The Triad of *Streptococcus Bovis* Bacteremia, Colonic Pathology, and Liver Disease

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The association of *Streptococcus bovis* endocarditis and colon carcinoma has been reported previously in small series in the medical, but not surgical, literature. Although the fecal carriage rate of *S. bovis* increases with colonic pathology, no explanation exists for the development of bacteremia in these cases. To explore the possible contribution of hepatic dysfunction to the development of portal and systemic bacteremia, the incidence of both colonic pathology and liver disease or dysfunction was determined in 92 patients with *S. bovis* endocarditis and/or bacteremia. Colonic and liver evaluation had been undertaken in 47% and 93% of patients, respectively. Among these patients, colonic pathology was identified in 51%, and liver disease or dysfunction was documented in 56%. Either the underlying colonic disease or alterations in hepatic secretion of bile salts or immunoglobulins may promote the overgrowth of *S. bovis* and its translocation from the intestinal lumen into the portal venous system. A compromised hepatic reticuloendothelial system may then contribute to the development of *S. bovis* septicemia and subsequent endocarditis. We conclude that *S. bovis* bacteremia is an indication to the clinician of the possibility of underlying liver disease as well as colon pathology.

THE ASSOCIATION OF *Streptococcus bovis* endocarditis with adenocarcinoma of the colon was first reported in 1977 by Klein and associates.[1] Since then several retrospective series and case reports, as well as two prospective studies, have further documented that *S. bovis* endocarditis and bacteremia are associated with colonic neoplasms and polyps.[2–16] In addition the fecal carriage rate of *S. bovis* has been shown to increase with colonic pathology.[1] However these reports have been published in the medical, but not surgical, literature and have included relatively small numbers of patients. Moreover no data have been presented in the literature that explain why systemic bacteremias occur in these cases.

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To introduce this association to surgeons and to explore the possible contribution of hepatic dysfunction to the development of systemic bacteremia, the incidence of both colonic and liver disease was determined in 92 patients with *S. bovis* septicemia.

Methods

Patient Population

The records of all adult patients with positive blood cultures for *S. bovis* hospitalized at The Johns Hopkins Hospital from 1979 through 1988 were reviewed. Nonenterococcal group D streptococcal species were identified by the method of Facklam et al.[17] The presence of endocarditis was defined as the development of a new heart murmur and echocardiographic or pathologic documentation of cardiac valvular vegetations. Of 92 patients with *S. bovis* bacteremia, 26 (28%) were diagnosed as having endocarditis. The mean age of the patients with and without endocarditis was 58 and 56 years, respectively. The ages ranged from 20 to 90 years. Sixteen of the twenty-six (62%) patients with endocarditis were men, whereas 29 of the 66 (44%) patients with *S. bovis* bacteremia, but without endocarditis, were men. Nineteen of the twenty-six (73%) patients with endocarditis were white, six (23%) were black, and one (4%) was Oriental. Of the 66 patients with only bacteremia, 36 (55%) were white and 30 (45%) were black.

The presenting illnesses of the patients with *S. bovis* endocarditis and bacteremia are presented in Table 1. Eighteen of the twenty-six (69%) patients with endocarditis were admitted for that problem. In comparison, among the patients with *S. bovis* bacteremia, the most common

TABLE 1. *Presenting Illnesses*

Illness	Endocarditis (n = 26)	Bacteremia (n = 66)	All Patients (n = 92)
Infectious disease	20 (77%)	17 (26%)	37 (34%)
Endocarditis	18	0	18
Pyelonephritis	0	5	5
AIDS	1	4	5
Cholangitis/cholecystitis	1	2	3
Fever unknown origin	0	3	3
Spontaneous peritonitis	0	1	1
Infected aortic graft	0	1	1
Infected chest wall	0	1	1
Neoplastic	2 (8%)	16 (24%)	18 (20%)
Leukemia or lymphoma	1	8	9
Pancreatobiliary	0	3	3
Head, neck, esophagus	1	2	3
Breast	0	2	2
Multiple myeloma	0	1	1
Cardiovascular	2 (8%)	11 (17%)	13 (14%)
Coronary artery disease	1	8	9
Arrythmia	1	1	2
Miscellaneous	0	2	2
Gastrointestinal	1 (4%)	7 (11%)	8 (9%)
Hemorrhage	0	3	3
Pancreatitis	0	2	2
Obstruction/ischemia	0	2	2
Cirrhosis	1	0	1
Neurologic	1 (4%)	4 (6%)	5 (5%)
Obstetric/gynecologic	0 (0%)	3 (5%)	3 (3%)
Diabetes mellitus	0 (0%)	3 (5%)	3 (3%)
Sickle cell disease	0 (0%)	2 (3%)	2 (2%)
Drug overdose	0 (0%)	2 (3%)	2 (2%)
Pulmonary	0 (0%)	1 (2%)	1 (1%)

