Streptococcus bovis Endocarditis and Its Association with Chronic Liver Disease: An Underestimated Risk Factor


Clinical and epidemiological characteristics of Streptococcus bovis endocarditis were prospectively studied among 199 patients with definite endocarditis. Thirty patients (15.1%) had S. bovis endocarditis. Compared with patients with non–S. bovis endocarditis, these 30 patients were older (mean age, 68.6 ± 12.4 years; P < .001) and had higher rates of bivalvular involvement (43.3% vs. 7.7%; P < .001), embolism (73.3% vs. 40.2%; P = .002), and diskitis (23.3% vs. 0.6% P < .001). In patients with S. bovis biotype I (S. bovis I) endocarditis, advanced liver disease was present in 56.7%, compared with 15.3% of patients with non–S. bovis endocarditis (P < .001), and colonic adenoma was present in 46.7%. The in-hospital mortality rate (16.7%) was correlated with delayed diagnosis and advanced liver diseases. In our city, S. bovis I endocarditis is frequently correlated with liver diseases; diskitis may be the first sign of the disease.

Streptococcus bovis comprises a group of gram-positive cocci that belong to group D of the Lancefield classification and are found in the intestinal flora of 10% of the healthy population and in 29%–55% of patients with inflammatory bowel diseases or colon cancer [1]. On the basis of DNA reassociation studies, a new taxonomic classification of the S. bovis group has been proposed: Streptococcus galolyticus for S. bovis biotype I (S. bovis I) and Streptococcus infantarius (recently renamed Streptococcus lutetiensis) and Streptococcus pasteurianus for S. bovis biotypes II/1 and II/2, respectively [2]. However, because the procedures that accurately identify the new species have not yet entered general use, we will use the traditional nomenclature of S. bovis I and S. bovis biotype II (S. bovis II).

S. bovis is increasingly recognized as a cause of infective endocarditis in southern Europe [3–5] but not in the United States. However, the current knowledge regarding this emerging condition appears to be both incomplete and controversial. Endocarditis caused by S. bovis I but not S. bovis II has been associated with underlying gastrointestinal malignancy [1, 6]. However, sporadic reports have also suggested the possible association of S. bovis I bacteremia or endocarditis with liver disease or neoplastic disease outside of the intestinal tract [3–5, 7].

Several cardiological centers have recently reported the clinical characteristics of S. bovis endocarditis [8–11]. In different settings, S. bovis endocarditis has been described as either a “relatively benign” disease with a high embolic risk but low mortality [8, 10, 11] or a “severe” condition associated with a high mortality rate despite the decreased embolic risk [9]. Moreover, besides the recognized association with intestinal lesions, these studies did not investigate the possible role of other predisposing conditions for S. bovis endocarditis.
nor did they differentiate between disease caused by *S. bovis* I and that caused by *S. bovis* II.

As a part of a prospective evaluation of consecutive patients with infective endocarditis treated at the University Hospital of Naples (Italy), we observed that *S. bovis* ranked as the second most common pathogen associated with endocarditis since 2000. Accordingly, in this study, we evaluated the epidemiological, microbiological, and clinical characteristics of *S. bovis* endocarditis in a series of Italian patients treated between January 1990 and August 2003. In particular, we studied whether, in our city, *S. bovis* endocarditis is associated with gastrointestinal lesions only or also with liver disease, and whether this emerging cardiac infection resembles or has a more aggressive course than endocarditis due to other streptococcal species that are easily treated (e.g., viridans group streptococci).

### PATIENTS AND METHODS

All patients with infective endocarditis hospitalized in our tertiary care center were prospectively evaluated to identify causative pathogens, antibiotic susceptibilities, complications, and efficacy of treatments. Among the 199 consecutive patients with definite infective endocarditis observed since January 1990, 30 (15.1%) had *S. bovis* endocarditis. The diagnosis of endocarditis was made according to the Duke criteria [12] for patients admitted since 1994 and was reviewed with the same criteria for those hospitalized earlier.

All patients underwent a comprehensive screening that included blood cultures (≥3 over ≥12 h), acute-phase response tests, complete blood count, and biochemical and virological evaluations, including tests for detection of hepatitis B virus (HBV) and hepatitis C virus (HCV) markers. For all patients, transthoracic and/or transesophageal echocardiography, chest radiography, and complete abdominal ultrasonography were performed in the first few days of hospitalization.

