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MAJOR ARTICLE

The Effect of Nomenclature Revision of *Streptococcus bovis* to *Streptococcus gallolyticus* on Subsequent Colon Cancer Screening

Sharanjeet K. Thind,[1,2] Dena R. Shibib,[3,4] and Chris A. Gentry[5]

[1]Section of Infectious Diseases, Medical Service, Oklahoma City VA Health Care System, Oklahoma City, Oklahoma, USA, [2]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA, [3]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA, [4]Department of Pathology, Oklahoma City VA Health Care System, Oklahoma City, Oklahoma, USA, and [5]Pharmacy Service, Oklahoma City VA Health Care System, Oklahoma City, Oklahoma, USA

Background. Lack of awareness of the taxonomic revision from the familiar *Streptococcus bovis* to the less familiar *Streptococcus gallolyticus* may be associated with a decrease in recommended colon cancer screening in patients with bacteremia from this organism. This could subsequently lead to a delay in diagnosis or underdiagnosis of colon cancer and other serious underlying gastrointestinal diseases. The aim of this study was to determine whether the nomenclature change of *S. bovis* to *S. gallolyticus* resulted in decreased colon cancer screening.

Methods. This study was a retrospective, observational, nationwide analysis of patients who had positive blood cultures for *S. bovis*/*S. gallolyticus* from any Veterans Affairs Medical Center (VAMC) between January 1, 2002, and December 31, 2017.

Results. There was no difference in the primary end point of intent for colonoscopy between the *S. gallolyticus* and *S. bovis* groups (66.5% [117/176] vs 62.1% [624/1005], respectively; $P = .26$). The overall mortality rate was 33.8% among 1181 patients included in the study, with a significantly lower mortality in patients with evidence of intent for colonoscopy (29.6% vs 42.5%; $P \leq .001$), gastroenterology (GI) consultation (29.8% vs 41.4%; $P < .001$), infectious diseases (ID) consultation (29.4% vs 39.0%; $P = .001$), or either consultation (31.9% vs 40.7%; $P = .013$), compared to those that did not.

Conclusions. There was no difference in colon cancer screening rates between patients with episodes of bacteremia reported as *S. bovis* and those reported as *S. gallolyticus*. Overall mortality was lower in patients who had ID consultation, GI consultation, or evidence of colonoscopy.

Keywords. bacteremia; colon cancer; colonoscopy; *Streptococcus bovis*; *Streptococcus gallolyticus*.

Klein and colleagues demonstrated a strong association linking *Streptococcus bovis* bacteremia with the presence of colorectal cancer in 1977 following several case reports that described episodes of *S. bovis* bacteremia associated with colorectal carcinoma and other gastrointestinal diseases [1, 2]. Since then, several reports have supported the relationship between isolation of *S. bovis* in the bloodstream and colorectal malignancy. Many have also shown an association with a number of other gastrointestinal conditions including inflammatory bowel disease, diverticular disease, and gastrointestinal bleeding, as well as hepatobiliary abnormalities [3, 4]. Due to these associations of *S. bovis* with colorectal malignancy and other gastrointestinal abnormalities, the Infectious Diseases Society of America (IDSA) guidelines recommend that patients found to have bacteremia from this organism be evaluated with a colonoscopy [5].

Several hypotheses about the mechanisms that underlie the association between *S. bovis* and malignancy have been proposed. Most theories favor that the organism itself leads to cellular changes that can cause premalignant lesions to develop into malignancy. More specifically, these mechanisms include proinflammatory changes causing cytokine release and the induction of mutations in tumor suppressor genes or oncogenes. Other contributing mechanisms include carcinogenesis due to destabilization of normal colonic flora and the induction of uncontrolled cellular proliferation [6]. In 2003, several authors proposed reclassification of *S. bovis* biotypes I, II/1, and II/2 based on genotypic studies and phylogenetic data. Consequently *S. bovis* biotype I and II/2, the biotypes most strongly associated with colorectal malignancy, were renamed *Streptococcus gallolyticus* [7]. Shortly thereafter, van't Wout and Bijlmer noted that the taxonomic changes could have deleterious effects on the evaluation and management of *S. bovis*/*S. gallolyticus* bacteremias due to lack of awareness,

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Correspondence: Sharanjeet K. Thind, MD, 921 NE 13th Street, Oklahoma City, OK 73104 (sharanjeet.thind@va.gov).

