Measurement of Lactate in Ascitic Fluid

An Aid in the Diagnosis of Peritonitis with Particular Relevance to Spontaneous Bacterial Peritonitis of the Cirrhotic

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Lactate concentrations were measured in the ascitic fluid of patients using the Monotest Lactate Kit, an inexpensive, reliable bedside test that gives results within 15 min. The values were significantly higher in 24 patients with proven bacterial peritonitis, eight of them with spontaneous bacterial peritonitis, than in 53 patients with uninfected ascites of various other etiologies. In only two patients from the latter group, both with hepatic carcinoma and peritoneal metastases, were the values in the range found in bacterial peritonitis. Lactate determination was at least as sensitive as measurement of WBC levels for diagnosing peritonitis. Serial determinations in two patients with peritonitis showed declining values as the disease responded to treatment. The test has particular relevance for patients with spontaneous bacterial peritonitis, because this disease, which is potentially life-threatening although frequently asymptomatic, requires immediate treatment, yet currently depends on time-consuming culture procedures for diagnosis.

Bacterial peritonitis is an important consideration when evaluating a patient with ascites (1, 2). The infection may be responsible for causing the ascites, such as can follow rupture of an intraabdominal organ, or it may complicate already existing ascites. The latter situation, which usually develops insidiously, occurs most commonly in persons with alcoholic cirrhosis and ascites and is referred to as spontaneous bacterial peritonitis (SBP) (3). This is a serious complication which may have a grave outcome unless immediate antibiotic treatment is instituted (4).

The diagnosis of peritonitis requires a high index of clinical suspicion, supported by the finding in the ascitic fluid of characteristics of an exudate and of large numbers of inflammatory cells (1, 5, 6). However, when SBP complicates preexisting ascites, the fluid often retains the features of a transudate. Thus, a definitive diagnosis depends on the results of culture of ascitic fluid for the presence of bacteria or fungi, a process which requires 24–48 hr for completion. Because early treatment can be critically important, even prior to receipt of culture results, heavy reliance has been placed on the ascitic fluid characteristics that suggest an infectious process. However, the data may be misleading because patients with peritonitis who have been partially treated with antibiotics may have low numbers of inflammatory cells and even negative cultures; conversely, patients with noninfected as-

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cites may have greater than expected numbers of inflammatory cells (4, 7). It is apparent that a rapid test that can reliably identify the presence of an infection would be of great value.

Recently, several investigators have shown increased levels of lactate in the cerebrospinal fluid (8, 9) and joint fluid (10) of patients with bacterial meningitis and septic arthritis, respectively. Furthermore, the test has appeared to reliably differentiate between aseptic and bacterial meningitis or arthritis and to be elevated even in patients who have been partially treated. Because a procedure has been developed recently that permits rapid determination of lactic acid, the present study was initiated to determine whether evaluation of lactate levels in ascitic fluid might be useful in identifying peritonitis and thus permit early institution of antibiotic treatment.

MATERIALS AND METHODS

Participants in this study were patients with ascites who had been admitted to the Veterans Administration Medical Center, Washington, D.C., the George Washington University Medical Center, Washington, D.C., and the Children's Hospital National Medical Center, Washington, D.C. between August 1, 1977, and February 1, 1980. There were 62 males and 17 females. Their ages ranged from 4 to 68 years, and averaged 40 years.

The ascitic fluid was obtained by direct aspiration of the peritoneal cavity using routine procedures. An aliquot of the fluid was placed at the time of paracentesis into a sterile tube for immediate measurement of the lactate levels or it was stored frozen at −20° C for later evaluation, performed in batches. From preliminary determinations of lactate levels in ascitic fluid, and, more recently, in cerebrospinal fluid (11), it is apparent that the level in these fluids remains stable provided they are stored at this low temperature. The aspirated fluid was analyzed also for the glucose and protein contents, examined by light microscopy for the presence of white blood cells (WBCs) and polymorphonuclear leukocytes (PMNs), subjected to examination after Gramstain, and cultured for aerobic and anaerobic bacteria by conventional techniques (12, 13). Patients were included in this study only if their ascitic fluid had been both cultured for organisms and evaluated for the lactate level. While every attempt was made to obtain results of the other listed tests, this could not always be accomplished because of logistical and practical considerations.

