Implications of Leukocytosis and Fever at Conclusion of Antibiotic Therapy for Intra-abdominal Sepsis

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Outcomes of 65 patients after operation who had exhibited a clinical response to treatment for intra-abdominal sepsis were compared based on the presence or absence of leukocytosis and fever at the conclusion of antibiotic therapy. Fifty-one patients were afebrile when antibiotics were stopped. Intra-abdominal infection developed in 7 of 21 (33%) who had a persistent leukocytosis, but no intra-abdominal infections developed after operation in 30 patients who had normal WBC counts at the end of antibiotic treatment ($p < 0.005$). Nosocomial infections developed in 6 (12%) of the 51 patients, and there was no difference in the incidence between patients with or without leukocytosis. Eleven of 14 (79%) patients who were still febrile when antibiotics were discontinued developed infections after operation. Nosocomial infections occurred in three (21%) and intra-abdominal infections in eight (57%). Of the 15 patients who developed intra-abdominal infection after operation, only four responded to appropriate antibiotic treatment without requiring further surgery. The other patients required surgical management for definitive control within two months of the initial operation. In conclusion, patients at risk of developing infection after operation after exhibiting a clinical response to treatment of intra-abdominal sepsis are those who are afebrile with a persistent leukocytosis or who are still febrile when antibiotics are stopped.

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A PERSISTENT LEUKOCYTOSIS in an afebrile patient who has exhibited a clinical response to therapy for intra-abdominal sepsis is associated with a risk of developing postoperative infectious complications that usually require surgical management.[1] This finding accrued from an interim analysis of 31 patients who were enrolled in an intra-abdominal sepsis study to compare the efficacy of two antibiotic regimens. The study has been completed, and a large number of patients has been evaluated. Other reports from that study are in preparation. In this report, the postoperative outcomes of 65 patients have been compared based on the presence or absence of both leukocytosis (white blood cell count [WBC] $\geq 10{,}000/mm^3$) and fever (temperature > 37.6 C) when antibiotic therapy was discontinued. All patients had exhibited a clinical response to treatment for intra-abdominal sepsis before the study antibiotics were stopped.

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Patients and Methods

Patients hospitalized at University Hospital or Harborview Medical Center at the University of Washington School of Medicine in Seattle and suspected of having intra-abdominal sepsis that would require surgical drainage were assigned to receive clindamycin-gentamicin or chloramphenicol-gentamicin after informed consent was obtained. Antibiotic regimens were started before or during operation, and patients in whom intra-abdominal sepsis was documented surgically by the presence of an abscess, an infected biliary tree requiring decompression, a perforated hollow viscus, or necrotic tissue requiring debridement were continued on the study. Antibiotics were administered after operation until the patient was afebrile for at least 24 to 48 hours or had received a maximum of 10 to 14 days of treatment when fever persisted.

The patients who are the subject of this report had demonstrated a clinical response to treatment with stabilization of hemodynamic and ventilatory values, return of intestinal activity, normalization of laboratory values, and clearing of the sensorium. Study antibiotics had been administered for at least five days (one patient was treated for four days) and were appropriate for the results of intraoperative cultures. Fifty-one patients had been afebrile for at least 24 to 48 hours before antibiotics were discontinued, and 14 patients were still febrile when treatment was stopped. No deaths occurred prior to the 14th day after operation, and all patients

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TABLE 1. *Postoperative Outcome for 30 Afebrile Patients with WBC Counts ≤10,000/mm³ at Conclusion of Antibiotic Therapy*

Patient	Age (yr)	Diagnosis at Surgery	Outcome
1	46	Ruptured tubo-ovarian abscess	Rectovaginal fistula developed on 8th day after operation treated with sigmoid colostomy and pelvic drainage. On chronic steroid therapy for rheumatoid arthritis.
2	90	Perforated cholecystitis	Presented with *S. aureus* wound abscess on 46th day after operation.
3	70	Perforated sigmoid diverticulitis	*S. aureus* and enterococcus UTI 22nd day after operation treated with ampicillin.
4	66	Small bowel infarct	Klebsiella pneumonia, and septicemia treated with chloramphenicol, gentamicin, and cephalothin beginning on 8th day after operation. Died on 14th day after operation of cardiorespiratory collapse and GI hemorrhage.
5	76	Empyema of gallbladder, small bowel ischemia	Recovered
6	28	Small bowel infarct	Recovered
7	47	Perforated sigmoid diverticulitis	Recovered
8	33	Subphrenic abscess	Recovered
9	29	Perforated appendicitis	Recovered
10	33	Pelvic abscess	Recovered
11	52	Small bowel and colon infarct	Recovered
12	50	Perforated duodenal ulcer	Recovered
13	51	Perforated duodenal ulcer	Recovered
14	25	Perforated appendicitis	Recovered
15	65	Perforated duodenal ulcer	Recovered
16	43	Perforated duodenal ulcer	Recovered
17	19	Appendiceal abscess	Recovered
18	18	Anastomotic leak with abscess	Recovered
19	53	Small bowel perforation	Recovered
20	26	Crohn's ileitis with perforation	Recovered
21	80	Strangulated femoral hernia	Recovered
22	27	Infected pelvic hematoma	Recovered
23	31	Perforated appendicitis	Recovered
24	59	Ileal infarct	Recovered
25	77	Acute cholangitis	Recovered
26	26	Crohn's ileitis with perforation	Recovered
27	71	Perforated duodenal ulcer	Recovered
28	30	Small bowel infarct	Recovered
29	74	Ischemia colitis	Recovered
30	94	Bile peritonitis	Recovered