AIDS, acquired immune deficiency syndrome.

presenting illnesses were other infectious diseases (26%), neoplasms (24%), cardiovascular disease (17%), gastrointestinal problems (11%), neurologic disorders (8%), and a variety of other problems (14%). Interestingly none of these patients presented with a colonic neoplasm, and only two presented with complications of cirrhosis. The associated illnesses, excluding colonic and liver disease, are presented in Table 2. Hypertensive cardiovascular (24%), cerebrovascular (14%), and coronary artery disease (12%) were common associated diseases. Chronic pulmonary disease (13%), diabetes (11%), peptic ulcer disease (11%), and chronic renal disease (9%) were other frequently associated illnesses.

Colonic Evaluation

Patients were considered to have undergone colonic evaluation if they had sigmoidoscopy, colonoscopy, a barium enema, or pathologic examination of endoscopic biopsies or surgically resected specimens. Overall 43 of 92 (47%) patients completed colonic evaluation (Table 3). Nineteen of twenty-six (73%) patients with endocarditis and 24 of 66 (36%) bacteremia patients had their colons evaluated. Colonoscopy was performed on 19 of 31 (61%) patients undergoing lower intestinal endoscopy. Twenty-four patients (26%) had barium enemas and 21 (23%) had pathologic examination of biopsies and/or surgical specimens. Colonic findings were classified as either cancer, neoplastic polyps, or inflammatory conditions such as colitis or ischemia. Diverticulosis without evidence of inflammation was not included as a positive finding.

TABLE 2. *Associated Illnesses**

Illness	Endocarditis (n = 26)	Bacteremia (n = 66)	All Patients (n = 92)
Hypertensive cardiovascular disease	8 (31%)	14 (21%)	22 (24%)
Cerebrovascular disease	2 (8%)	11 (17%)	13 (14%)
Pulmonary disease	4 (15%)	8 (12%)	12 (13%)
Coronary artery disease	5 (19%)	6 (9%)	11 (12%)
Diabetes mellitus	3 (12%)	7 (11%)	10 (11%)
Peptic ulcer disease	2 (8%)	8 (12%)	10 (11%)
Chronic renal failure	2 (8%)	6 (9%)	8 (9%)
Chronic pancreatitis	0 (0%)	4 (6%)	4 (4%)
Carcinoma†	2 (8%)	1 (2%)	3 (3%)
Seizure disorder	0 (0%)	2 (3%)	2 (2%)
Myasthenia gravis	0 (0%)	1 (2%)	1 (1%)
Schizophrenia	0 (0%)	1 (2%)	1 (1%)

* Excluding colon and liver diseases.
† Lung-2, endometrial-1.

Liver Evaluation

Patients were considered to have undergone liver evaluation if serum chemistries were performed, including bilirubin, transaminase, and alkaline phosphatase levels; computerized tomographic (CT) or ultrasound scans of the liver; and/or liver biopsy. Eighty-four of ninety-two (91%) patients had serum bilirubin, transaminase, or alkaline phosphatase levels determined (Table 3). In addition 39 (42%) patients had either computerized tomographic or ultrasonic examination of the liver. Abnormal liver function tests were defined as either elevation of the transaminase or alkaline phosphatase values to twice normal values or a serum bilirubin of more than 2.0 mg/dL. Evidence of diffuse parenchymal liver disease on CT or ultrasound in association with abnormal chemistries or a

TABLE 3. *Colonic and Liver Evaluations*

Evaluation	Endocarditis (n = 26)	Bacteremia (n = 66)	All Patients (n = 92)
Colonic evaluation	19 (73%)	24 (36%)	43 (47%)
Endoscopy*	13 (50%)	18 (27%)	31 (34%)
Barium enema	14 (54%)	10 (15%)	24 (26%)
Pathology	11 (42%)	10 (15%)	21 (23%)
	(n = 26)	(n = 66)	(n = 92)
Liver evaluation	25 (96%)	61 (92%)	86 (93%)
Serum chemistries	25 (96%)	59 (89%)	84 (91%)
Liver scan†	15 (54%)	25 (38%)	39 (42%)
Liver biopsy	6 (23%)	12 (18%)	18 (20%)

* Colonoscopy or sigmoidoscopy.
† Computed tomography or ultrasound.

clinical history of alcoholism, cirrhosis, or hepatitis was also considered evidence of liver disease. Eighteen patients (20%) also had liver biopsies.