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which could lead to the underdiagnosis of colon cancer and other serious underlying gastrointestinal diseases. The authors proposed that the old name for the bacteria be reported along with the new name to prevent confusion [8]. Additional authors have continued to express the concern that the new name for *S. bovis* biotypes may not be familiar to providers [9, 10]. To the best of our knowledge, no studies have been undertaken to assess whether this taxonomic change influenced patient management, specifically compliance with the recommendation for colon cancer screening in bacteremic patients. The aim of this study was to determine whether the nomenclature change of *S. bovis* to *S. gallolyticus* led to a decrease in recommended colon cancer screening in these patients, utilizing a nationwide clinical database in the Veterans Health Administration.

METHODS

Eligible patients ≥18 years of age were included in the study with data collected through the Veterans Affairs Informatics and Computing Infrastructure (VINCI) database across all Veterans Affairs Medical Centers (VAMC) in the United States. Patients were assigned a de-identified patient identification number ("PatientSID") within VINCI, making them un-identifiable by the investigators. Investigators accessed VINCI from a secure, password-protected computer intranet at the Oklahoma City VAMC. Baseline demographic data, diagnosis codes, admission, discharge, and microbiological data were collected. An order for a colonoscopy and/or a gastroenterology (GI) consultation was a surrogate marker for acknowledgement of the need for colon cancer workup and was referred to as "intent for colonoscopy." For this retrospective study, our Institutional Review Board approved waiver of patient consent.

Data Collection and Definitions

This study was a retrospective, observational, nationwide analysis of patients who had positive blood cultures for S. *bovis*/*S. gallolyticus* from any VAMC between January 1, 2002, and December 31, 2017. We excluded patients who had *S. bovis*/*S. gallolyticus* isolated from sites that were not associated with concomitant bacteremia. Microbiology records were examined to determine whether the organism was identified as *S. bovis* or *S. gallolyticus* in the report. If any attempt (such as both names presented in the organism's name field) was made to inform the clinician that *S. gallolyticus* was formerly called *S. bovis*, the patient was placed into the *S. bovis* group. Identifications were performed on various platforms including BioMerieux Vitek2, BD Phoenix, and matrix-assisted laser desorption ionization time of flight (MALDI-ToF) mass spectrometers. The *S. gallolyticus* group included organisms identified and reported as *S. gallolyticus* and *S. gallolyticus* subspecies (subsp. *pasteurianus*, subsp. *gallolyticus*), *S. infantarius* and *S. infantarius* subspecies (subsp. *infantarius*, subsp. *coli*, subsp. *lutetiensis*), *S. pasteurianus*, *and S. lutetiensis*. Further reference to "*S. gallolyticus*" includes these specific species and subspecies. Records were searched for any evidence that a colonoscopy or GI consult was requested from the date of the positive blood culture up to 1 year from that date by searching for a specific Current Procedural Terminology (CPT) code for a colonoscopy or a GI consultation request. The first date of such evidence was recorded. Patient disposition (ie, mortality) up to 1 year from the date of the positive blood culture was recorded.

The primary outcome was evidence of colonic evaluation or GI consultation within 90 days of a positive blood culture. Secondary outcomes included request for infectious diseases (ID) consultation, request for GI consultation, and all-cause mortality within 1 year. The primary and secondary outcomes were also delineated by age (≥75 years vs <75 years), and were further delineated by excluding early death (defined as death within 14 days from the date of first positive blood cultures and presumed to be infection-related or due to other complications).

Statistical Analysis

The Wilcoxon/Kruskal-Wallis test was used for continuous variables. Chi-square likelihood ratios were reported for categorical data. A P value of ≤.05 was considered statistically significant. Univariate variables associated with the intent to perform colonoscopy were identified. Those variables with a P value of ≤.1 were entered into nominal logistic multivariate analysis to determine the independent variables associated with the intent to perform colonoscopy.

RESULTS

After exclusion of *Streptococcus* species other than *S. bovis* or *S. gallolyticus*, 1181 unique cases of bacteremia due to either *S. bovis* (n = 1005) or *S. gallolyticus* (n = 176) were included from 102 Veterans Affairs (VA) sites. Out of the 1005 episodes included in the *S. bovis* group, 53 positive blood cultures (5.3%) from 7 VA sites were reported as *S. gallolyticus* with mention of the former name of *S. bovis* in the report. The 2 groups were largely comparable, except that patients with *S. gallolyticus* bacteremia were slightly older (Table 1).