were followed for at least 30 days. Postoperative infectious complications have been compared overall and for nosocomial (postoperative wound, urinary, pulmonary, and intravenous catheter) and intra-abdominal infections. Statistical analysis of the data was by the chi square, Student's t-test, and binomial tests.

TABLE 2. *Postoperative Outcome for 21 Afebrile Patients with WBC Counts > 10,000/mm³ at Conclusion of Antibiotic Therapy*

Patient	Age (yr)	Diagnosis at Surgery	Outcome
1	54	Pelvic abscess	Sigmoid resection with colostomy and drainage pelvic abscess on 15th day after operation.
2	27	Perforated appendicitis	Febrile on 5th day and pelvic phlegmon diagnosed on 7th day after operation. Responded to IV clindamycin and gentamicin and postoperative doxycline.
3	36	Perforated Crohn's ileitis	Febrile on 8th day after operation. Antibiotic therapy restarted. Laparotomy on postoperative day 16 to drain intra-abdominal abscess secondary to multiple ileal fistulae.
4	76	Emphysematous cholecystitis	Pericholecystic abscess drained at cholecystectomy on 41st day after operation.
5	21	Appendiceal abscess	Transrectal drainage of pelvic abscess on postoperative day 12.
6	58	Cecal necrosis and intra-abdominal abscess	Died on 28th postoperative day with cardiorespiratory failure, septicemia, enterocutaneous fistula, and wound dehiscence.
7	56	Pelvic abscess	Incision and drainage of LLQ abscess complicating an enterocutaneous fistula on 36th day following operation.
8	20	Gangrenous appendicitis	Infected wound seroma drained 7th day after operation.
9	73	Perforated diverticulitis	Laparotomy for intra-abdominal sepsis on 29th day after operation revealed pancreatitis. Died on 48th day after operation of progressive renal failure.
10	54	Malignant cecal perforation	Died three months after operation of metastatic pulmonary disease.
11	90	Appendiceal abscess	Recovered
12	36	Cecal necrosis and intra-abdominal abscess	Recovered
13	57	Acute cholangitis	Recovered
14	48	Perforated gastric ulcer and intra-abdominal abscess	Recovered
15	22	Toxic megacolon	Recovered
16	57	Acute cholangitis	Recovered
17	80	Perforated duodenal ulcer	Recovered
18	70	Perforated appendicitis	Recovered
19	22	Perforated appendicitis	Recovered
20	51	Perforated duodenal ulcer	Recovered
21	27	Subphrenic abscess	Recovered

Results

The postoperative outcomes for 51 patients who were afebrile and clinically well at the conclusion of antibiotic therapy for intra-abdominal sepsis are presented in Tables 1 and 2. Thirty patients (Table 1) had normal WBC counts when study antibiotics were stopped, and 21 patients (Table 2) had leukocytosis. The diagnoses confirmed at the initial operation for treatment of intra-abdominal sepsis are listed for all patients. The average age for both groups of patients was 50 years. Patients with normal WBC counts ranged in age from 18 to 94 years, and those with leukocytosis ranged from 20 to 90 years. The average length of time study antibiotics were administered to patients with leukocytosis (9.3 days) exceeded by 1.7 days, the average length of ad-

TABLE 3. *Analysis of Postoperative Infectious Complications in 51 Patients Who Were Afebrile and Clinically Well at Conclusion of Antibiotic Therapy*

WBC Count No./ mm³	Patients No.	Nosocomial Infection* No. (%)	Intra-abdominal infection No. (%)	Total Infections No. (%)
≤10,000	30	4 (13)†	0 (0)§	4 (13)‖
>10,000	21	2 (10)†	7 (33)‡§	9 (43)‖
TOTAL	51	6 (12)	7 (14)	13 (26)

* Includes postoperative wound infections.
† NS (chi square).
‡ One patient responded to continuing culture-specific antibiotic treatment and did not require further surgery.
§ $P < 0.005$ (chi square).
‖ $P < 0.025$ (chi square).

ministration to patients with normal WBC counts ($p < 0.025$). There was no significant disparity between the two antibiotic regimens in the distribution of patients with or without leukocytosis or in the distribution of patients who recovered with treatment (chi square). One patient without leukocytosis died on the 14th day after operation from complications of sepsis. Three patients with leukocytosis died within three months of surgery, and one death was due to sepsis on the 28th day after operation.

