

# Association of bacteremias of *Streptococcus gallolyticus* with the development of colorectal cancer in people 65 years of age

## Abstract

**Objective:** To establish the etiological mechanisms of *Streptococcus gallolyticus* bacteremia in the development of colorectal cancer in 65-year-olds.

**Methods:** A review of articles published in PubMed, BioMed Central, Scielo, Elsevier, Springer, among others, was carried out using the following keywords: *Streptococcus bovis* and colorectal cancer, *Streptococcus gallolyticus* and colorectal cancer, *Streptococcus gallolyticus Streptococcus bovis* and Association between *Streptococcus bovis* and colorectal cancer “.

**Results:** A total of 568 patients with colorectal cancer and a total of 362 patients with colorectal adenomas presenting with *S. gallolyticus* bacteremia were determined from a total of 15 case reports from the 1974 to 2017 period. Patient age was reported in the 15 reports with an average of 65 years.

**Conclusions:** It was concluded that the association between colorectal tumors with *S. gallolyticus* appears to be of etiological nature. Evidence presented through 15 case reports retrospectively assessed from the period 1974 to 2017 shows that there is a fundamental relationship between *S. bovis* bacteremia and colorectal cancer.

**Keywords:** streptococcus gallolyticus, streptococcus bovis, bacteremia, colorectal cancer

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## Introduction

In Mexico, colorectal cancer ranks fourth in incidence in both men and women, and is the sixth cause of cancer mortality. Those over 50 years old are the most vulnerable according to the International Agency for Research on Cancer. *S. gallolyticus* (ex bovis) is a commensal microorganism of the human intestine in 2.5 to 15% of population.<sup>1</sup> however, in 1974 Klein first observed the direct association it has with colorectal neoplasms. It is estimated that around 25 to 80% of patients with bacteremia of *S. gallolyticus* have concomitant colon tumors and an incidence of 18-62% of cases of infective endocarditis, which orders a screening colonoscopy in a minimum period of 2 days at 4 years in patients with bacteremia of *Streptococcus gallolyticus* since the infection could be a silent sign of pre-malignant or malignant neoplasms. *S. gallolyticus* belongs to the family Streptococcaceae and is an facultative anaerobic Gram+bacterium, in the form of cocci or diplococci, also belonging to group D of Lancefield, which gives it the ability to hydrolyze esculin and grow in the presence of bile.<sup>1-4</sup> Initially *S. gallolyticus* received the name of *Streptococcus “bovis”* however the taxonomy changed in 2003 by Schlegel in the following way: *Streptococcus bovis* biotype I is now known as *S. gallolyticus* subspecies *gallolyticus* (mannitol positive); *S. bovis* biotype II/1 that are now known as *S. infantarius* subspecies *infantarius* (negative mannitol and negative  $\beta$ -glucuronidase) and *S. infantarius* subspecies *coli* (negative mannitol and negative  $\beta$ -glucuronidase) and *S. bovis* biotype II/2 a *S. gallolyticus* subsp. *Pasteurianus* (negative mannitol and positive  $\beta$ -glucuronidase).<sup>5-8</sup> The literature analyzed suggests that the age of prevalence in patients with *S. gallolyticus* bacteremia is 65 years ( $\pm$  12 years) on average, and a predominance of male patients.<sup>1-11</sup> Multiple factors can lead to the transformation of healthy intestinal mucosa to cancer, both inheritance and environmental factors such as

personal and/or family history of colorectal cancer and adenomatous polyps, hereditary syndromes, diet (fat consumption) and obesity, physical inactivity, alcoholism, smoking, inflammatory bowel disease (such as ulcerative colitis) and pot agents Essentially infectious.<sup>10-13</sup> Specifically in patients with bacteremia due to *S. gallolyticus*, according to statistics, the most associated factors are obesity, alcohol abuse, smoking, diabetes mellitus, gastrointestinal surgery and cancer present or ancient.<sup>14</sup>

*S. gallolyticus* was first associated with colorectal cancer and infective endocarditis in 1951 by McCoy and Mason, however it was not until 1977 that *S. gallolyticus* was recognized by Robert Klein as the pathogen specifically related to the concomitant development of cancer. of colon through a report in which he made a complete evaluation of 15 patients with bacteraemia due to *S. gallolyticus*.<sup>1,6,8,10,13-15</sup> With the report of Klein, a barrier that prevented directly related to *Streptococcus* was overcome *gallolyticus* with colorectal cancer, since through this study it was possible to formally establish the association that *S. gallolyticus* bacteremia has with the concomitant development of colorectal cancer, malignant or pre-malignant colorectal neoplasms and even with gastrointestinal neoplasms. This additionally suggests with certainty the performance of colonoscopy exams in infected patients, since the performance of colonoscopy after *S. gallolyticus* bacteremia could allow the detection of colorectal neoplasms in early or precancerous stages in affected patients, and thus, its clinical evolution would be beneficial for the reduction of morbidity and general mortality.<sup>11</sup> The process by which an adenomatous polyp is transformed into carcinoma is not yet clear. However, the evidence suggests that oncogenes could be activated by mutations that promote the altered mucosal proliferation of the colon, accompanied by the inhibition of genes that suppress tumor

