Bowel Perforation in Steroid-Treated Patients

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Gastrointestinal perforation in patients receiving glucocorticosteroid (GCS) therapy has been reported to have mortality rates as high as 100%. From 79 patients seen during a nine-year period, three groups were formed according to GCS dosage: group 1 (steroid perioperative coverage), group 2 (low-dose steroids, prednisone < 20 mg daily), and group 3 (high-dose steroids, prednisone ≥ 20 mg daily). Of 11 clinical presentation factors, only abdominal tenderness was consistently present in group 3. The mean delay from onset of symptoms to treatment for group 3 was 8.3 days and was in marked contrast to that for group 1 or 2, 1.7 and 2.2 days, respectively ($p < 0.005$). Mortality increased from 11.8% in group 1 to 13.3% in group 2 to 85% in group 3. High-dose GCS therapy decreased the clinical expression of peritonitis to the point that recognition and, therefore, treatment of gastrointestinal perforation were markedly delayed. In a patient receiving high-dose GCS, a high degree of clinical suspicion must accompany any new abdominal discomfort, and aggressive diagnostic efforts should be made to establish the cause. If abdominal pain persists, surgical exploration should be considered.

SINCE 1949, WHEN COMPOUND F was given to patients with rheumatoid arthritis, a number of glucocorticosteroids have been shown to be therapeutically effective against various medical conditions, including asthma, shock, disorders of connective tissues, inflammatory bowel disease, chemotherapy, and transplantation.

Unfortunately, numerous complications associated with glucocorticosteroids have become apparent. As early as 1950, Beck and co-workers[2] warned of an increased risk of colonic perforation in patients receiving steroids, and subsequently, other investigators[5,7,12,13,16,17] reported an anecdotal relationship between the use of glucocorticosteroids and colonic perforation. Furthermore, the risk of steroid-induced gastric and small bowel perforations was reported soon thereafter.[9,10,14,15]

The association between glucocorticosteroid use and gastrointestinal ulceration and perforation now is well established. Of additional concern is the recognition that mortality rates associated with intestinal perforation in patients receiving steroids range from 27 to 100%.[3,16,19]

We analyzed retrospectively 79 cases in which glucocorticosteroid use was coincidental with gastrointestinal perforation in an effort to determine the factors responsible for morbidity and mortality.

Materials and Methods

During the nine-year period from 1970 to 1978, 780 patients with gastrointestinal perforations (excluding those due to appendicitis) were treated at the Mayo Clinic. Of these, 369 patients had free intraperitoneal perforation and gross peritonitis documented either at surgical exploration or at autopsy. Only those patients in whom glucocorticosteroids were in use at or near the time of perforation were selected for this study. Seventy-nine patients met these criteria, and they were divided into three groups according to dosage of steroids. Because prednisone was the most common glucocorticosteroid used in this series, all other glucocorticosteroids have been expressed as prednisone equivalents with regard to their anti-inflammatory effects. The duration of glucocorticosteroid therapy was recorded for all three groups.

In group 1, there were 17 patients who were given preoperative steroid preparation (cortisone acetate, 200 mg, and prednisolone, 40 mg before surgery) as a precaution because of prolonged use of glucocorticosteroids within the previous two years. However, none was receiving glucocorticosteroid at the time of intestinal perforation. In group 2, there were 15 patients who were receiving glucocorticosteroids in an amount less than an equivalent of 20 mg of prednisone per day at the time of perforation of the bowel; the mean time on steroid therapy was 17.7 months. In group 3, there were 47 patients who were receiving glucocorticosteroids in doses greater or equal to an equivalent of 20 mg of prednisone per day at the

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TABLE 1. *Clinical Presentation of 79 Patients with Bowel Preforation*

Sign/symptom	Group 1 (17 pt)		Group 2 (15 pt)		Group 3 (47 pt)	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Abdominal pain	17	100	15	100	46	98
Fever*	17	100	11	73	23	50
Guarding	11	65	8	53	13	29
Rigidity	6	35	6	40	6(42)†	14
Increased leukocyte count‡	16	94	10	67	12(45)†	27
Decreased bowel sounds	10	59	7	47	12	26
Decreased bowel function	5	29	5	33	5(42)†	12
Abdominal distension	6	35	6	40	18	38
Nausea and vomiting	5	29	2	13	3(45)†	7
Abdominal mass	3	18	2	13	2(42)†	5
Free intra-abdominal air on x-ray	4(8)†	50	6	40	22	47

* Temperature higher than 38.3 C.
† Number within parentheses represents patients with available data.
‡ More than 9,500/mm³.

time of perforation of the bowel; the mean time on steroid therapy was 4.6 months.

