3	31/31†	8/3	15/16	5+/0	1/9	4	
15	2/4	27/31	12/10	27/29	5+/3+	1/3	5	
16	2/6	20/28	18/1	40/49	5+/0	2/20	5	
17	1/15	14/27†	22/15	11/15	4+/0	No data	6	
Mean	2.6/6.0	25/31	13/6	25/28	4.3+/0.1+	2.4/29.0	6.3	

*SI denotes stimulation index. Pretreatment studies were performed within one week of the initiation of combination therapy, and post-treatment studies were done within one week of the completion of therapy, except for the stimulation index, which was determined 20 to 30 days after treatment was completed.

†The patient received a transfusion during therapy.

matic response, we subsequently treated seven more patients with refractory visceral leishmaniasis (Group 1) and nine patients with previously untreated visceral leishmaniasis (Group 2). The patients' clinical characteristics and laboratory-test results are summarized in Table 1.

Patients in Group 1 had a mean age (\pm SD) of 6.5 ± 3.6 years. The duration of their illness was 17 ± 9

months, and they had previously undergone 46 ± 21 days of antimony therapy. They had a mean hematocrit of 23 ± 7 percent, a spleen size of 14 ± 4 cm, and a leishmania index of $5.5+$ (SD, $0.8+$) in splenic aspirates. Despite their refractory disease, the combination of interferon and antimony resulted in a dramatic improvement in the clinical signs and symptoms of all patients in Group 1. Six of the eight patients in Group

I have remained asymptomatic for a mean of 10 ± 5 months (range, 3 to 17). The remaining two patients in Group 1 (Patients 6 and 7) had initial clinical improvement with combined therapy. Patient 6 became afebrile after 40 days of treatment with interferon and antimony and had an increased leukocyte count, but leishmaniasis persisted in the splenic aspirate (leishmania index, 1+). The patient had a clinical relapse within several weeks, with a leishmania index of 4+ in the splenic aspirate. An additional 20 days of combined therapy did not alter the leishmania index. The patient then received amphotericin B (total dose, 700 mg), with a resulting decrease in the leishmania index to 1+ after 35 days of therapy. Three months after the end of amphotericin B therapy, leishmaniasis could no longer be found in the splenic aspirate. Patient 7 also improved clinically after combined therapy, and the leishmania index in the splenic aspirate decreased from 6+ to 3+. During the next two weeks, however, his symptoms increased, and the leishmania index in a second splenic aspirate was 5+. Amphotericin B was given for 45 days (total dose, 450 mg), with a resulting reduction of the index to 1+. At the three-month follow-up, the patient's spleen had diminished markedly in size, and leishmaniasis was not found in the splenic aspirate.

Patients in Group 2 were severely ill with previously untreated leishmaniasis (Table 1). Their mean duration of illness was 6 ± 4 months. They were leukopenic (mean white-cell count, $2.6 \pm 1 \times 10^6$ per liter) and anemic (mean hematocrit, 25 ± 5 percent) and had splenomegaly (mean span, 13 ± 5 cm), with a large parasite burden (mean leishmania index, 4.3+ [SD, 0.7+]). Eight of the nine patients in Group 2 were successfully treated with the combination of interferon and antimony, with a mean follow-up of 6 ± 2 months (range, 4 to 10). The remaining patient, Patient 15, received the combination therapy for 10 days, with clinical improvement and a reduction in the leishmania index in the splenic aspirate from 5+ to 1+. Fever recurred after six weeks, however, and the leishmania index rose again to 3+. Subsequently, the patient received pentavalent antimony (20 mg per kilogram per day) for an additional 20 days; the symptoms resolved, and parasites were absent in the splenic aspirate.

Patients in both Group 1 and Group 2 had improvement in most of their laboratory-test results and clinical characteristics immediately after combined therapy. The mean increase from pretreatment values in the white-cell counts was 75 ± 59 percent in Group 1 and 170 ± 223 percent in Group 2. The mean increase in the hematocrit was 5 percentage points (from 26 to 31 percent) for all except the four patients who received transfusions. All the patients who received combined treatment had a diminution of splenic size within one week of completing therapy. The mean reduction in the longitudinal diameter of the spleen was 40 ± 16 percent in Group 1 and 54 ± 26 percent in Group 2. Weight gain was noted in 15 of the 17 patients. Finally, in 12 of 15 patients studied, a positive

blastogenic response to leishmania antigen (stimulation index ≥ 4) was observed 20 to 30 days after the end of therapy.

