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Referral for Colonoscopy in Patients with *Streptococcus bovis* Bacteremia and the Association with Colorectal Cancer and Adenomatous Polyps: A Quality Assurance Study

Derek H. W. Little [1], Kristyne M. Onizuka [1] and Khurram J. Khan [1,2,*]

[1] Department of Medicine, McMaster University, Hamilton, ON L8S 4L8 Canada; derek.little@medportal.ca (D.H.W.L.); kristyne.onizuka@medportal.ca (K.M.O.)
[2] Division of Gastroenterology, St Joseph's Healthcare Hamilton, Hamilton, ON L8N4A6, Canada
* Correspondence: khankj@mcmaster.ca; Tel.: +01-905-522-1155

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Abstract: The association between *Streptococcus bovis (S. bovis)* bacteremia and colorectal cancer is well established. We aimed to review patients with *S. bovis* bacteremia at our local hospital system and determine the percentage of patients referred for colonoscopy. Methods: We searched the regional database to identify *S. bovis*-positive blood cultures from 2002 to 2016 and the clinical characteristics and outcomes of those patients. Results: A total of 86 patients with *S. bovis* bacteremia were identified. From the 86 patients, 14 were excluded. The mean age of the 72 remaining patients was 74.5 (SD 13), 42/72 (58%) were male, 12/72 (17%) had infective endocarditis, and 19 (26%) died during admission. Of the 53 patients who survived, 37 (70%) were referred for colonoscopy or CT colonography, of which 30 had a colonoscopy. Thus, 3/30 (10%) cases showed adenocarcinoma and 11/30 (37%) cases showed adenomatous polyps. Age, gender, or the presence of infective endocarditis were not associated with adenocarcinoma or adenomatous polyps. Discussion: In our local centers, a significant proportion of patients with *S. bovis* were found to have colon cancer or significant polyps, and thus the importance of referral to colonoscopy remains paramount.

Keywords: *Streptococcus bovis*; colonoscopy; colonography; colon cancer

1. Introduction

Streptococcus bovis (*S. bovis*) is a Gram-positive group D streptococcus found in the gastrointestinal tract of 11% of asymptomatic patients [1]. As early as 1951, an association between colorectal cancer (CRC) and group D streptococci in patients with endocarditis was identified by McCoy and Mason [2]. In 1974, Hopes and Lerner reported a case series that suggested a relationship between *S. bovis* and CRC [3]. In 1977, Klein et al. found an association between *S. bovis* fecal carriage and CRC [4], which was supported by a recent 2014 meta-analysis demonstrating that fecal carriage of *S. bovis* is 2-fold greater in patients with a colorectal neoplasm (carcinoma or adenoma) [1]. This was further supported by Paritsky et al. who found malignant tumors in 35% of patients colonized with *S. bovis*, while none were found in those without [5]. Since these early reports, numerous other studies have shown an association between *S. bovis* bacteremia or endocarditis and CRC. The pathogenesis of CRC in the setting of *S. bovis* may involve its high affinity for type IV collagen found in colonic mucosa and by the production of proinflammatory cytokines (NF-κB, interleukin-1, interleukin-8, and cyclooxygenase-2) promoting proliferation and angiogenesis, while inhibiting apoptosis [6].

Initially *S. bovis* was classified into subgroups, known as biotypes I, II/1, and II/2. However, in 2003, following further genetic analysis, Schlegel proposed a new taxonomic system for these biotypes:

Streptococcus equinus, Streptococcus infantarius subsp. coli, Streptococcus infantarius subsp. infantarius, Streptococcus alactolyticus, Streptococcus gallolyticus subsp. gallolyticus, Streptococcus gallolyticus subsp. pasteurianus, and Streptococcus gallolyticus subsp. Macedonicus [7]. *Streptococcus gallolyticus subsp. gallolyticus* was formerly biotype I, *Streptococcus infantarius subsp. coli* and *Streptococcus infantarius subsp. infantarius* were formerly biotype II/1, and *Streptococcus gallolyticus subsp. pasteurianus* was formerly biotype II/2.