Results

Colonic Pathology

Colonic pathology was identified in 22 of 43 (51%) patients who underwent colonic evaluation (Table 4). A colon lesion was detected in 58% of patients with endocarditis and in 46% of those with *S. bovis* bacteremia (Table 4, Fig. 1). A colon cancer was identified in six (32%) of the patients with endocarditis who underwent either endoscopy or a barium enema (Fig. 2). Of the 6 patients with adenocarcinoma of the colon, 2 had carcinoma *in situ*, 2 had Duke's B, and 2 had Duke's C lesions. Furthermore two of these six patients had two separate carcinomas. Colonic polyps were found in an additional 5 of 19 patients with endocarditis (26%). These polyps were classified as tubulovillous adenomas in two patients, as tubular adenomas in two patients, and as a mixture of both in a patient with multiple polyps. No patient with endocarditis had an inflammatory colonic problem, although diverticulosis was identified in five of these patients. All cancers and polyps were identified concurrently with the episode of endocarditis. Interestingly one patient had a previous episode of *S. bovis* endocarditis 4 years before the current infection. Colonic evaluation at that time showed no evidence of disease. However, at the time of the current episode of endocarditis, colonoscopy revealed a cancer of the right colon. Overall 11 of the 26 patients (42%) with endocarditis had colonic disease (Fig. 3).

The spectrum of pathology was different in the 24 patients with *S. bovis* bacteremia without endocarditis who underwent colonic evaluation. Only 1 of the 24 (4%) evaluated patients was found to have a colorectal carcinoma, and this tumor was diagnosed 4 years after the episode of bacteremia. Four of these twenty-four (17%) patients with

TABLE 4. *Positive Evaluations**

Evaluation	Endocarditis (n = 19)	Bacteremia (n = 24)	All Patients (n = 43)
Colonic evaluation*	11 (58%)	11 (46%)	22 (51%)
Endoscopy	10 (77%)	6 (33%)	16 (50%)
Barium enema	3 (21%)	0 (0%)	3 (13%)
Pathology	11 (100%)	10 (100%)	21 (100%)
	(n = 25)	(n = 61)	(n = 86)
Liver evaluation*	13 (52%)	35 (57%)	48 (56%)
Serum chemistries	3 (12%)	24 (41%)	27 (32%)
Liver scan	7 (50%)	16 (64%)	23 (59%)
Liver biopsy	6 (100%)	12 (100%)	18 (100%)

* Percentages are of those evaluated.

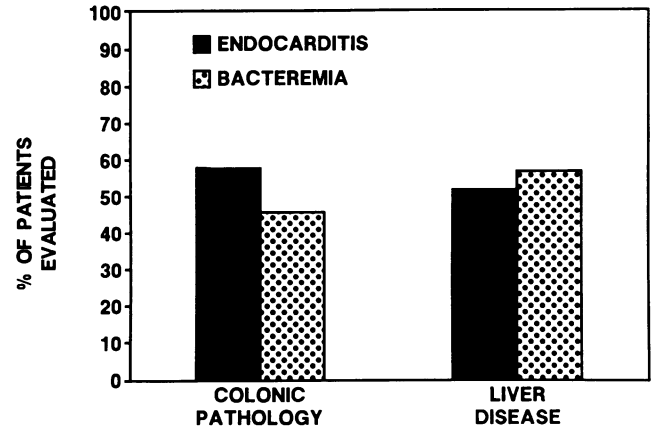

FIG. 1. Prevalence of colonic pathology (left) and liver disease (right) among evaluated patients with *S. bovis* endocarditis and bacteremia.