The clinical presentation of each patient was evaluated as to the presence or absence of 11 clinical factors (Table 1) most often involved in patient management decision. These were noted at the time of diagnosis or just before death, if no diagnosis was made.

Case management was evaluated by estimating three time periods: from onset of symptoms to diagnosis, from diagnosis to appropriate therapy, and from onset to therapy. With the limitations of charting formats, times were approximated to within eight-hour limits. Overall mortality and surgical mortality were recorded for each group. Surgical procedures performed and postoperative convalescence were reviewed.

Results

The 17 patients in group 1 had a mean age of 44.3 ± 3.8 (SEM) years and a male–female ratio of 1.1:1. The 15 patients in group 2 had a mean age of 47.4 ± 5.5 (SEM) years and a male–female ratio of 1.3:1. The 47 patients in group 3 had a slightly higher mean age of 54 ± 5.4 (SEM) years, but a similar male–female rato of 1:1.

In most categories other than abdominal pain, the presenting signs and symptoms were considerably less prevalent in group 3 compared with those in either group 1 or 2 (Table 1). The clinical presentation in group 3 was often vague, making the diagnosis difficult or incorrect.

The indications for the administration of steroids varied among the three groups (Table 2). In groups 1 and 2, inflammatory bowel disease was the principal primary disease for which glucocorticosteroids were given, and small bowel sites predominated. Although free perforations are not seen frequently in Crohn's disease, group 1 included three patients who had free perforations without significant inflammatory reaction and four who had a localized abscess perforated, causing a more generalized peritonitis. All other pa-

TABLE 2. *Indication of Glucocorticosteroid Therapy in 79 Patients with Bowel Perforation*

Indication	Group 1 (17 pt)		Group 2 (15 pt)		Group 3 (47 pt)	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Inflammatory bowel disease	10	59	5	33	7	15
Crohn's	(7)*		(3)		(3)†	
chronic ulcerative colitis	(3)		(2)*		(4)	
Pulmonary disease	2*	12	4	27	1	2
Connective tissue disease	0	0	4*	27	12†	26
Myeloproliferative disease	1	6	1	7	11‡	23
Metastatic cancer	1	6	0	0	6†	13
Shock	2	12	0	0	2	4
Craniotomy	1	6	1	7	0	0
Hepatitis	0	0	0	0	2	4
Renal transplant	0	0	0	0	2	4
Others	0	0	0	0	4‡	8

* One death in groups 1 and 2.
† One survivor.
‡ Two survivors.

tients in group 1 had free perforations. In group 3, large bowel sites predominated and malignancies plus collagen-vascular diseases were more numerous. The sites of perforation are detailed further in Table 3.

The mean times to diagnosis ranged from 1.4 ± 0.86 (SEM) days in group 1 to 6.0 ± 1.09 (SEM) days in group 3 (Table 4). Not included in the figures for group 3 were 13 (27.7%) patients whose condition was not diagnosed before death (mean: 14 days before death).

Leukocyte counts recorded at diagnosis decreased from a mean of 16,135/mm^3 in group 1 to a mean of 14,700/mm^3 in group 2 to a mean of 10,035/mm^3 in group 3.

The overall mortality was similar in groups 1 and 2, 11.7 and 13.3%, respectively. Surgical mortality was 6.2% for group 1 and 7.1% for group 2. The overall mortality rate of 85.1% for group 3 is a sharp contrast to that of groups 1 and 2 (11.7 and 13.3%). Excluding the 13 patients of group 3 whose condition was never diagnosed, as well as the three patients whose condition was diagnosed but for whom surgery was not offered, the operative mortality was 77.4% (24 of 31 patients).

Perforations while the patients were receiving steroid therapy occurred after a mean of 17.7 and 4.1 months for groups 2 and 3, respectively. Furthermore, 27.3% of group 2 and 46.3% of group 3 suffered perforations within three weeks of the initiation of steroid therapy. No perforation occurred before the sixth day of steroid therapy.

The average postoperative stay for survivors in groups 1, 2, and 3 was 18.7, 19.5, and 16 days, respectively. Six of the seven survivors in group 3 had their condition diagnosed and were operated on within 2.5 days.