Infectious complications after operation are analyzed for these 51 patients in Table 3. Postoperative wound infections occurred in two patients without leukocytosis and in one with leukocytosis when antibiotics were stopped. The total nosocomial infection rate was 12%, and there was no significant difference in the rate between patients with or without leukocytosis. No intra-abdominal infections occurred after operation in 30 patients who had normal WBC counts when antibiotics were stopped. Seven of 21 (33%) patients who had leukocytosis developed intra-abdominal infection ($p < 0.005$), and only one responded to continuing culture-specific antibiotic treatment without requiring operation. The total infection rate after operation for 51 patients was 26%, and the rate for patients with leukocytosis was significantly higher (43% vs. 13%, $p < 0.025$).

The postoperative outcomes for 14 patients who had responded to treatment but were still febrile (average maximal temperature = 38.0 ± 0.3 C) when study antibiotics were discontinued are shown in Table 4. These patients received study antibiotics for an average of ten days (range 5–15 days). There were two late deaths after operation (patients 1 and 11), and neither was related to the original septic episode. Twelve of the 14 patients had a persistent leukocytosis, and nine (75%) of these developed infectious complications after operation. Both febrile patients without leukocytosis developed an infection after operation. The total incidence of infection was 11 of 14 (79%), and the infections were not manifested until 4 to 18 days after discontinuing the study antibiotics (average nine days). Of the 11 patients who developed infection after operation, eight had an abdominal source. Three of these responded to appropriate culture-specific antibiotic therapy without requiring further surgical treatment. The nosocomial infections that developed in the three other patients were wound infections, and two required surgical drainage for control.

Three temperature patterns were observed during the study in these 14 patients. In three patients daily maximum temperatures progressively decreased to the normal range following termination of study antibiotic administration. These three patients recovered without further complications. Two patients whose fevers decreased while they received study antibiotics developed increasing temperatures when the antibiotics were discontinued, and the temperature did not decrease during antibiotic administration in the remaining nine patients. All 11 patients whose fevers persisted after antibiotics were stopped developed infectious complications after operation ($p < 0.001$), and only four of these patients responded to appropriate culture-specific antibiotic treatment without requiring further surgery.

Discussion

When antibiotics are discontinued in afebrile patients who have exhibited a clinical response to treatment for intra-abdominal sepsis, a persistent leukocytosis identifies those who are at risk of developing infections within one to two months after operation.[1] This analysis of 51 patients who were afebrile at the conclusion of antibiotic treatment has confirmed the predictive value of a persistent leukocytosis for infection after operation in this setting, and no patient who had a normal WBC count developed a subsequent intra-abdominal infection. Nosocomial infections occurred with comparable frequency in both groups of patients at a total rate of 12%. This value is very close to the average incidence of 10.4% reported from surgical services by other investigators.[2] The susceptibility of these patients to subsequent urinary, wound, pulmonary, and intravenous

TABLE 4. *Postoperative Outcome for 14 Patients Who Were Febrile at Conclusion of Antibiotic Therapy*

1*	76	Cecal necrosis	Postoperative ileostomy retraction with ileitis and wound soilage. Pneumonia complicated a chronic subdural hematoma. Required burr hole drainage and was treated with methicillin 18–22 after operation. Died 38 days after operation with ventilatory failure and coma secondary to recurrent head trauma and subdural hematoma
2*	37	Traumatic transection of pancreas and duodenal laceration	Operative removal of retained stent in pancreaticojejunostomy on 17th day after operation.
3*	29	Perforated appendicitis	Admitted on 16th day after operation with pelvic phlegmon. Treated with chloramphenicol and gentamicin.
4*	80	Acute cholangitis and hydrops of gallbladder	Cholecystectomy and common duct exploration with removal of stones on 7th day after operation.
5*	54	Perforated gastric ulcer	Recovered
6*	22	Gastric fistula (traumatic) with bilateral subphrenic abscesses	Spontaneous closure of gastric fistula documented by UGI on 14th day after operation.
7*	33	Pancreatic pseudocystjejunostomy anastomotic leak with abscess	Recovered
8*	22	Acute gangrenous cholecystitis	Abdominal wound abscess drained on 9th day after operation.
9*	55	Sigmoid anastomotic leak with pelvic and subphrenic abscesses	Treated with ampicillin between postoperative days 14–24 for pelvic phlegmon and drain tract infection.
10*	66	Pancreaticojejunostomy anastomotic leak with lesser sac abscess and necrotizing pancreatitis, body and tail	Resection of body and tail of pancreas, excision of pancreatic fistula, and jejunal limb closure on 29th postoperative day. No residual undrained infection.
11*	72	Malignant perforation of colon	Required resection of fistula and small bowel segment and drainage of intra-abdominal abscesses on 25th day after operation. Died of multisystem failure and disseminated lymphoma 51 days after operation.
12*	60	Appendiceal abscess, hydrops of gallbladder	Treated with penicillin and cephalothin between day 17 and 26 after operation for drain tract infection with localized abscess.
13†	80	Omental necrosis	*S. aureus* wound infection treated with methicillin between postoperative days 20–23.
14†	28	Intra-abdominal and pelvic abscesses, enterocutaneous fistula	Enterocutaneous fistula documented on postoperative day 15. Fistula tract infection treated with ampicillin days 24–30 after operation.