Lactate measurements were performed utilizing a standardized Monotest Lactate Kit (MLK) (Boehringer-Mannheim, Mannheim, West Germany) method (14), according to the technique of Noll (15) with modifications as directed by the manufacturers. In this test, lactate is oxidized to pyruvate by NAD and catalyzed by the enzyme lactate dehydrogenase (LDH), during which an equimolar concentration of NADH is produced. The amount of NADH, which can be measured spectrophotometrically, is equivalent to the concentration of lactate in the original specimen. The entire assay requires 15 min to complete and can be performed at the bedside. The specificity and reliability of this procedure has been established by comparison with a sensitive gas–liquid chromatography technique (16). In most instances, lactate was measured in only a single specimen; in a few, repeated aspirations were performed during the course of therapy as indicated by the clinical course.

For purposes of analysis, the patients were divided into three groups:

Group I consisted of 45 patients with ascites resulting from congestive cardiac failure or cirrhosis of the liver without evidence of malignancy and with negative bacterial and fungal cultures of the ascitic fluid. Two patients in this group had systemic sepsis caused by *E. coli*.

Group II consisted of 10 patients with ascites associated with metastatic carcinoma of the liver and with negative bacterial cultures. These patients were further subdivided into those without peritoneal metastases (8 patients) as defined at necropsy, and those with peritoneal metastases (2 patients).

Group III consisted of 24 patients whose ascites was associated with various aerobic or anaerobic bacteria or fungi. In 16 of the 24 cases, peritonitis followed the rupture of an abdominal viscus diagnosed either at surgery or necropsy. The status of the liver was recorded in 10 of these 16 patients and none had cirrhosis. The remaining 8 of the 24 cases, all patients with alcoholic cirrhosis, had SBP.

RESULTS

The ascitic fluid lactate concentrations of the 79 patients, grouped according to the predefined categories, are shown in Table 1 and Figure 1. The average value for group I patients (ascites of cardiac or hepatic origin) was 14.0 ± 1.2 mg/100 ml (standard error of the mean), none of them, including the two with generalized *E. coli* sepsis, having values in excess of 32 mg/100 ml. Among group II patients (ascites associated with hepatic malignancy), the average lactate level was 21.6 ± 4 mg/100 ml. The levels did not exceed 16 mg/100 ml in any of the eight patients without peritoneal metastases; in the two with peritoneal metastases, the values were 50 and 79 mg/100 ml, respectively. The results among the 24 patients with infected ascitic fluid differed strikingly. The average lactate value for this group was 77 ± 11.7 mg/100 ml, and no patient had a value that was less than 33 mg/100 ml. The values did not differ between those with SBP and those with peritonitis following a ruptured viscus. Moreover, with the exception of unusually high lactate values in both patients with fungal infection, the values in the patients with infected ascites were similar regardless of the offending organism. Thus, the

TABLE 1. ASCITIC FLUID LACTIC ACID LEVELS IN 79 PATIENTS WITH ASCITES OF DIFFERENT ETIOLOGIES

Group	*No. of patients*	*Average lactic acid levels (mg/100 ml)*	*Range of lactic acid levels (mg/100 ml)*
Ascites of cardiac or hepatic origin	45	14.0	2–32
Cardiac	15	17.2	2–30
Hepatic	30	12.5	5–32
Ascites due to malignancy	10	21.6	6–79
With peritoneal metastases	2	64.0	50, 79
Without peritoneal metastases	8	11.0	6–16
Ascites due to infection	24	77.0	33–226
According to type			
Spontaneous	8	83.0	33–195
Ruptured viscus	16	76.0	33–126
According to organism			
Klebsiella pneumoniae	4	57.0	32–44
Escherichia coli	10	78.5	33–190
Pseudomonas aeruginosa	2	63.5	48, 79
Enterococcus sp.	4	37.5	33–44
Bacteroides fragilis	2	78.5	68, 89
Candida albicans	2	213.0	20, 226

mean value was significantly higher in the group with infected ascites than it was in the group with ascites associated with hepatic or cardiac disease ($P < 0.001$) or the group with ascites due to malignancy ($P < 0.05$). Also, with the exception of the two cases of hepatic malignancy with peritoneal metastases, there was no overlap in the lactate levels between patients with and without peritonitis.