TABLE 3. *Site of Free Intraperitoneal Perforation in 79 Patients with Bowel Perforation*

Site	Group 1 (17 pt)		Group 2 (15 pt)		Group 3 (47 pt)	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Stomach	0	0	1	7	2	4†
Small bowel	11	65	7	47	17	36
duodenum	(2)	(12)	(4)	(27)	(8)	(17)
jejunum	(2)	(12)	(0)	(0)	(2)	(4)
ileum	(6)*	(35)	(3)	(20)	(7)	(15)
Meckel's diverticulum	(1)	(6)	(0)	(0)	(0)	(0)
Large bowel	6	36	7	47	29	60
ascending	(1)	(6)	(2)*	(13)	(4)	(9)†
transverse	(2)	(12)	(1)	(7)	(2)	(4)
descending	(0)	(0)	(1)	(7)	(2)	(4)
sigmoid	(3)*	(18)	(3)*	(20)	(20)	(43)‡

* One death at that site.
† Two survivors.
‡ Three survivors.

TABLE 4. *Clinical Correlations in 79 Patients with Bowel Perforation*

	Group 1 (17 pt)	Group 2 (15 pt)	Group 3 (47 pt)
Onset to diagnosis (days)	1.4 ± 0.86*	1.7 ± 0.46	6.0 ± 1.09
Diagnosis to treatment (days)	0.34 ± 0.08	0.50 ± 0.14	1.25 ± 0.49
Total time (onset to treatment) (days)	1.67 ± 0.90	2.20 ± 0.54	8.27 ± 1.31
Overall mortality (%)	11.7 (2/17)	13.3† (2/15)	85.1‡ (40/47)
Surgical mortality (%)	6.2 (1/17)	7.1 (1/15)	77.4 (24/31)

* Mean ± 1 Standard Error.
† Diagnosis not made in one case (2%); patient died 12 days after onset.
‡ Diagnosis not made for 27.7% of patients; mean time until death was 14 days.

The following two case histories reveal the vague features of the clinical presentations noted frequently in the overall series.

Case Reports

Case 1. A 52-year-old woman, who was receiving prednisone (80 mg daily for four weeks) for systemic lupus erythematosus, suffered intermittent, mild-to-moderate abdominal pain. Bowel function persisted, significant abdominal findings were absent, and neither temperature nor leukocyte count was elevated. Surgical exploration, which was prompted by the persistence of abdominal pain, past history of diverticulitis, and blood cultures that were positive for enteric bacteria, was performed within 12 hours of the notification of the positive blood cultures but 18 days after the onset of abdominal discomfort. Gross peritoneal contamination was found from a sigmoid diverticular perforation, and a Hartmann procedure was performed. Despite appropriate surgical care, the patient died on the second postoperative day.

Case 2. A 65-year-old woman with quiescent chronic ulcerative colitis while on prednisone therapy (20 mg daily for two months) because of dementia of unknown origin noted the onset of abdominal pain, fever, and gradual increase in abdominal girth. On physical examination, there was abdominal guarding. The leukocyte count was increased. The daily prednisone dose was increased to 60 mg, and all symptoms ceased and the fever and the leukocyte count returned to normal. During the next week, bowel function remained normal and abdominal examination revealed no abnormalities, so the steroid dose was reduced gradually. As the dose of glucocorticosteroid was decreased, first the abdominal tenderness returned, followed by abdominal guarding, and finally one week later, by a spiking fever. Hemodynamic instability resulted, and the patient died. Postmortem examination showed an old right subphrenic abscess, as well as 750 ml of purulent intra-abdominal fluid from an old, yet unhealed, perforation of the descending colon.

Discussion

Diffuse peritonitis secondary to gastrointestinal perforation is associated with a high mortality rate, even in patients who have no additional medical risks. Medical problems existing when perforation occurs further increase morbidity and mortality. However,

TABLE 5. *Clinical Presentation of Group 3 and Subgroup with Malignancy*

Sign/Symptom	Percentage of Patients: Subgroup with Malignancy (17 pt)	Percentage of Patients: Entire Group 3 (47 pt)
Abdominal pain	92	98
Fever*	58	50
Guarding	58	29
Rigidity	17	14
Increased leukocyte count†	33	27
Decreased bowel sounds	17	26
Decreased bowel function	8	12
Abdominal distension	0	38
Nausea and vomiting	0	7
Abdominal mass	0	5
Free intra-abdominal air on x-ray	33	48

* Temperature greater than 38.3 C.
† More than 9,500/mm³.

in this at-risk group, the mortality becomes unacceptably high when perforation occurs in patients receiving large doses of glucocorticosteroids. In this series, the overall mortality of 85.1% in group 3 (more than 20 mg of prednisone per day) is in sharp contrast to that in groups 1 and 2, in which mortality was 11.7 and 13.3%, respectively.