Many of the studies examining the association between *S. bovis* and CRC neither identified the subspecies nor biotyped their samples. This variability in reporting is of importance as the association with CRC varies by subspecies.

A 2011 systematic review and meta-analysis by Boleji et al. found that the prevalence of CRC in patients with *S. bovis* biotype I (*Streptococcus gallolyticus subsp. gallolyticus*) bacteremia ranged from 33–71% with a median of 60% (when only colonic-evaluated patients were included) [8]. They also reported that the risk with biotype I vs. biotype II had a pooled odds ratio of 7.26 (95% CI 3.94–13.36) [8]. Thus, the incidence of CRC in patients with biotype II infection is substantially lower than that in patients with biotype I infection and may not even exceed that in the general asymptomatic population.

To specifically address this, Corredoira et al. performed a combined analysis with prospectively examined cases and cases from the literature [9]. They showed no association between biotype II and colorectal neoplasms, questioning the need for colonoscopy in these patients. Unfortunately, many laboratories do not identify the subspecies or biotype, making it imperative that all patients with *S. bovis* bacteremia are screened with colonoscopy.

The objective of this study was to determine the percentage of patients referred for colonoscopy after a *S. bovis* bacteremia at our local centres. Secondary objectives were to assess the prevalence of CRC (adenoma or adenocarcinoma) in patients who underwent colonoscopy and to evaluate whether any patient characteristics were associated with a finding of CRC.

2. Results

Eighty-six patients with *S. bovis* bacteremia were identified (Figure 1). Fourteen were excluded (three were made palliative, six had insufficient data, four were under 18 years of age, and one had known CRC), leaving 72 patients for analysis. The patient demographic and clinical characteristics are shown in Table 1. The mean age of the patients was 74.5 (SD 13) years and 58% were male. Twelve patients (17%) had a diagnosis of infective endocarditis.

Table 1. Patient demographic and clinical characteristics (SD: standard deviation, ESRD: end-stage renal disease, RRT: renal replacement therapy, IBD: inflammatory bowel disease, GI: gastrointestinal).

Characteristic	Patients Survived *n* = 53
Age mean (SD)	74.5 (13)
Male *n* (%)	31 (58)
Infective endocarditis *n* (%)	12 (17)
Diabetes *n* (%)	21 (40)
Liver cirrhosis *n* (%)	1 (2)
ESRD on RRT *n* (%)	3 (6)
IBD *n* (%)	1 (2)
History of malignancy *n* (%)	16 (30)
Family history of GI malignancy *n* (%)	9 (17)
Smoking status n (%)	
Current	4 (8)
Former	19 (36)
Non-smoker	24 (67)
Unknown	6 (11)