Primary Outcome

Evidence of intent for colonoscopy was present in 62.7% (741/1181) of patients. There was no statistically significant difference in the rate of intent for colonoscopy between the *S. gallolyticus* group and the *S. bovis* group (66.5% [117/176] vs 62.1% [624/1005], respectively; P = .26) (Figure 1). Similarly, no difference between groups was found in patients age <75 years (69.8% [67/96] vs 61.9% [336/543]; P = .13) or patients age ≥75 years (62.5% [50/80] vs 62.3% [288/462]; P = .98). One hundred twenty-one patients died within 14 days of diagnosed bacteremia; after excluding these patients, there was still no difference in the intent for colonoscopy between the

Table 1. Patient Characteristics of *S. bovis* and *S. gallolyticus* Groups

	S. bovis	S. gallolyticus	Total	
	n = 1005	n = 176	n = 1181	P Value
Male gender, % (No.)	98.5 (990)	98.30 (173)	98.48 (1163)	.83
Race/ethnicity, % (No.)				.27
White	65.77 (661)	67.61 (119)	66.05 (780)	
Black	13.83 (139)	11.93 (21)	13.55 (160)	
Hispanic or Latino	7.96 (80)	11.36 (20)	8.47 (100)	
Other[a]	12.44 (125)	9.09 (16)	11.94 (141)	
Age, y	71.8	74.0	72.1	.033

[a]American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, Asian, unknown.

S. gallolyticus group and the *S. bovis* group (69.3% [115/166] vs 67.6% [604/894], respectively; $P = .66$).

Secondary End Points

There was no statistically significant difference in the rate of GI consults within 90 days between the *S. gallolyticus* group (65.3% [115/176]) and the *S. bovis* group (60.2% [605/1005]; $P = .19$). After excluding those patients who died within the first 14 days of bacteremia, there was still no difference in the rate of GI consultation (68.1% [113/166]) in the *S. gallolyticus* group vs the *S. bovis* group (65.4% [585/894]; $P = .51$). The rate of GI consultation did not differ between the *S. gallolyticus* group and the *S. bovis* group in patients aged ≥75 years (62.5% [50/80] vs 61.7% [285/462]; $P = .89$) and in patients <75 years of age (67.7% [65/96] vs 58.9% [320/543]; $P = .10$).

Infectious Diseases consultation occurred in 601 (50.9%) patients. Patients who had an ID consult had a higher rate of evidence of intent for colonoscopy (76.2% [458/601]) vs patients who did not have an ID consult (48.8% [283/580]; $P < .001$), regardless of reported name of bacteria (Figure 2). In those patients who were still alive at 15 days after bacteremia diagnosis, there was a higher number of ID consults in the *S. gallolyticus* group compared with the *S. bovis* group (65.7% [109/166] vs 52.8% [472/894]; $P = .002$).

There was a significantly higher rate of ID consultations in the *S. gallolyticus* group compared with the *S. bovis* group in patients age ≥75 years (61.2% [49/80] vs 48.7% [225/462]; $P = .037$) and those <75 years of age (65.6% [63/96] vs 48.6% [264/543]; $P = .019$). There was an overall higher consult rate (GI or ID) in the *S. gallolyticus* group vs the *S. bovis* group (84.9% [141/166] vs 77.5% [693/894]; $P = .027$).

In patients who did not have an ID consult, there was no difference in the rate of GI consults between groups in the *S. gallolyticus* and *S. bovis* groups (50% [35/70] and 44.7% [195/436], respectively; $P = .41$). Bacteremias reported as *S. gallolyticus* prompted more ID consults than those reported as *S. bovis* (63.6% [112/176] vs 48.7% [489/1005]; $P < .001$). The *S. gallolyticus* group had a higher number of combined GI and ID consults (83.0% [146/176]) than the *S. bovis* group (72.1% [725/1005]; $P = .002$).