All signs and symptoms suggestive of an embolic event (i.e., sudden neurologic or visual dysfunction, abdominal pain, hematuria, ischemia in the peripheral circulation, chest discomfort, and abrupt dyspnea) were evaluated. Patients with suspected peripheral embolisms or who had recurrence of fever were evaluated. Patients with suspected peripheral embolisms or who had recurrence of fever during antibiotic treatment underwent CT scanning or MRI, bone or lung scintigraphy, vascular echo-color Doppler examination, or additional abdominal ultrasonography, as clinically indicated. Major embolic events were considered to be those involving the brain, spleen, kidney, eye, or lung.

Patients with *S. bovis* I endocarditis underwent colonoscopy. Intestinal polyps were histologically evaluated, and the term “advanced adenoma” was reserved for adenomas with a diameter >1 cm concomitant with tubulovillous or villous histological findings, high-grade dysplasia, or early carcinoma [13].

The diagnosis of liver cirrhosis was established on the basis of results of clinical and biochemical examinations and ultrasonography (coarse pattern, irregular borders, left lobe hypertrophy, and portal hypertension). Bacteria were identified using conventional methods (Gram staining and catalase testing), and species determination was performed using API 20 Strep (BioMérieux). Antibiotic susceptibility studies were performed by the Kirby-Bauer method; determination of MIC and bactericidal concentration was made using a microdilution method, in accordance with NCCLS guidelines [14, 15].

For statistical analysis, differences between continuous variables, summarized as mean values ± SD, were analyzed with Student’s *t* test when normally distributed; otherwise, they were analyzed using the Mann-Whitney *U* test. Differences between frequencies were analyzed using the χ² test. A *P* value of ≤.05 was assumed to denote statistical significance.

### RESULTS

Thirty patients had *S. bovis* endocarditis (28 cases were due to *S. bovis* I, and 2 were due to *S. bovis* II). The demographic and clinical characteristics of these patients and 169 patients with non-*S. bovis* endocarditis are reported in table 1. The age was 58.6 ± 12.4 years for the *S. bovis* endocarditis group and 46.0 ± 17.0 years (*P* = .001) for all endocarditis patients. Of note, 23 (77%) of 30 patients with *S. bovis* endocarditis had been observed since 2000. *S. bovis* endocarditis had a prevalence of 7% during 1990–1999 and, since 2000, has had a prevalence of 25.3%. Details of patients with *S. bovis* endocarditis are reported in table 2.

**Echocardiographic studies.** Twenty-seven patients had an infected native valve, and 3 had an infected prosthetic valve. Of the 27 cases of native valve infection, 12 involved mitral and aortic valves, 8 involved aortic valves, 4 involved mitral valves, 1 involved aortic and tricuspid valves, and 2 involved tricuspid valves. The 3 cases of prosthetic valve infection involved 2 aortic valves and 1 mitral valve. A bivalvular involvement was seen more frequently in patients with *S. bovis* endocarditis than in those with endocarditis due to other microorganisms (13 [43.3%] of 30 vs. 13 [7.7%] of 169; *P* < .001). All patients had at least 1 valve vegetation, and 14 had ≥2 vegetations. Nine patients had a ruptured valve.

**Liver evaluation.** Chronic liver disease was observed in 17 (60.7%) of 28 patients with *S. bovis* I endocarditis. Liver disease was virus related in 14 patients (12 with HCV disease and 2 with HBV disease), was associated with ethanol abuse in 2, and was cryptogenic in 1 (patient 19). None of the patients had a history of drug abuse. Eleven patients had liver cirrhosis, 3 had diffuse fibrosis, and 3 had chronic hepatitis. Among cirrhotic patients, 1 (patient 12) had undergone previous partial hepatectomy for hepatocellular carcinoma, and 4 (patients 4,
The prevalence of chronic liver disease was observed in 26 (15.3%; 25 had HCV disease, and 1 had HBV disease); 3 patients had liver cirrhosis, and 14 had a history of injection drug use. Thus, the prevalence of chronic liver disease among patients with S. bovis I endocarditis was significantly higher than in those with endocarditis with another etiology (60% vs. 15.3%; P < .001).