Medical problems antedating perforation of the bowel for which glucocorticosteroids were given were formidable and, undoubtedly, adversely influenced the overall mortality. Patients with myeloproliferative disorders (23%), connective tissue disease (26%), and metastatic cancer (13%) made up 62% of group 3. When these subgroups are compared with the entire group 3, no major differences are noted. For example, the clinical presentation of a subgroup with malignancy (17 of 47 patients) when compared with the clinical presentation of the entire group 3 (Table 5) is similar in most areas except for a higher frequency of peritoneal irritation on physical examination and of elevated leukocyte counts. A slightly lower percentage of undiagnosed cases, 23.5%, was found. In all other areas, there were no differences. Of the seven survivors in group 3, three were from the malignancy subgroup. The more severe disease states in group 3 may account for some of the high mortality. However, because none of the subgroups demonstrated significant differences from the others in clinical presentation and because the survivors in group 3 were distributed randomly throughout the entire group, other major factors must be involved in causing the high mortality for group 3.

Group 3 included a higher percentage of patients with perforations of the large bowel than did either group 1 or 2. Because of the higher bacterial colony count in the colon, colonic perforations would be expected to have a higher incidence of complications. However, five of the seven survivors in group 3 had colonic perforations. This trend in group 3 suggests that factors other than site of perforation alone contributed to the high mortality rate.

The high incidence of sigmoid colonic perforations and major medical problems must contribute to the mortality in group 3. However, a third factor—the elapsed time from onset of symptoms to treatment—appears to be more significant with respect to the high mortality. The mean time from onset of symptoms to surgical treatment in group 3 (8.27 days) for those receiving treatment is almost five times that in group 1 (1.67 days) and four times that in group 2 (2.20 days). The difference between the delay before treatment in group 3 and the delay before treatment in either group 1 or 2 is significant ($p < 0.005$), particularly when considering that six of the seven survivors in group 3 were treated within 2.5 days. Furthermore, among the 47 patients in group 3, the time from diagnosis to treatment was less than 2.5 days for only eight patients. The mortality rate for the nine patients from groups 1 and 2, in whom the total delay was greater than 2.5 days, was 44% (four patients). Of the three factors discussed (site, primary disease, and delay), delay in treatment appears to be the most important factor affecting mortality.

Prolonged delay before treatment in group 3 can be explained on the basis of the differences in clinical presentation among the three groups. Only three of 11 categories showed a similar frequency in all three groups. The remaining eight demonstrated a dramatic decrease in frequency for group 3.

The only consistent aid to the correct diagnosis in group 3 was the subjective expression by the patient of abdominal pain. Signs of peritoneal irritation were minimal or frequently absent. Rather than showing bowel defunctionalization, more than 85% of group 3 demonstrated normal daily bowel activity despite many patients having documented pneumoperitoneum or culture-positive septicemia. The presence of abdominal distention, nausea, or vomiting is of limited value in evaluating these groups. The method of patient selection tends to select those patients who have localized abscesses and, therefore, palpable masses. However, between 13 and 18% of groups 1 and 2 had abdominal masses on physical examination, while less than 5% of group 3 had abdominal masses. A search for free intraperitoneal air is often made to confirm the clinical suspicion of acute gastrointestinal perforation. Although the incidence that this roentgenographic sign was present is similar in all three groups, there are differences. In group 1 and less so in group 2, the diagnosis was made before roentgenographic confirma-

tion and frequently did not require roentgenographic confirmation. For example, in group 1, only eight of 17 (47%) patients had roentgenographic studies done, as compared with 15 of 15 (100%) in group 2 and 42 of 47 (89%) in group 3. For 27.7% of group 3, the correct diagnosis was never made. For those who had a correct diagnosis, the finding of free intraperitoneal air had an important role in making the diagnosis and frequently was a serendipitous finding. Although free intraperitoneal air was found in 47.6% of group 3, it was present in 67% of those who had a correct diagnosis.