There was no difference in mortality between the *S. gallolyticus* (38.1% [67/176]) and *S. bovis* (41.0% [412/1005]) groups ($P = .47$). There was no difference in mortality between the *S. gallolyticus* and *S. bovis* groups in those age ≥75 years (51.2% [41/80] vs 47.2% [218/462]; $P = .50$) and those age <75 years (27.1% [26/96] vs 35.7% [195/543]; $P = .095$). In the first 14 days after the first positive blood culture for *S. bovis*/*S. gallolyticus*, 121 patients died. After exclusion of the 121 patients, there was an overall mortality of 33.8% (358/1060), with a significant lower mortality in

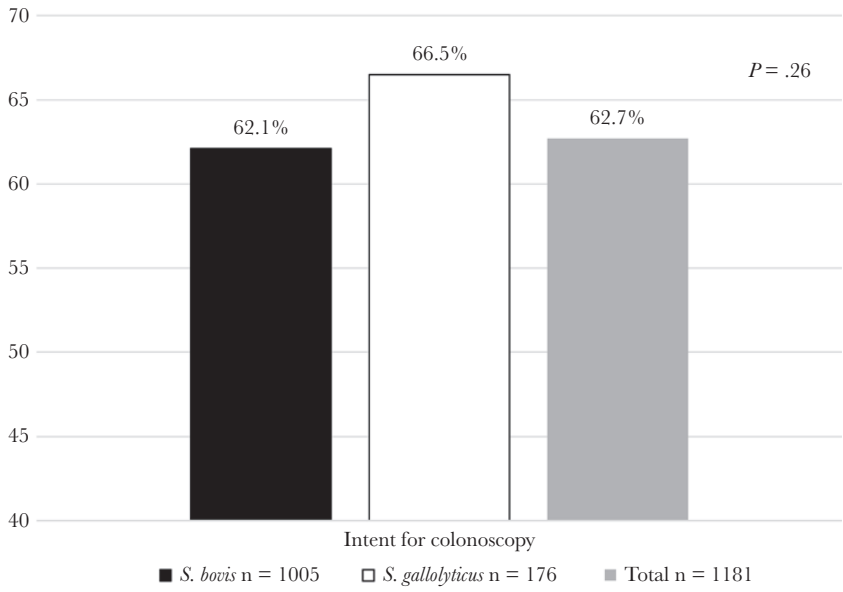


Figure 1. Primary end point of colonoscopy in *S. bovis* and *S. gallolyticus* groups.

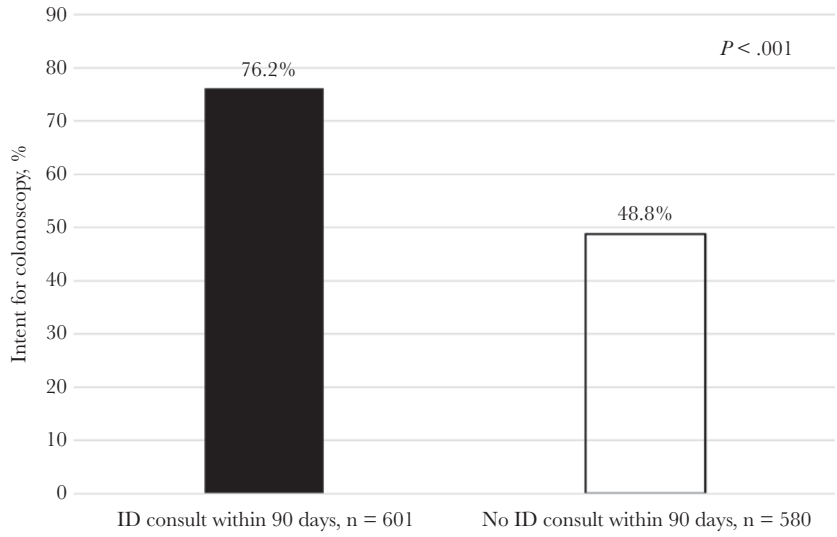


Figure 2. Infectious diseases consultation and intent for colonoscopy in combined *S. gallolyticus* and *S. bovis* groups. Abbreviation: ID, infectious diseases.

those patients who had evidence of intent for colonoscopy (29.6% [213/719]) vs those who did not (42.5% [145/341]; $P \leq .001$) GI consult (29.8% [208/698]) vs no GI consult (41.4% [150/362]; $P < .001$), ID consult (29.4% [171/581]) vs no ID consult (39.0% [187/479]; $P = .001$), or either GI or ID consult (31.9% [266/834]) vs no consult (40.7% [92/226]; $P = .013$) (Figure 3).