In two cases of *E. coli* peritonitis, ascitic fluid was obtained on three occasions during treatment

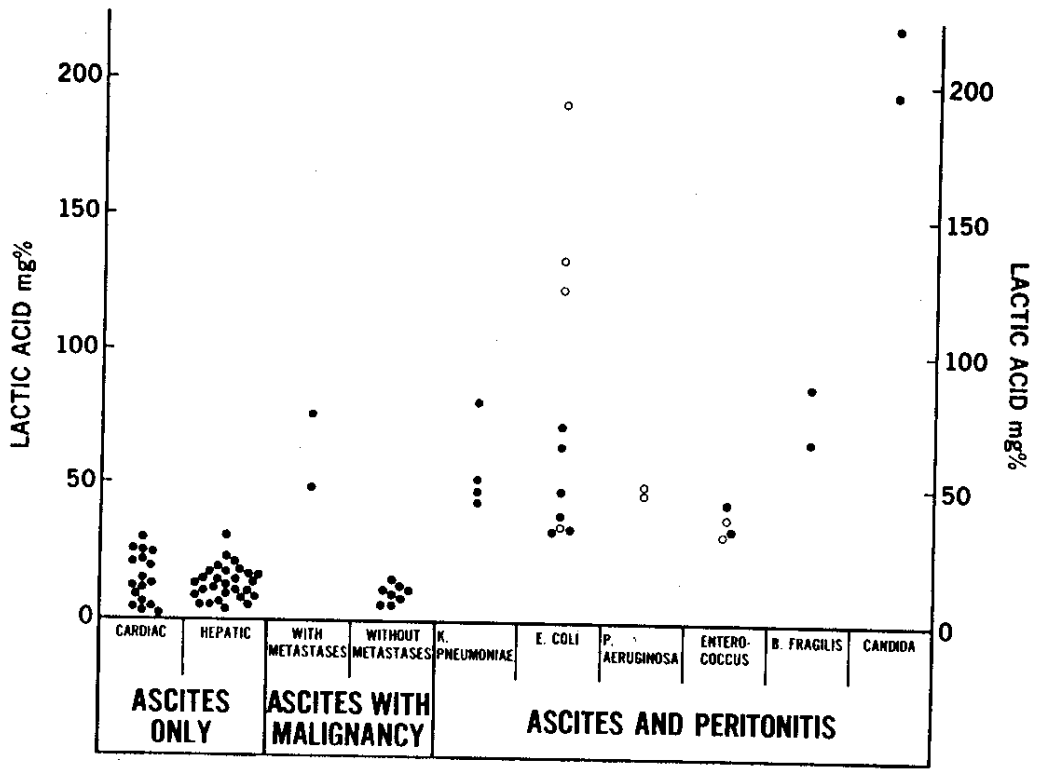

Fig 1. Lactic acid concentrations in the ascitic fluid of 79 patients with ascites due to cardiac and hepatic disease, carcinoma, and infection. (Note: Open circles in patients with ascites and peritonitis represent patients with spontaneous bacterial peritonitis).