**Colonoscopy evaluation.** Twenty-seven of the 28 patients with S. bovis I endocarditis underwent colonoscopy, and polyps were found in 14 (52%). One patient (patient 9) did not undergo this procedure because of severe clinical conditions (congestive heart failure and multiple embolisms) and died 7 days after hospitalization. Among the 14 patients with adenoma, 5 had adenotubular polyps, 8 had advanced adenoma (4 of whom had several polyps), and 1 had a colonic adenocarcinoma. Four patients (patients 10, 17, 26, and 27) had both colonic lesions and chronic liver disease (table 2).

The 2 patients with S. bovis II endocarditis had normal liver function. One (patient 6) underwent colonoscopy, and no intestinal lesions were found. He had a very poor dental status, which was a possible portal of entry for the pathogens. The other (patient 18) was a 21-year-old woman with inflamed anal rhabdages.

**Embolic events.** Thirty-four embolic events occurred in 22 (73.3%) of 30 patients (table 2). The incidence of embolic events among patients with S. bovis I endocarditis was higher than that among those with endocarditis due to another etiology (22 [73.3%] of 30 vs. 68 [40.2%] of 169 patients; P = .002). Among these 22 patients, embolism involved the brain in 40.9%, the spleen in 27.3%, and both the kidney and lung in 9.1%. No differences in the distribution of peripheral embolisms were noted between patients with S. bovis I endocarditis and patients with non–S. bovis I endocarditis.

Emboli were already present at admission in 14 (46.7%) of 30 patients. In-hospital embolic events occurred in 18 patients (60%), despite appropriate antibiotic treatment. Most of these embolic events were seen 8–21 days (15.6 ± 9.8 days) after initiation of therapy. Of interest, 9 patients with in-hospital embolisms had had an embolic event before admission. Furthermore, embolism occurring during hospitalization appeared to be more frequent among patients with liver disease.

**Diskitis.** At admission, 7 patients with S. bovis I endocarditis (23.3%) showed signs and symptoms of diskitis, and 5 of them had also experienced major embolic events before hospitalization. In contrast, only 1 patient (who had Staphylococcus aureus endocarditis) among the 169 patients with endocarditis caused by other agents had vertebral involvement (P < .001). Of interest, for the 7 patients with spine involvement, the symptoms of diskitis were the initial clinical manifestations of the disease. The MRI of the spine of patient 16 with severe diskitis is shown in figure 1.

**Antibiotic susceptibility studies.** All strains were susceptible to penicillin, ampicillin, vancomycin, and teicoplanin. Resistance to several antibiotics was noted: 73% of the strains were resistant to tetracycline, 63% were resistant to erythromycin, 40% were resistant to trimethoprim-sulfamethoxazole.
Table 2. Demographic and clinical characteristics of 30 patients with *Streptococcus bovis* endocarditis.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex/age</th>
<th>Time to diagnosis, days</th>
<th>Valve(s)</th>
<th>Involvement</th>
<th>Embolic event(s), location/type</th>
<th>Before</th>
<th>During</th>
<th>Therapy</th>
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<th>Outcome</th>
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<td>Kidney</td>
<td>Gm</td>
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<td>Net</td>
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<td>None</td>
<td>Cfx</td>
<td>No</td>
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<td>No</td>
<td>Cured</td>
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<td>None</td>
<td>Gm</td>
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<td>Cured</td>
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<td>Gm</td>
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<td>Gm</td>
<td>No</td>
<td>Cured</td>
</tr>
<tr>
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<td>Adv. adenoma</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>Gm</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
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<td>85</td>
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<td>None</td>
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<td>None</td>
<td>Gm</td>
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<tr>
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<td>Adv. adenoma</td>
<td>Fibrosteatosis (alcohol abuse)</td>
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<td>None</td>
<td>Gm</td>
<td>Yes</td>
<td>Cured</td>
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<tr>
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<td>Anal rhagades</td>
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<td>Kidney</td>
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<td>Gm</td>
<td>No</td>
<td>Cured</td>
</tr>
<tr>
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<td>Gm</td>
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<tr>
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<td>120</td>
<td>Aortic prosthesis</td>
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<td>None</td>
<td>HBV cirrhosis</td>
<td>None</td>
<td>None</td>
<td>Gm</td>
<td>Yes</td>
</tr>
<tr>
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<td>120</td>
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<td>None</td>
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<td>Brain</td>
<td>Gm</td>
<td>No</td>
<td>Cured</td>
</tr>
<tr>
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<td>60</td>
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<td>HBV cirrhosis</td>
<td>None</td>
<td>None</td>
<td>Gm</td>
<td>No</td>
<td>Cured</td>
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<td>40</td>
<td>Mitral prosthesis</td>
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<td>HBV cirrhosis</td>
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<td>None</td>
<td>Brain</td>
<td>Gm</td>
</tr>
<tr>
<td>24</td>
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<td>Adv. adenoma</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>Gm</td>
<td>Yes</td>
</tr>
<tr>
<td>25</td>
<td>M/61</td>
<td>15</td>
<td>Aortic</td>
<td>None</td>
<td>HBV cirrhosis (TIPS)</td>
<td>Spleen</td>
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<td>Gm</td>
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<td>Gm</td>
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<td>Mitral</td>
<td>None</td>
<td>HBV cirrhosis</td>
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<td>Brain</td>
<td>Gm</td>
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<td>Tricuspid</td>
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<td>Gm</td>
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<td>None</td>
<td>Brain</td>
<td>None</td>
<td>Gm</td>
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</table>