There was no increase in the level of compliance to order a colonoscopy in the years following the nomenclature change compared with years prior ($P = .61$). There was no significant delay in ordering of a GI consult or colonoscopy based on organism name. The median number of days from diagnosis of bacteremia to date of colonoscopy order was 9.11 days in the *S. gallolyticus* group and 8.74 days in the *S. bovis* group ($P = .96$).

Univariate analysis revealed that the presence of an ID consult, Hispanic or Latino ethnicity, and the time period of bacteremia diagnosis (Table 2, Figure 4) were associated with intent for colonoscopy. Multivariate analysis showed that patients who received an ID consult or who were Hispanic or Latino were independently associated with intent for colonoscopy (Table 3). Intent for colonoscopy and ID consultation were significantly higher in the years after 2005 as compared with the time period of 2002–2005 (Figure 4).

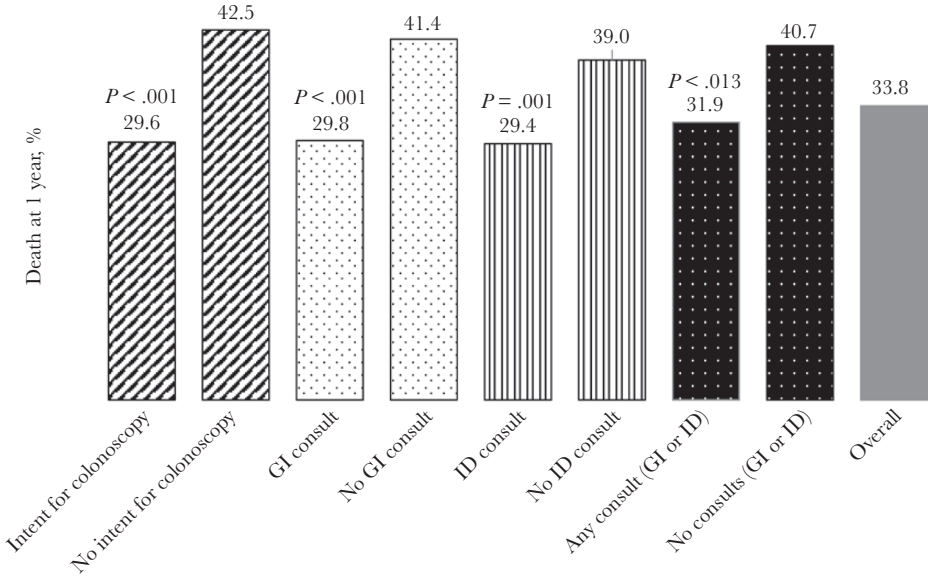


Figure 3. All-cause mortality at 1 year in patients surviving the first 14 days of bacteremia. Abbreviations: GI, gastrointestinal; ID, infectious diseases.