S. bovis bacteremia were found to have colonic polyps. These polyps included 2 tubular adenomas, 1 tubulovillous adenoma, and 1 villous adenoma. Six of these 24 (25%) patients had acute inflammatory conditions, including diverticulitis in 1, colonic ischemia with perforation in 1, and pseudomembranous, ulcerative, nonspecific, and radiation colitis in 1 each. All of these six patients presented with acute gastrointestinal complaints, and *S. bovis* was recovered from the blood during the septic presentation. In addition 5 of the 66 bacteremia patients also had evidence of diverticulosis without inflammation. Not counting these five patients, the prevalence of colonic disease in patients with *S. bovis* bacteremia undergoing co-

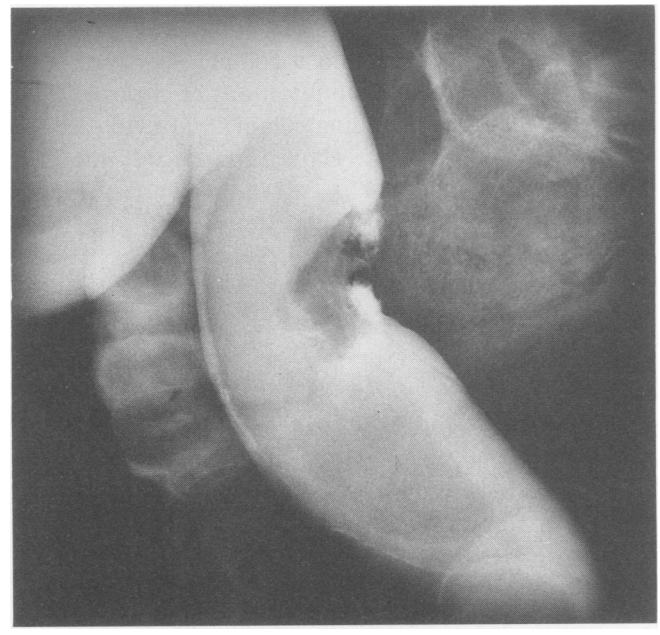

FIG. 2. Barium enema demonstrating a colon cancer in a patient with *S. bovis* endocarditis.

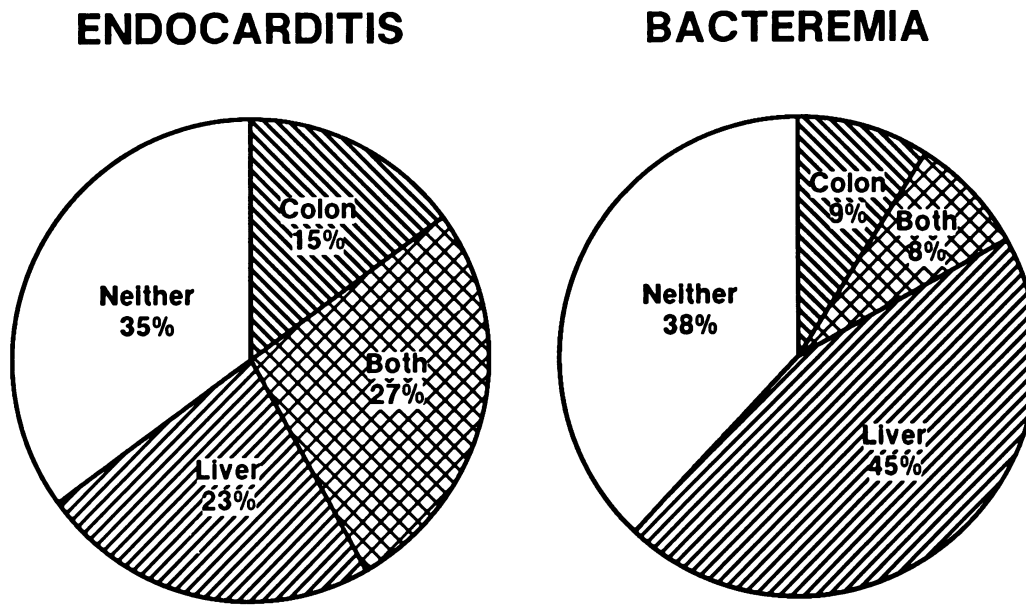

FIG. 3. Prevalence of colon pathology, liver disease, or both among all patients with *S. bovis* endocarditis (left) and bacteremia (right).

lonic evaluation was 46% (Table 4, Fig. 1). However only 11 of the 66 (17%) patients with *S. bovis* bacteremia had colonic pathology (Fig. 3).