* WBC > 10,000/mm^3 at conclusion of antibiotic therapy.

† WBC ≤ 10,000/mm^3 at conclusion of antibiotic therapy.

catheter infections appeared independent of the leukocyte response at the time antibiotics were discontinued.

A leukocytosis at the end of antibiotic treatment in an afebrile patient may reflect a persistance of bacteria or their products in the original intra-abdominal septic focus that is stimulating neutrophil release into the peripheral circulation. Phagocytosis of bacteria and endotoxin by neutrophils releases leukocyte endogenous mediators (LEM), including endogenous pyrogen (EP), into the circulation. Fever is induced by EP, and the LEM interact with the bone marrow to stimulate granulopoiesis and the release of neutrophils into the circulating pool.[3-9] While these proteins share some properties, they may not be identical, and it is possible that bacteria can persist in tissues and be associated with leukocytosis without a febrile response.[10,11] Leukocytosis at the end of antibiotic treatment for intra-abdominal sepsis should alert the clinician to the possibility of a residual septic focus even in the absence of

fever. The results of this study do not support a blind continuation of antibiotic administration, since most intra-abdominal infections after operation were suppurative in nature, required operative management, and could have been masked by antibiotic treatment. When a specific treatable infection cannot be identified in an afebrile patient who appears well but has a leukocytosis, antibiotics should be discontinued. Close follow-up is necessary for one to two months, since additional antibiotic or surgical treatment may eventually be required.[1]

Included in this study population were 14 patients whose clinical response to treatment fulfilled the criteria outlined in the protocol, except that they were still febrile when antibiotics were stopped. The decision to stop treatment was based either on the fact that the temperature was decreasing in association with a clinical response to treatment or on the protocol criterion that study antibiotics would not be continued beyond 10 to 14 days without a careful bacteriologic and clinical reevaluation. These patients were probably the more seriously ill in the study. Nosocomial infections occurred in three (21%), intra-abdominal infections in eight (57%), and the total infection rate after operation was 79%. Because these infections were not manifested for an average of nine days after the study antibiotics were discontinued, recurrence or persistence of fever in these otherwise well-appearing patients proved to be a sensitive predictor of subsequent infection that frequently required surgical management. The number of patients without leukocytosis (two) was too small to allow comparisons of risk for intra-abdominal and nosocomial infections to be statistically valid.

In this series of patients, the average duration of antibiotic treatment for intra-abdominal sepsis was 8 to 10 days. For most patients who were either febrile or had leukocytosis without fever when antibiotics were discontinued, reliance on a blind continuation of antibiotic administration would have been a potentially hazardous practice by delaying the manifestation of an occult infection. Other risks would include the induction of microbial resistance, suprainfections with resistant bacterial and fungal pathogens, and an increased incidence of adverse reactions.[12,13] A careful search for an infection that will respond to a culture-specific antibiotic or an appropriate operative procedure is mandatory in both groups of patients, especially when fever increases or persists after stopping antibiotics. If no source is identified, patients must be followed closely for at least two months to insure that appropriate treatment is administered if an infection after operation develops.

Conclusion

Patients with intra-abdominal sepsis who have exhibited a clinical response to operative and antibiotic management but have a leukocytosis without fever when antibiotics are discontinued, are at risk (33%) of developing an intraabdominal infection within two months after operation. Approximately 10% of the patients will develop a nosocomial infection. If fever persists when antibiotics are stopped, postoperative intra-abdominal infections may occur in over 50%, and the nosocomial infection rate may reach 20%. Most patients at risk for postoperative infection will require further surgical treatment for control, and in most patients, a blind continuation of antibiotics can mask a suppurative infection, delay definitive treatment, and exert other adverse effects. An afebrile patient with a leukocytosis and any febrile patient must be carefully evaluated to detect an infection that will respond to additional antibiotics or an operative procedure. If no infection is found, the patient should be followed closely after antibiotics have been stopped for at least two months to insure that any infectious complications that develop are appropriately managed.

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