Table 2. Univariate Variables Associated With Intent for Colonoscopy

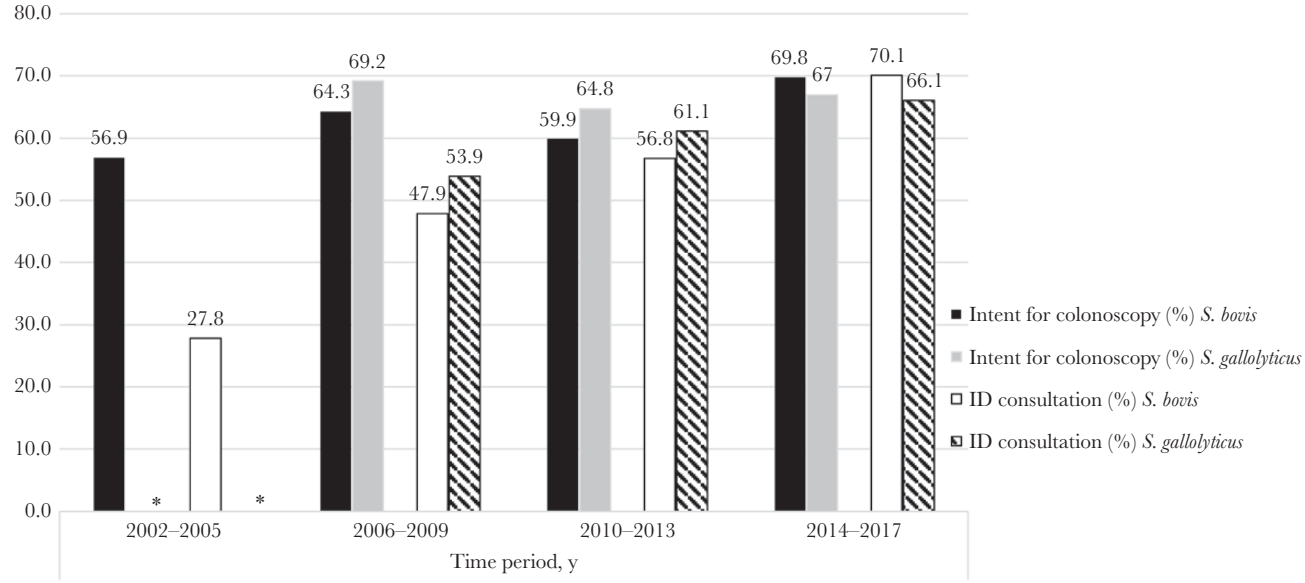
Variable	No. (%) With Evidence for Intent for Colonoscopy	P Value
Gender		.27
Male	732/1163 (62.9)	
Female	9/18 (50.0)	
Age		.80
≥75 y	338/542 (62.4)	
<75 y	403/639 (63.1)	
Hispanic or Latino race/ethnicity		.003
Yes	76/100 (76.0)	
No	665/1081 (61.5)	
White race		.18
Yes	500/780 (64.1)	
No	241/401 (60.1)	
Black race		.55
Yes	97/160 (60.6)	
No	644/1021 (63.1)	
Organism nomenclature		.26
Streptococcus bovis	624/1005 (62.1)	
Streptococcus gallolyticus	117/176 (66.5)	
Period of bacteremic episode		.028
2002–2005	145/255 (56.9)	
2006–2009	198/307 (64.5)	
2010–2013	205/338 (60.6)	
2014–2017	193/281 (68.7)	
Infectious diseases consult		<.001
Yes	458/601 (76.2)	
No	283/580 (48.8)	

DISCUSSION

Colonoscopy rates for patients who are diagnosed with *S. bovis*/*S. gallolyticus* bacteremia range widely from 33% to 77% [9, 11, 12]. Even in cases where the more familiar species name of *S. bovis* is reported, thorough workup for gastrointestinal malignancy may not be performed, which could lead to detrimental and potentially preventable outcomes [10]. Based on concern that providers may not be as familiar with the name change of *S. bovis* biotypes to *S. gallolyticus* initially described by van't Wout and Bijlmer [8], we hypothesized that patients who had bacteremias reported as *S. gallolyticus* may be less likely to have a colonoscopy compared with when the bacteremia was reported as *S. bovis*. However, we found no difference in the rate of intent for colonoscopy between the *S. gallolyticus* and *S. bovis* groups. Interestingly, the *S. gallolyticus* group had significantly more ID consults than the *S. bovis* group, and multivariate analysis showed that patients who received an ID consult were independently associated with intent for colonoscopy, with an odds ratio of 3.4. It is possible that the primary provider's unfamiliarity with the *S. gallolyticus* nomenclature could have prompted more ID consults. Infectious diseases providers are more likely to be aware of changes in microbiology nomenclature, which could have led to appropriate colon cancer screening in the *S. gallolyticus* group despite the relatively unfamiliar name. Conversely the fact that orders for colonoscopies increased over time, could also be an indication that primary providers may have become more aware of the need for GI evaluation over time. In addition, we saw an overall increase in ID consultation and GI consultation, as well as an increase in colonoscopy orders over the years (2002–2017), which could have contributed to the increase in colonoscopies in the *S. gallolyticus* group. Overall, there was no difference in rate of GI consultation between the 2 groups. Again, this may be due to the fact that there were more ID consults in the *S. gallolyticus* group, possibly leading to more GI consults and subsequent colonoscopies in the *S. gallolyticus* group and resulting in no difference between groups. In patients who had an ID consult, there was a higher intent for colonoscopy than in those without an ID consult, regardless of the reported name of the bacteria.