Liver Disease

Liver disease and/or dysfunction was identified in 48 of 86 patients (56%) who underwent evaluation (Table 4). Liver disease was detected in 52% of patients with endocarditis and in 57% of those with *S. bovis* bacteremia (Table 4, Fig. 1). Abnormal liver chemistries were present in only 3 of 25 (12%) patients with *S. bovis* endocarditis in whom results were available. One patient was jaundiced, with a total bilirubin level of 6.7 mg/dL, whereas the other two had significant elevations of serum transaminase levels. Liver scans suggested parenchymal disease in seven (28%) endocarditis patients. Liver biopsies were abnormal in six (24%) endocarditis patients. Histologic findings of cirrhosis were present in three patients, whereas fatty infiltration, liver abscess, and a large benign cyst were each observed in one patient. Overall liver disease and/or dysfunction was documented in 13 of 26 (50%) patients with endocarditis (Fig. 3). Furthermore seven (27%) of these patients had documentation of both colon and liver disease.

Abnormal liver chemistries were present in 24 of 59 (41%) patients with *S. bovis* bacteremia (Table 4). Twelve of these twenty-four patients had jaundice, with total bilirubin levels ranging from 2.9 to 10.7 mg/dL. Sixteen of twenty-five (64%) bacteremia patients undergoing diagnostic imaging had evidence of liver disease (Fig. 4). Furthermore liver biopsies in 12 patients documented chronic passive congestion in 4, cirrhosis in 3, metastatic infiltration in 2 (breast cancer and leukemia), and central lobular necrosis, a liver abscess, and nonspecific changes in 1 each. Overall liver disease and/or dysfunction was documented in 35 of 66 (53%) patients with *S. bovis* bacteremia (Fig. 3). In addition 5 of 66 (8%) patients with bacteremia had both colonic and liver disease.

Discussion

In this retrospective analysis of 92 patients with *S. bovis* bacteremia, the previously described association with colonic pathology was confirmed. This study is the largest series documenting this association and the first in the surgical literature. Colonic evaluation was carried out in 47% of the patients with endoscopy, barium enema, and/or pathologic examination of biopsy or surgical specimens. Fifty-eight per cent of patients with *S. bovis* endocarditis and 46% of those with bacteremia had colonic pathology. Liver evaluation was also performed with serum chemistries in 91%, with liver CT or ultrasound scans in 42%, and/or liver biopsy in 20%. Liver disease was identified in 52% of patients with endocarditis and in 57% of those with bacteremia. Furthermore both colon pathology and liver disease were associated in 27% of the patients who developed *S. bovis* endocarditis. This additional association with liver disease has not been reported.

In recent decades an increasing proportion of endocarditis has been due to nonenterococcal group D streptococcus, and specifically the *S. bovis* species.[18] This association was first suggested in 1951 in a case report of 'enterococcal' endocarditis as the initial manifestation of carcinoma of the colon.[19] As bacteriologic techniques have allowed differentiation of *S. bovis*, Klein et al.[1] reported this association with two cases of colonic adenocarcinoma in patients with bacterial endocarditis. After this initial

FIG. 4. Computed tomogram demonstrating a small, nodular, cirrhotic liver and splenomegaly due to portal hypertension in the same patient (Fig. 2) with *S. bovis* endocarditis and colon cancer.

report, a number of case reports and small series have followed to support this association.[2–4,6,9–12,14,15] In three retrospective series the incidence of colorectal neoplasia, both benign and malignant, ranged from 18% to 50%.[5,13,16]

Two prospective analyses have also been completed to further define this association.[7,8] In 1981 Wilson and colleagues[8] studied 21 patients with *S. bovis* endocarditis and found that 62% of the patients had colonic disease, including 24% with inflammatory bowel disease, 14% with diverticular disease, 10% with colonic polyps, 10% with colonic villous adenomas, and 5% with carcinoma of the colon. Klein and associates,[7] in another prospective analysis of 15 patients with *S. bovis* bacteremia (five with endocarditis and four with probable endocarditis), performed colonoscopy or barium enema and sigmoidoscopy as part of a complete colonic evaluation in all patients. In that series, 13 patients were found to have gastrointestinal tumors or polyps. Eleven colonic neoplasms were detected, including 2 adenocarcinomas, 5 villous adenomas with microscopic evidence of carcinoma, 1 adenomatous polyp with microscopic evidence of carcinoma, and 3 adenomatous polyps without carcinoma. In this series two other patients had gastrointestinal malignancies, with one gastric carcinoma and one esophageal carcinoma. In addition one of the two patients without a gastrointestinal neoplasm had colonic diverticulosis. These prospective studies suggest that colon neoplasia can be expected in most cases of *S. bovis* endocarditis.