genesis. The time in which a polyp can transform is greater than about 5 years.<sup>16-18</sup> Possible pathogenic mechanisms lie at the molecular level and could be involved in uncontrolled cell proliferation that involves various factors such as the nuclear factor kB (NFkB), free radicals and protein kinases activated by mitogens, and which may be the responsible for the progression of pre-neoplastic colorectal lesions associated with bacteremia due to *S. gallolyticus* that lead to the development of colorectal cancer.<sup>4,10,16,19,20-24</sup> The bacterium *S. gallolyticus* is part of the microbiota in 2.5-15% of the total population, however, its increase in fecal load is frequent in patients with bacteremia, probable pre-neoplastic or neoplastic lesions and/or endocarditis, and that the bacteria follows a selective pathway of adhesion to collagen and histone as protein A for collagen I, IV, fibronectin and fibrinogen. From the active colonization of *S. gallolyticus*, its growth is activated in the colorectal tissue. To which three consequent processes are obtained.<sup>4,5,16</sup> Inflammation and action of cytokines. TNF, IL-1 and IL-6 are produced in response to the proliferation of *Streptococcus gallolyticus* in the colorectal tract as the immune mechanism of the host, and this leads to the formation of radicals which begins to damage the DNA and causes mutations that promote injury. neoplastic or preneoplastic and/or cancer-induced from scratch. Infection through cytokines and the free radicals produced causes the activation of cyclooxygenase-2 (Cox-2) and nuclear factor Kb (NF-kb). COX-2 through prostaglandins increases cell proliferation and angiogenesis and inhibits apoptosis and/or induces cancer from scratch. IL-8 is a potent angiogenic factor and acts as a chemotactic factor for neutrophils and its increase promotes the diffusion and spread of tumors that promote neoplastic or preneoplastic lesions. Tissue alteration: The above factors lead to increased blood vessel permeability which may cause the translocation of *S. gallolyticus* within the portal circulation and move to general circulation transport, causing bacteremia and through selective factors of adhesion that *Streptococcus gallolyticus* has can adhere to the endocardial tissue through the collagen and histone binding pathway as protein A. This event leads to the formation of a biofilm and consequently causes infective endocarditis. The translocation of *S.*

*gallolyticus* within the portal circulation may also cause a liver disease that alters bile acids and immunoglobulins, in addition to changing the intestinal microbiota, which leads to the loss of the biological balance of the intestine and facilitates colorectal carcinogenesis. Induction of uncontrolled cell proliferation. *S. gallolyticus* leads to increased phosphorylation of 3 classes of mitogen-activated protein kinases (MAPKs), which increases DNA synthesis, causing uncontrolled cell proliferation and promotes neoplastic or pre-neoplastic lesions and/or inducing cancer from scratch.

## Methods

Design of retrospective and descriptive study in which a bibliographic review of the scientific literature is presented on the association that exists between *Streptococcus gallolyticus* (ex bovis) and its relevance at a medical level, before the possible measures that should be taken to make a timely diagnosis. We performed a search for review articles published on sites such as PubMed, BioMed Central, Scielo, Elsevier, Springer, among others, using the keywords: “*Streptococcus bovis* and colorectal cancer”, “*Streptococcus gallolyticus* and colorectal cancer”, “*Streptococcus gallolyticus*”, “*Streptococcus bovis*” and “Association between *Streptococcus bovis* and colorectal cancer”

## Results

From a total of 15 case reports retrospectively evaluated from the period of 1974 to 2017, a total of 568 patients reported with colorectal cancer and a total of 362 patients with colorectal adenomas who had bacteremia due to *Streptococcus gallolyticus* were determined. The age of the patients was reported in the 15 reports with an average of 65 years (64.99%). Therefore, these reports constitute a clear association between patients with *S. gallolyticus* bacteraemia and the concomitance that it has with the development of colorectal cancer and colorectal adenomas. The incidence in these reports was greater for colorectal cancer compared to cases with colorectal adenomas, which may indicate the importance of timely detection of premalignant lesions, in order to prevent their progression (Table 1).