Total all-cause mortality was high at 40.6% (479/1181), but there was no difference in mortality between the *S. bovis* and *S. gallolyticus* groups. After exclusion of 121 patients who had died in the first 14 days, there was a significant decrease in overall mortality of the 1060 remaining patients if they had evidence of intent for colonoscopy, GI consultation, ID consultation, or any consultation compared with those patients who did not, suggesting that ID and GI consultations in patients with *S. bovis*/*S. gallolyticus* bacteremia are associated with lower mortality. ID consultation has been illustrated to decrease mortality in patients suffering from a number of infections such as those caused by multidrug-resistant organisms [13] and *Staphylococcus aureus* [14] and in enterococcal bacteremias [15]. Though we did not investigate specific causes of mortality, based on these studies, appropriate antimicrobial agent use, duration of therapy, and identification and control of the source of bacteremia may explain this finding.

There are several limitations to this study. First and foremost, the organisms assigned to the *S. bovis* group and classification of *S. bovis* biotypes and *S. bovis* subspecies are very inconsistent in the literature. Several different streptococcal species such as *Streptococcus equinis* have been included in the *S. bovis* group by some authors but not all. In addition, when an organism such as *S. bovis*/*S. gallolyticus* is reclassified and subsequently renamed, there is no specific document where this information is published; thus there is no specific time or date that an organism is "renamed." As a result, different laboratories adopt the revised name at different times. Furthermore, for the information to disseminate to health care providers, it requires that they read educational materials or published literature that uses the new name of the organism or rely on laboratories or other providers to educate them. Another limitation was the inability to gather certain data within our VINCI clinical administrative database that could have affected results. For instance,



*No reported *S. gallolyticus* bacteremias during this time period

Figure 4. Increase in intent for colonoscopy and ID consultation in *S. bovis* and *S. gallolyticus* groups over time. Abbreviation: ID, infectious diseases.

we were unable to see if a referral was made to gastroenterologists outside the VA for further gastrointestinal workup after a result of *S. bovis*/*S. gallolyticus* was acknowledged. We were also unaware of any "curbside" consults regarding the clinical significance of *S. bovis*/*S. gallolyticus* to either the infectious diseases service or gastroenterology service, which may have triggered further workup. Of note, 18 out 102 sites did not have any of their bacteremic cases result in ID consultation; however, 12 of these sites had only 1 or 2 bacteremic episodes. It is likely that many of these 18 sites did not have ID consultation available. Lastly, there may be alternative mechanisms that microbiology laboratories use to communicate nomenclature updates in their reports that may have been missed by our methods of data collection. For instance, we were unable to see the text portion of blood culture reports, which may have contained the former and more familiar name of *S. bovis*. These factors could have contributed to a lack of difference in the screening rates between the 2 groups.

Although a difference in screening rates between both the *S. bovis and S. gallolyticus* groups was not seen in the current study, the proposal to include both the old and revised names of *S. bovis/ S. gallolyticus* by all laboratories in United States, including the VA Healthcare Network, with a statement or other form of communication to the provider recommending workup for colorectal malignancy would appear beneficial. Further clarification of the role and importance of distinguishing *S. bovis* biotypes to fully understand their relationships with different gastrointestinal and other associated pathologies is needed, as well as appropriate education to providers on the recommendations to pursue screening for individuals with *S. bovis*/*S. gallolyticus* bacteremia. Notably, colon cancer screening guidelines by the American Cancer Society, American College of Gastroenterology, and United States Preventative Task Force do not recognize *S. bovis*/*S. gallolyticus* as a risk factor for colon cancer despite the abundance of evidence illustrating the relationship. We suggest guidelines to incorporate this pathogen as risk factor for colon cancer. In addition, we hope that this study will educate providers on the nomenclature revision of *S. bovis*/*S. gallolyticus* and encourage providers to be aware of new evidence and recommendations in the medical literature, particularly when they lead to a change in management that directly impacts patient morbidity and mortality.

Table 3. Independent Variables Associated with Intent of Colonoscopy

Variable	Relative Risk (95% CI)	P Value
Infectious diseases consult	1.57 (1.46–1.66)	<.001
Hispanic or Latino race/ethnicity	1.21 (1.04–1.34)	.016

CONCLUSIONS

No statistically significant difference in colon cancer screening rates between patients with bacteremias reported as *S. bovis* vs *S. gallolyticus* was found. There was a decrease in overall mortality in all *S. bovis*/*S. gallolyticus* bacteremic patients who had an ID consult, GI consult, or evidence of colonoscopy.

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Patient consent. For this retrospective study, our Institutional Review Board approved waiver of patient consent. The "Methods" section has been updated to incorporate this information.

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