Glucocorticosteroids have predictable effects that help explain the vague expression of clinical peritonitis. A single large dose of glucocorticosteroid causes remarkable shifts in the leukocyte population in peripheral blood, resulting in lymphocytopenia, monocytopenia, and eosinopenia as well as a relative neutrophilic leukocytosis. Lymphocyte counts may decrease to 70% of the initial count and monocyte counts may decrease to 90%.[18] However, these counts return to normal within 24 hours.[6] Functional effects of glucocorticosteroids on leukocyte activity, such as suppression of phagocytosis and bactericidal activities of neutrophils, have been seen, but a major deficiency is that the cells do not reach the site of injury or toxin exposure. Chronic high-dose glucocorticosteroid treatment has been associated with depression of some cell-mediated lymphocyte functions.[1,4,20] Gill, et al.[8] observed that the administration of glucocorticosteroids to patients in a febrile state of septic shock consistently results in a dramatic reduction in temperature, often to below normal levels. This effect remains for four to six hours after each dose. These effects correspond to the observations from our present study.

Glucocorticosteroid use in a septic patient can predictably decrease the leukocyte count and cause hypothermia, as well as stop the inflammatory process responsible for the clinical expression of peritonitis. This masking effect of glucocorticosteroid appears to work by 1) decreasing the number and availability of immunoreactive participants, 2) depressing the chemotactic homing mechanisms to an area of insult, and 3) minimizing the necessary interreactions required for cellular immune defense. The dosage and dose-interval of glucocorticosteroid determine the chronicity and extent of immune tolerance and, thus, the inability to express clinical peritonitis.

If ideal, surgical treatment of a perforated viscus should be associated with a low mortality. The surgical mortality rates of 6.2% and 7.1% for groups 1 and 2, respectively, are low for gross peritonitis. However, the mortality rate of 77.4% for group 3 is unacceptably high. Although none of the numerous surgical procedures used in group 3 demonstrated any clear trends, there were fewer problems with further peritoneal contamination when both ends of the colon were exteriorized. Therefore, the surgical procedure alone probably does not change the mortality rates, but rather the early diagnosis combined with prompt appropriate surgical care does.

The length of time on glucocorticosteroid therapy suggests that the first three weeks of therapy may have the greatest potential risk for perforation. Although the mean time on glucocorticosteroid therapy when the perforation occurred (in groups 2 and 3) was 6.6 months (range: 6 days to 4 years), 40.3% perforated in less than three weeks. In addition, group 3 had a considerably higher incidence of perforation within three weeks than did group 2, 46.3% versus 27.3%. In Menguy's report[11] on free perforation in Crohn's disease, six of six patients were on glucocorticosteroid therapy, and five had perforation within three weeks of the introduction of glucocorticosteroid.

When a gastrointestinal perforation occurs in a patient taking high doses of glucocorticosteroids, the mortality rate can increase to more than 80%, as it did in this series. Because of the masking effect of glucocorticosteroid, the clinical presentation may be vague from onset to diagnosis. Abdominal discomfort is the only presenting factor that occurs with a high frequency in these patients. With most pertinent presenting signs and symptoms subdued, the diagnosis of perforation is often made from a serendipitous roentgenographic finding, unless there is a clinical awareness of the potential problems. A mean delay of 8.27 days from onset of symptoms to surgical therapy in group 3 appears to account for much of the increased mortality. Furthermore, the demonstrable effects of glucocorticosteroid on limiting the inflammatory reaction contribute to the delay in diagnosis by masking the clinical expression of peritonitis.

If better survival is to be obtained in patients receiving high doses of glucocorticosteroid when gastrointestinal perforations occur, a high level of suspicion must be maintained when the patient presents with any new abdominal discomfort. If pain persists, aggressive diagnostic efforts should be made, and early abdominal exploration should be considered. The exteriorization of colonic perforation prevents further peritoneal soiling from delayed suture line healing or breakdown. If the patient shows signs of sepsis while on glucocorticosteroid therapy, massive doses of glucocorticosteroid and appropriate antibiotics may offer enough time to initiate surgical care. When glucocorticosteroid use and gastrointestinal perforation occur together, the most important factors for patient survival are early recognition and prompt appropriate surgical intervention.

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