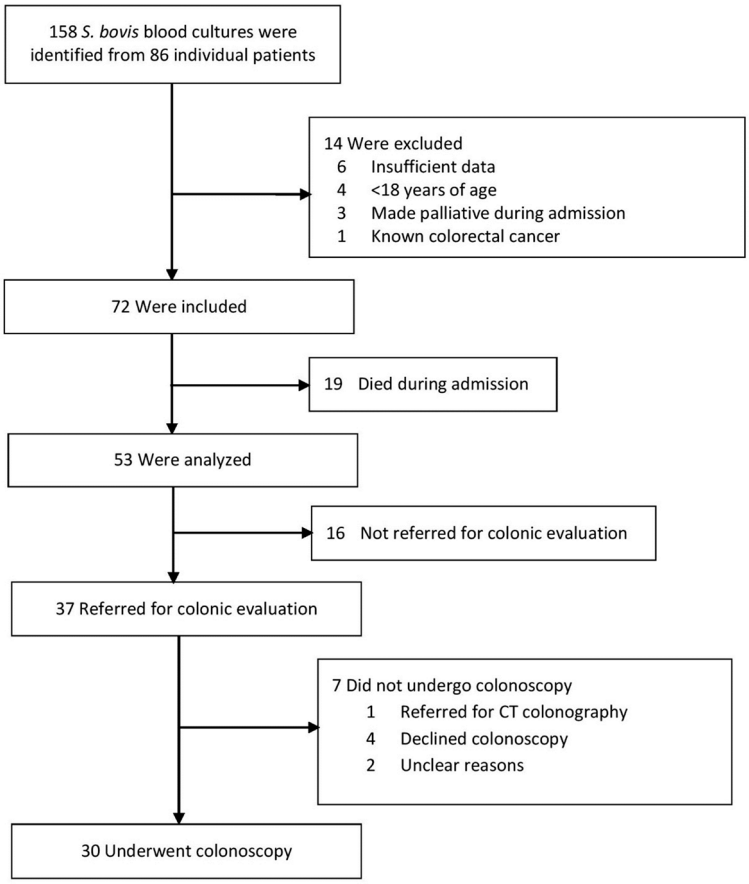

Figure 1. Flow diagram of patients.

Only three (4%) of all isolates were biotyped. One patient had *Streptococcus equinius*, one patient had *Streptococcus gallolyticus subsp. pasteurianus* (formerly biotype II/2), and one patient had both *Streptococcus gallolyticus subsp. pasteurianus* and *Streptococcus gallolyticus subsp. gallolyticus.* The only patient with confirmed *Streptococcus gallolyticus subsp. gallolyticus* was made palliative and therefore did not undergo colonoscopy.

One-quarter (26%) of the patients died during hospital admission. Of the 53 patients who survived, 70% were referred for colonoscopy or CT colonography (one patient underwent CT colonography because they had a recent myocardial infarction). In approximately half of the cases, the gastroenterology service was consulted (29/53, 55%), and the majority of these patients (26/29, 90%) were referred for colonoscopy.

Thirty patients underwent colonoscopy with three (10%) having adenocarcinoma and 11 (37%) having adenomatous polyps. One patient whose initial colonoscopy showed a hyperplasic polyp had a repeat colonoscopy five years later and was found to have an adenocarcinoma. Of the 12 patients with infective endocarditis, 11 underwent colonoscopy with five (45%) having adenomas and two (18%) with adenocarcinomas. Of the three patients with adenocarcinoma, two were former smokers and two had a family history of CRC. Of the 11 patients with adenomatous polyps, four were current or former smokers and two had a family history of CRC. Histopathologic findings are shown in Table 2.

Table 2. Endoscopic and histopathologic findings.

Pathology	[1] N (%)
Adenocarcinoma	3 (10)
Adenomatous polyps	11 (37%)
Adenoma with focal high-grade dysplasia	1
Tubulovillous adenoma	7
Tubular adenoma	3
Hyperplastic polyp	2 (7)
Focal hyperplastic changes	1 (3)
Inflammation	1 (3)
No abnormality	1(3)
No pathology sent	11 (37)

[1] Out of 30 patients who had colonoscopy.

On univariate logistic regression analysis, age, gender, or the presence of infective endocarditis were not associated with a finding of adenocarcinoma or adenomatous polyps. There were insufficient data for the other clinical characteristics to include in the analysis. Gastroenterology consultation was significantly associated with having a colonoscopy ($p = 0.001$).

3. Discussion

At our local center, only 70% of patients with *S. bovis* bacteremia were referred for colonoscopy; however, this increased to 90% when the gastroenterology service was consulted. European guidelines on the management of infective endocarditis recommend proper classification of *S. bovis* blood cultures and in cases of *Streptococcus gallolyticus subsp. gallolyticus* infective endocarditis, colonoscopy during hospitalization to rule out occult CRC [10]. The percentage of patients undergoing colonoscopy varies widely in reports from other centers (38–100%) [9,11–16]; however it is not always clear whether they excluded patients who died during the index hospitalization, were made palliative, or had known CRC. One study auditing the consistency of specialist referral found that 10/13 (77%) cases were referred to gastroenterology after excluding seven patients judged to have a prognosis so poor as to preclude further investigations [17]. We found that a similar percentage of patients were referred for colonoscopy in our study. Perhaps the rate of referral could be improved by mandating referral for colonic evaluation, or by adding a notification to the microbiology report reminding the ordering physician of the association with CRC.