As another measure of the efficacy of treatment with both interferon and antimony, we compared the clinical response of the patients in Groups 1 and 2 with that of 87 patients with parasitologically confirmed visceral leishmaniasis who were hospitalized at the same hospital during the period from 1976 through 1985. These historical-control patients received pentavalent antimony (20 mg per kilogram per day) for a minimum of 10 days. Thirteen of 17 of the patients in Groups 1 and 2 (76 percent) were successfully treated with 20 or fewer days of combined therapy, whereas only 37 of 87 historical-control patients (43 percent) responded to antimony alone within 20 days ($P = 0.001$). To examine specific manifestations of disease, we compared a randomly selected sample of the control patients who received only antimony with the patients who underwent combined therapy (Table 2). The most striking difference was the greater reduction in the size of the spleen observed in the patients who underwent combined therapy as compared with the historical controls ($P = 0.0009$).

The principal side effect of interferon gamma was fever. All patients had elevations of temperature of at least 1°C within three to four hours of the interferon injections. The maximal temperature recorded was 40°C . Although 60 percent of the patients had fever associated with the administration of interferon throughout therapy, fever was readily controlled with either acetaminophen or dipyrone. We noted no seizures, abnormalities of liver chemistry, or renal, cardiac, or pulmonary dysfunction. One patient had mild nausea during interferon therapy. No local reactions were observed at the site of the injection of interferon. Four patients reported a sensation of "ant bites" at the site of the injection, and eight had mild fatigue, myalgia, and headache.

DISCUSSION

We treated 17 patients with visceral leishmaniasis with a combination of interferon gamma and pentavalent antimony. Six of eight patients (75 percent) with leishmaniasis that had been unresponsive to multiple courses of antimony were successfully treated with this regimen; two patients received additional therapy with amphotericin B. Eight of nine patients (89 percent) with previously untreated severe visceral leishmaniasis were also successfully treated with the combination of interferon gamma and antimony. All 17 patients, including the three patients who later received additional therapy, had improvement in symptoms, signs, and relevant laboratory measures; among other things, they gained weight and had a decrease in both the size of the spleen and the leishmania index in splenic aspirates.

The clinical response of patients with leishmaniasis to interferon and antimony was compared with that of historical-control patients given antimony alone. The combination therapy resulted in a greater reduc-

Table 2. Response of Patients with Visceral Leishmaniasis to Treatment with Interferon Gamma and Antimony and Response of Historical-Control Patients to Antimony Alone.*

PATIENT GROUP	No.	AGE (Yr)	DURATION OF ILLNESS (Mo)	LABORATORY INDEXES			REDUCTION IN SIZE OF SPLEEN (%)†
				HEMATOCRIT (%)	WHITE-CELL COUNT (×10 ⁶ /LITER)	SIZE OF SPLEEN (CM)	
				value before treatment/value after treatment			
Group 1	8	6.5±3.5‡	17.0±8.5	22.0±7.0/32.0±7.0	3.1±1.2/5.6±0.6	13.7±3.6/8.8±4.4	40±16
Group 2	9	9.8±7.0	6.1±4.1	25.0±5.0/31.0±3.0	2.6±0.9/6.0±4.0	12.7±5.0/6.0±4.8	54±26
Historical controls	55	10.2±6.8	7.1±5.6	23.9±4.9/29.6±5.4	3.1±1.7/4.8±1.9	12.5±4.2/9.8±5.1	24±25

*Plus-minus values are means \pm SD. See the text for an explanation of the patient groups. The size of the spleen was measured as the span below the left costal margin at the anterior axillary line.

†P = 0.0009 for the comparison of Groups 1 and 2 with the historical controls; P = 0.004 for the comparison of Group 1 with the historical controls; P = 0.001 for the comparison of Group 2 with the historical controls.

tion in the size of the spleen and may have reduced the duration of treatment, since 76 percent of the patients in Groups 1 and 2 were successfully treated with 20 or fewer days of therapy, as compared with 43 percent of the historical control patients. This observation requires confirmation in a double-blind comparison of interferon gamma and antimony with antimony alone.

Fever was the most common adverse reaction to interferon but was readily controlled with antipyretic agents. Treatment with interferon (up to 400 μ g per square meter per day) had no other clinically important toxic effects over a 10-to-60-day interval. Constitutional symptoms of fatigue, myalgia, and headache were common but not severe. Thus, the combination of interferon and antimony was efficacious and had no important toxic effects.