**NOTE.** All patients were infected with *S. bovis* biotype I, unless otherwise indicated. Adv, advanced; Cfx, ciprofloxacin; Gm, gentamicin; HBV, hepatitis B virus; HCC, hepatitis C virus; HCC, hepatocellular carcinoma; Net, netilmicin; TIPS, transjugular intrahepatic portosystemic shunt.

* After onset of fever.
* Before or during hospitalization.
* All patients received ampicillin.
* *S. bovis* biotype II.
* Splenectomy.

23% were resistant to ciprofloxacin, and 17% were resistant to ofloxacin. Among aminoglycosides, 57% of the strains were resistant to amikacin, 53% were resistant to tobramycin, 13% were resistant to gentamicin, and 10% were resistant to netilmicin; none were cases of high-level resistance. Twenty-two (73%) of 30 strains were resistant to streptomycin; of these, 6 (27%) showed high-level resistance (MIC of streptomycin, >2000 mg/L).

**Treatment.** Eighteen patients were treated with medical therapy alone and 12 with medical therapy and surgery. Three patients (patients 13, 28, and 30) required early cardiac surgery shortly after hospitalization. The antibiotic treatment was, in most cases, a combination of ampicillin (12 g iv) and either gentamicin (3 mg/kg per day iv) or netilmicin (5 mg/kg per day iv) for the first 2 weeks, followed by ampicillin alone for 2 additional weeks. For the patients with diskitis, ciprofloxacin or levofloxacin replaced the aminoglycoside after the second week of treatment. These latter patients were treated for 2 months.

Five (16.7%) of 30 patients died; 3 had received medical...
thirty-compensated HCV cirrhosis in patients 4 and 25, and post-result of a severe cerebral embolism in patients 9 and 28, de-
therapy alone, and 2 had undergone surgery. Death was the
The interval between the onset of fever and diagnosis was
The association of
Figure 1. MRI of the spine showing severe diskitis in patient 9

**DISCUSSION**

This study was performed to further elucidate some important
aspects of *S. bovis* endocarditis, a disease that has recently
aroused interest for its apparently increasing incidence in the
last few years. Indeed, 77% of the patients in this series were
seen in the last 4 years.

We confirmed that endocarditis due to *S. bovis* I infection
was associated with advanced age and a more frequent involve-
ment of native valves (aortic alone or in combination with
other valves) [11]. However, the most interesting finding in
our patients with *S. bovis* I endocarditis was that, besides the
already established association with colonic lesions (47% in this
series) [1, 6, 16], we found a remarkable association with
chronic liver disease (60%). These data are more noteworthy
if we consider that the prevalence of liver disease in our patients
with endocarditis due to other microorganisms was 15.3% and,
if drug abusers are excluded, 7.1%.

The association of *S. bovis* bacteremia or endocarditis with
chronic liver disease has been previously reported only in an-
ceedtal case reports or retrospective studies [5, 17]. In recent
series, the association with liver disease was not evaluated [8–
11]. A retrospective study involving 92 patients with either
bacteremia or endocarditis due to *S. bovis* showed the presence
of liver disease in 50% of patients as a single associated con-
dition or, less often, combined with colonic lesions [17]. We
also observed that liver disease and colonic adenomas were
mutually exclusive in all but 4 of our patients.