In our study, only 4% of isolates were biotyped. When a previous meta-analysis included all biotypes, *S. bovis* bacteremia was associated with an odds ratio of 7.48 (95% 95% CI 3.10–18.06) [1] for the occurrence of colorectal adenoma or carcinoma. However, when analyzed separately, *S. bovis* biotype I demonstrated a stronger association with CRC than *S. bovis* biotype II [8,9] and Corredoira et al. did not find an association between biotype II bacteremia and colorectal adenomas or carcinomas [9]. In a meta-analysis by Boleij et al., *S. bovis* biotype I bacteremia significantly increased the risk of CRC (adenoma or carcinoma) compared with *S. bovis* biotype II bacteremia (pooled OR 7.26, 95% CI 3.94–13.36) [8]. These findings suggest that in patients with *S. bovis* bacteremia, only those with biotype I (*Streptococcus gallolyticus subsp. gallolyticus*) require colonic evaluation, emphasizing the importance of subspecies classification. The need for proper microbiological classification to guide colonic evaluation has also been highlighted in guidelines on the management of infective endocarditis [10]. This is an area for quality improvement in our local center, and until offered routinely, all patients with *S. bovis* bacteremia should be referred for colonic evaluation.

In patients who underwent colonoscopy, 10% were found to have an adenocarcinoma and 37% had adenomas in comparison to the baseline population rate of 0.5% and 32%, respectively [18]. This is consistent with the results of a meta-analysis of 20 case series reporting a median prevalence of carcinomas of 18% (interquartile range 13%) and adenomas of 43% (interquartile range 22%) when all biotypes are included [8]. A greater percentage of our patients with infective endocarditis had

CRC; however, this did not reach statistical significance on the univariate logistic regression analysis. Previous literature has shown that patients with *S. bovis* biotype I infection are more likely to present with infective endocarditis than those with *S. bovis* biotype II infection [8]. Consequently, *S. bovis* infective endocarditis is more highly associated with a finding of CRC than *S. bovis* infection at other sites [8]. The lack of a significant difference in our study may have been due to a low number of patients with infective endocarditis. Reassuringly, all patients with infective endocarditis in our study were referred for colonoscopy.

There are several limitations to the present study. First, it is a retrospective study conducted at a single academic center. Second, the association between *S. bovis* bacteremia and CRC is likely to be underestimated as patients who died during admission or became palliative would not have undergone colonoscopy. Third, some colonoscopy reports may have been unavailable if patients were referred to a private endoscopy clinic or outside our hospital system. Finally, given the relatively low number of completed colonoscopies, our analysis of clinical characteristics associated with a finding of CRC was limited.

4. Materials and Methods

We searched the Hamilton Regional Laboratory Medicine Program (HRLMP) database from January 2002 to December 2016 for all *S. bovis*-positive blood cultures. The HRLMP provides laboratory testing for four hospitals in Hamilton, Canada. The charts of all patients with a *S. bovis*-positive blood culture were retrospectively reviewed. Data extracted included age, gender, comorbidities (diabetes, end-stage renal disease, inflammatory bowel disease, liver cirrhosis, malignancy, smoker), biotype, GI service consultation, referral for colonoscopy, endoscopic and histologic findings, hemoglobin at time of positive blood culture, and presence of infective endocarditis. We excluded patients who were palliative, under 18 years of age, had a previous diagnosis of CRC, and those with insufficient data. Research ethics approval was obtained from the Hamilton Integrated Research Ethics Board.

Clinical characteristics were analyzed using descriptive statistics. Categorical data were described using frequencies and percentages. Continuous data were described using means and standard deviations. Univariate logistic regression analysis was performed to examine the association of clinical characteristics with a finding of adenocarcinoma or adenomatous polyps. A p-value < 0.05 was considered statistically significant. All statistical analysis was performed using SPSS Statistics for Windows Version 20.0 (IBM Corp, Armonk, NY, USA).

5. Conclusions

In our study, 70% of patients were referred for colonoscopy following an episode of *S. bovis* bacteremia, demonstrating a need for improved recognition of the association of *S. bovis* bacteremia and CRC. Future work should be done to improve the biotyping of *S. bovis* isolates, and whether a recommendation for specialist referral in all *S. bovis*-positive microbiology reports is warranted.

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