Interferon gamma is a glycoprotein with a molecular weight of 20,000 to 25,000 whose chief physiologic source is T cells. It has been shown to inhibit cell growth in the presence of lymphotoxin,²⁴ induce the expression of major histocompatibility complex Class I and Class II molecules,^{25,26} prime macrophages for killing tumor cells,²⁷ and enhance natural-killer-cell cytotoxicity.²⁸ In addition to its antiviral activity, it enhances the antimicrobial action of macrophages and a wide variety of host cells against approximately 20 different microbial pathogens, including both bacteria and protozoa.²⁹ Studies in patients with cancer have demonstrated that interferon gamma has antitumor effects.^{30,31} The administration of interferon gamma partially corrects the phagocytic-oxidative-metabolic defect in patients with X-linked chronic granulomatous disease.²¹ In patients with lepromatous leprosy, interferon gamma induces histologic changes in the skin at the injection site that are "similar to certain features of delayed-type hypersensitivity reactions of tuberculous leprosy."¹⁹

A potential explanation for the efficacy of interferon gamma in our study is that it enhances the intracellular killing of leishmanias. The normal immune response requires the interaction of macrophages and T cells.^{32,33} This response is mediated by presentation by the macrophage of processed antigen in conjunction with major histocompatibility complex Class II molecules to the T-cell receptor, in concert with the elaboration of interleukin-1 by activated macrophages. T-cell activation is triggered, resulting in a

blastogenic response and the production of interleukin-2, interferon gamma, and other cytokines. Interferon gamma enhances the ability of macrophages to eliminate intracellular pathogens.²⁹ Although it is likely that the administration of interferon corrects the immunosuppression associated with acute visceral leishmaniasis, we cannot exclude other explanations, such as the intracellular accumulation of antimony, an alteration in the pharmacokinetics of antimony, or a synergistic effect of interferon and antimony.

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SPECIAL ARTICLE

THE INCREASED NEEDS OF PATIENTS IN NURSING HOMES AND PATIENTS RECEIVING HOME HEALTH CARE

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Abstract To evaluate the effects of Medicare's prospective payment system and Medicaid's preadmission regulations on long-term care, we constructed clinical profiles in 1982 and 1986 of about 500 randomly selected patients from each of three types of facilities: nursing homes with relatively high proportions of Medicare patients (high-Medicare nursing homes; $n = 23$), traditional nursing homes ($n = 19$), and home health agencies ($n = 18$). Data were obtained directly from the care givers on the medical problems, problems requiring skilled nursing, and functional problems of these representative patients from 12 states.

For Medicare patients in high-Medicare nursing homes, the prevalence of medical problems and problems requiring skilled nursing increased substantially, whereas the prevalence of functional problems remained relatively unchanged. For example, from 1982 to 1986 there was a marked increase in the frequency of tube feedings (21 to 29 percent), oxygen use (6 to 14 percent), urinary tract

infection (7 to 13 percent), and diastolic hypertension (1 to 10 percent), but not difficulty in eating (48 to 51 percent) or speaking (28 to 29 percent). In contrast, in traditional nursing homes there was an increase in the prevalence of functional disability, but virtually no change in that of problems requiring medical and skilled nursing care. In home health care the functional care needs of Medicare patients increased significantly, and there was a slight increase in the prevalence of problems requiring medical and skilled nursing care.

We conclude that from 1982 to 1986 the needs of patients in long-term care increased substantially. This trend appears to result from Medicare's prospective payment system, which encourages earlier hospital discharge to long-term care settings, and from Medicaid's policy of deinstitutionalization. Meeting this greater need for care will be costly. We require a better system of reimbursing for long-term care and ensuring its quality. (*N Engl J Med* 1990; 322:21-7.)

THE rising demand for geriatric and long-term care in the United States as a result of increases in the elderly population^{1,2} may be straining our already

overtaxed and fragmented long-term care delivery system. Anecdotal evidence suggests that recent Medicare and Medicaid reimbursement and regulatory practices have increased the need for patient care in nursing homes and home health agencies. Evidence of the effect of such practices on hospital care is now available,³⁻⁶ but their effect, if any, on long-term care is unclear.

Implemented in 1983, Medicare's prospective payment system provides reimbursement based on diagnosis-related groups. It has reduced the length of stays

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