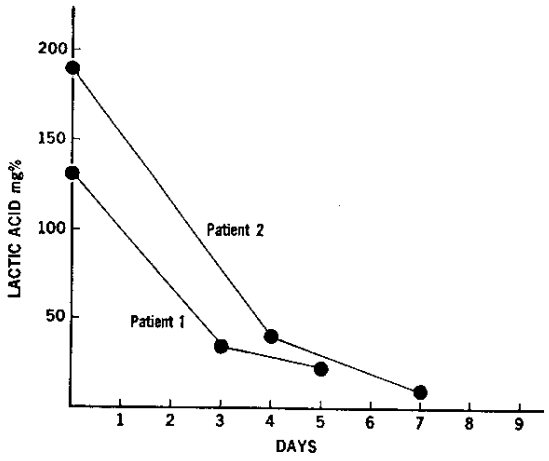

Fig 2. Sequential changes in ascitic fluid lactic acid concentrations in two patients with *E. coli* peritonitis during antimicrobial therapy.

with parenteral gentamicin and carbenicillin. As shown in Figure 2, lactate values declined as the disease improved.

As stated, because of logistic problems or miscommunication, not all of the requested tests were performed on each of the samples of the ascitic fluid examined for their lactate concentration. Thus, measurement of the ascitic fluid glucose and protein values and microscopic examination for the presence of WBCs and PMNs were all performed in only 40 of the patients, 20 in group I, 7 in group II, and 13 in group III. The chemical values did not reveal consistent findings. There were instances of exceedingly low glucose values in the absence of infection and, conversely, increased levels in patients with established peritonitis. Values for the ascitic fluid WBC and PMN counts, shown in Table 2, were helpful. In the group I patients, the WBC count did not exceed 400 cell/mm^3, with the exception of one patient with hepatic disease who had a count of 650 cells. The values were slightly higher in the patients with malignant ascites. The single value of 2200 cells/mm^3 was unexpected and unexplained, since the next highest value was 250 cells. The range and mean values of both the WBC and PMN counts in group III patients were strikingly higher than they were in the other two groups. With the exception of the one patient with a total WBC count of 400 cells, all patients in this group had a WBC count of 800 cells/mm^3 or more.

DISCUSSION

The rationale for a rapid, dependable, diagnostic test is the fact that bacterial peritonitis is a potential medical emergency. Generally, there is little difficulty in diagnosing peritonitis when it complicates an obvious catastrophic intraabdominal event such as a perforated viscus, in contrast to SBP which may be quite subtle in its presentation, often occurring in the absence of the classical findings associated with peritonitis. This is exemplified by the report from Correia and Conn that included 25 patients seen at one hospital during a 4-year period, representing 6.2 patients with SBP per year affecting approximately 16% of the patients entering the hospital with alcoholic cirrhosis and ascites during that time (4). They noted the presence of fever in only 63% of patients, local signs of peritonitis in only 46%, and a peripheral WBC count that was normal in 19% and even depressed in 4%. Nevertheless, the serious nature of SBP is evident from the fact that, although 48% responded to treatment, 24 of the 25 patients included in this report died, 15

TABLE 2. WHITE BLOOD CELLS AND POLYMORPHONUCLEAR LEUKOCYTES IN ASCITIC FLUID

Type of ascites	*No. of patients*	*White blood cells (number/mm^3)*		*Polymorphonuclear leukocytes (number/mm^3)*	
		Range	*Mean*	*Range*	*Mean*
Group I					
Cardiac-related	8	1–400	161	1–147	41
Hepatic-related	12	60–650	202	4–380	86
Group 2					
Malignant with peritoneal metastases	1	275		36	
Malignant without peritoneal metastases	6	15–2,200	446	1–132	30
Group 3					
Ascites due to infection	13	400–10,000	3823	12–10,000	2843