In the current retrospective review, patients with *S. bovis* infection were classified as having either endocarditis or bacteremia without endocarditis. The results of the current study confirm the previously reported association of colonic neoplasms in patients with *S. bovis* endocarditis. Among the 19 patients with endocarditis undergoing colonic evaluation, 58% were found to have colonic adenocarcinoma or neoplastic polyps. Although a similar overall incidence of colonic pathology (46%) was present in patients with *S. bovis* bacteremia undergoing evaluation, the spectrum of disease was markedly different. Neoplasia was much less frequent in the group with bacteremia, with only one cancer being detected several years after the episode. However the incidence of non-neoplastic colonic conditions such as colitis, diverticulitis, or ischemia were more common in these patients. In several of these patients the colonic disease was the primary indication for hospitalization, with the bacteremia developing during the course of the hospitalization. Although significantly fewer patients with bacteremia alone underwent colonic evaluation, follow-up suggests that these patients were not harboring colon cancers.

The association of *S. bovis* endocarditis with colonic neoplasia is most likely the result of two factors. The first key factor is a change in colonic flora in patients with colon cancer. *S. bovis* is found in the gastrointestinal tract of only 5% to 16% of normal human subjects.[1,20] However, in a study by Klein et al.,[1] the fecal carriage rates for *S. bovis* was 56% in patients with carcinoma of the colon. Whether this increased prevalence of *S. bovis* in patients with colon carcinoma and polyps is cause or effect is unknown. Second this organism may have a specific pro-

pensity for both transmucosal invasion and the development of the bacterial endocarditis. *S. bovis* accounts for 14% of all microbiologic endocarditis, 24% of streptococcal endocarditis, and 63% of group D streptococcal endocarditis.[5] However the factor or factors promoting (1) fecal overgrowth, (2) access to the portal venous system, (3) entry into the systemic circulation, and (4) lodgement on cardiac valves have yet to be elucidated.

In the present analysis, 50% of patients with *S. bovis* endocarditis and 53% of those with bacteremia had associated liver disease and/or dysfunction. Liver disease was documented by biopsy in 18 of these 48 (38%) patients. In ten of the forty-eight (21%) patients, the diagnosis of cirrhosis was clearly established. However a variety of other liver problems, including passive congestion, neoplastic infiltration, extrahepatic obstruction, and fatty infiltration, were documented by liver biopsy, scans, and/or laparotomy. Each of these liver problems may result in a compromised hepatic reticuloendothelial system and other host-defense mechanisms.[21-23] Furthermore alterations in hepatic secretion of bile salts and/or secretory immunoglobulins may promote the translocation of bacteria from the intestinal lumen into the portal venous system.[24,25] Finally the presence of portal hypertension with portal-systemic shunting may bypass the hepatic reticuloendothelial system and allow direct access to the systemic venous system.

This study suggests that all patients with documented *S. bovis* endocarditis or bacteremia should undergo both colonic and hepatic evaluation. A colonoscopy should be performed to detect symptomatic colonic neoplasia. This follow-up should be maintained for a number of years after the episode of endocarditis because cases of colonic carcinoma have been reported years after the episode of endocarditis.[14] Complete liver function tests, hepatitis screens, and CT or ultrasound of the liver should be adequate to detect underlying liver disease. Liver biopsy should be performed selectively if more information is required. We conclude that *S. bovis* bacteremia should alert the clinician to the possibility of underlying liver and colon disease.

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Discussion

DR. EDWIN A. DEITCH (Shreveport, Louisiana): That an association exists between intestinal colonization with *Streptococcus bovis* and the presence of colonic diseases or endocarditis is clear; however, the pathophysiologic relationship between *S. bovis* colonization and these disease processes remain unresolved. For example, there is no clear understanding of the mechanisms by which *S. bovis* either populates the gut or spreads from the gut to cause endocarditis. Thus the current studies documenting an association between liver disease and *S. bovis* endocarditis or bacter-