*S. bovis* I is a normal inhabitant of the gastrointestinal tract,
and fecal carriage is even higher for patients with colonic ne-
plasms [1]. Therefore, it is conceivable that spontaneous bac-
teriaemia, via tumoral neoangiogenesis and vessel wall necrosis,
may lead to valve colonization and endocarditis. Furthermore,
diseases other than colon cancer, such as liver cirrhosis, may
predispose patients to systemic bacteremia due to intrahepatic
blood shunting and impaired bacterial clearance from the portal
blood [18, 19]. Favorable microenvironment conditions for the
proliferation of anaerobic bacteria and *S. bovis* may be induced
by TNF-α [20]. High levels of this cytokine are found in pa-
ents with chronic viral liver disease and are correlated with
the severity of the disease [21].

Another important observation that emerged from this study
is the particularly high rate of bivalvular involvement (43%) and
embolism (73.3%) in patients with *S. bovis* endocarditis,
compared with those with endocarditis caused by other agents.
Similar data have recently been reported by others [8, 9, 11].

Endocarditis involving multiple valves is infrequent
[22]. In our series, bivalvular involvement was 12.3% in the
general population (43.3% in *S. bovis* endocarditis and 7.7%
in other endocarditis). Continuous bacteremia and the ability
of *S. bovis* to adhere to collagen, fibronectin, and laminin may
explain the tendency of *S. bovis* to infect >1 valve [20].

Endocarditis caused by *S. bovis* I was frequently complicated
by a high rate of embolic events (73.3% of patients), often
multiple. Because of their lower albumin levels, cirrhotic pa-
ients seemed more prone to embolisms. This finding is con-
sistent with our previous report that low albumin levels may
be a predictor of embolism [23]. Although most of these major
embolisms occurred in an earlier phase of the disease, it was
not uncommon to observe them even in a later phase, despite
appropriate antibiotic treatment. This is in contrast with the
assumption that the risk of embolism should decrease as specific
therapy continues [24]. The high rate of late embolism in our
series may be explained, at least in part, by the high rate of
bivalvular involvement, the presence of multiple vegetations,
and the high rate of embolisms already present at admission.
Indeed, a high incidence of late embolisms has been reported
in patients who have already had an embolic event during the
course of the disease [25].

A peculiar aspect of *S. bovis* infective endocarditis appears
to be vertebral involvement, which is rare in cases of infective
endocarditis due to other pathogens. In this series, it was 23.3%,
which is similar to that observed elsewhere [11]. Spondylodiskitis due to S. bovis during bacteremia with or without endocarditis has been reported [26, 27]. To date, the pathogenesis of spinal involvement during endocarditis is controversial. In particular, one may question whether diskitis should be considered an embolic phenomenon or the result of seeding during bacteremia. In our series, diskitis was always the first sign of disease. It seems that this microorganism may have a particular tropism for the spine [20], and it may be argued that bone colonization occurs simultaneously with valve colonization during sustained bacteremia rather than as a consequence of peripheral embolism. Diskitis symptoms may result in a delayed diagnosis of endocarditis and the consequent risk of severe complications.

A particular finding of this series was the observation of 2 patients with endocarditis of the tricuspid valve. Tricuspid valve endocarditis due to S. bovis seems to be an infrequent condition; to date, only 7 cases have been reported in the literature [28, 29]. The virulence of the organisms and septal defects or abnormal valve findings may play a role.

Hospital mortality from S. bovis endocarditis has been reported to be 2%–18% [8–11]; in our series, it was 16.7%. It is logical to assume that mortality in this series may be influenced by a combination of different factors, such as underlying clinical conditions, delay in diagnosis, and severity of embolism and valve involvement. Indeed, there was a significant delay in the diagnosis for patients who died or required surgery.

In conclusion, this report emphasizes that, in addition to colonic involvement, there is a close relationship between liver disease and S. bovis I endocarditis, at least in our city; therefore, a careful study of the liver function in these patients is recommended. S. bovis endocarditis is characterized by a high rate of bivalvular involvement and embolism. The onset of the disease may be atypical, with unusual complications such as diskitis that may delay the diagnosis and worsen the prognosis. In the near future, specific studies of subspecies diversity may clarify the different epidemiological and clinical behavior of strains belonging to the S. bovis group.

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References