(60%) as a direct consequence of peritonitis. In another study designed to analyze the characteristics of the ascitic fluid in the alcoholic with cirrhosis, Wilson and coworkers noted that a significant number of noninfected patients had increased numbers of WBCs in the ascitic fluid, an increased percentage of granulocytes, an increased specific gravity, and elevated total protein concentrations (7). Thus, diagnostic reliance cannot be placed on the presence of fever, abdominal pain, or rebound tenderness, or on the specific gravity, protein concentration, glucose concentration, or gross appearance of the ascitic fluid. The most helpful ancillary test is the determination of the WBC and differential cell counts in ascitic fluid, although this examination has been subject to varying opinions regarding the appropriate diagnostic cutoff value. Weinstein et al reported that there is a high likelihood of the existence of SBP if the leukocyte count in the ascitic fluid is greater than 1000 cells/mm^3 and more than 85% of them are granulocytes (17). Bar-Meir et al, on the basis of an extensive analysis of 347 cirrhotic patients with ascites with differing etiologies, recommended that these patients receive treatment under the following circumstances: (1) if there are the typical clinical features of SBP, regardless of the WBC count in the ascitic fluid; (2) if the ascitic fluid contains more than 1000 WBCs/mm^3, even in the absence of symptoms; or (3) if the ascitic fluid contains more than 500 WBCs/mm^3 (or greater than 250 polymorphonuclear leukocytes) with clinical features compatible with SBP (6). However, in the study by Wilson et al, WBC counts in cirrhotic patients with noninfected ascites exceeded 1000 cells/mm^3 in 4% and 500 cells/mm^3 in 22% of them (7). In addition, 35% of these noninfected patients had polymorphonuclear leukocyte counts that were greater than 30%. In the present study, the WBC counts were helpful in distinguishing infected from noninfected ascites, although false positive and false negative results occurred.

Accordingly, the present data, although preliminary, suggest that the measurement of lactate levels in ascitic fluid may be a useful adjunctive test for establishing a diagnosis of peritonitis and differentiating it from other conditions which it can simulate. Lactate values greater than 32 mg/100 ml were found in all patients with infected ascites, regardless of the responsible organism. This finding was present more consistently in association with peritonitis than are the traditionally accepted features of fever, abdominal pain, abdominal tenderness, rebound tenderness, leukocytosis, and increased neutrophils in the ascitic fluid (3, 4). Furthermore, in the two patients in whom multiple samples of ascitic fluid were obtained, levels of ascitic fluid lactate declined sequentially as the patient's illness responded to antibiotic therapy. The only circumstance in which false positive results occurred was in patients with peritoneal metastases.

These findings, with obvious clinical relevance, are preliminary and require additional studies for confirmation. Unfortunately, the data from this study did not permit determination of the sensitivity of lactate measurement in patients who have been partially or inadequately treated with antibiotics. Furthermore, patients with ascites who had systemic lactic acidosis were not available during the course of this study for evaluation. Indeed, the mechanism responsible for the elevated lactate levels in infected ascitic fluid is presently uncertain. One explanation that has been offered for the elevated levels in the cerebrospinal fluid of patients with bacterial meningitis is that it might result from an alteration in the metabolism of WBCs (18). However, *in vitro* experiments indicate that leukocytes produce only minute amounts of lactate (8). Furthermore, patients with nonbacterial meningitis and normal concentrations of lactate usually have many polymorphonuclear leukocytes in the cerebrospinal fluid (9). Another suggestion is that elevated lactate levels may result from anaerobic glycolysis when leukocytes accumulate during meningitis in association with anoxic conditions in tissues (19). This mechanism has also been offered as accounting for the increased lactate levels in infected joints. Indeed, studies of synovial membrane metabolism have shown that there is a decrement in oxygen partial pressures in joints of patients with rheumatoid arthritis, accompanied by a decrease in pH and an increase in P_{CO_2} and lactate concentrations (20). These findings are taken to signify a changeover in local tissues from essentially aerobic to primarily anaerobic (glycolytic) metabolism. Other investigators have reported an inverse relationship between synovial lactate and glucose levels (21).

It is possible that the same mechanism accounts for the increased levels that occur in bacterial peritonitis; lactate may form as a "metabolic blind alley" in the metabolism of glucose, especially when anaerobic conditions prevail during infection. With regard to the high levels found in patients with

peritoneal metastases, it is conceivable that neoplastic tissue may create anoxic conditions which could enhance the production of lactate. It is apparent that additional studies are needed to confirm the specificity and sensitivity of this test for the diagnosis of peritonitis, determine the relationship between ascitic fluid and peripheral blood lactate values, and define the mechanism responsible for the increase in lactate levels. Such studies are presently in progress.

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