**Table 1** Report of cases of bacteremia due to *Streptococcus gallolyticus* in patients with colorectal cancer and adenomas

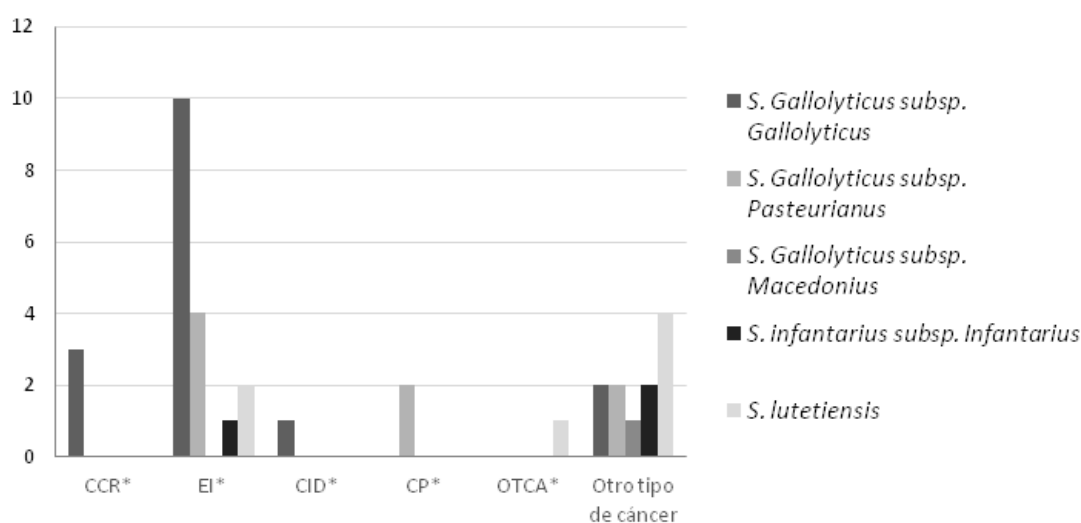
Reference	Author - year	Age promedio	Patients with colorectal cancer and bacteremia due to <i>Streptococcus gallolyticus</i>	Patients with adenomas colorrectales and bacteriemia <i>Streptococcus gallolyticus</i>
[7]	Boleij, 1974-2010	64	321	295
[3]	Amado, 2003-2014	72.7	1	6
[21]	Tsai, 2004-2014	65	15	35
[15]	Ferrari, 2008	46	1	
[5]	Bartolomé, 2009	84		1
[4]	Abdulmir, 2010	59.22	52	
[28]	Shanan, 2011	58	1	
[23]	Paritsky, 2012-2013	62.53	17	22
[2]	Galdy, 2012	61	1	
[27]	Abeni, 2013	57	1	
[25]	Nemoto, 2014	79		1
[18]	Pérez, 2014	57	1	

Table continued..

Reference	Author - year	Age promedio	Patients with colorectal cancer and bacteremia due to <i>Streptococcus gallolyticus</i>	Patients with adenomas colorrectales and bacteriemia <i>Streptococcus gallolyticus</i>
[24]	Fregoli, 2014	68.5	1	1
[11]	Chand, 2016	71		1
[12]	Franch, 2017	70	156	
	<b>Total</b>	<b>64.99 (65)</b>	<b>568</b>	<b>362</b>

The species of *S. gallolyticus* have been studied over time, however, in 2016 ELSEVIER established through a report based on the incidence, the most frequent pathologies in each species, among which colorectal cancer is found generally associated with *S. gallolyticus* subspecies *gallolyticus*; infectious endocarditis with *S. gallolyticus*

subsp. *gallolyticus* and *S. gallolyticus* subsp. *pasteurianus*; small bowel cancer only to *S. gallolyticus* subsp. *gallolyticus*; Pancreatic cancer is associated only with *S. gallolyticus* subsp. *pasteurianus* and other types of abdominal cancer are associated only with *S. Lutetiensis* (Figure 1).



**Figure 1** Pathologies associated with *Streptococcus gallolyticus*.

CCR \*, colorectal cáncer; EI \*, infectious endocarditis; CID \*, small bowel cáncer; CP \*, pancreatic cáncer; OTCA \*, other types of cáncer

## Discussion

The data collected lead to the evident existing need for the mandatory performance of a screening colonoscopy in patients with bacteremia due to *Streptococcus gallolyticus* as a follow-up and as a complete diagnostic evaluation. Unfortunately, this association has been underestimated in the medical community, and the nomenclature trap in the literature and laboratories makes bacterial identification difficult. However, through the observation and adequate and timely monitoring of the patient, due to the possible pathogenic role of *Streptococcus gallolyticus* in colorectal cancer, it is possible to perform an early diagnosis and potentially curative treatment that saves the patient's life <sup>4,5, 9-15,22-24</sup>. Therefore, the detection of this bacterial group in blood cultures or serum levels of elevated IgG antibodies against *Streptococcus gallolyticus* indicates the need for an evaluation to establish the origin of bacteremia and the presence of possible complications.<sup>3,18,23,24</sup> The present analysis describes a series of case reports that represent the evidence that exists between bacteraemia due to *S. gallolyticus* and its association with the presence of colorectal cancer and colorectal adenomas in patients with an average age of 65 years. The incidence in the reports was higher for colorectal cancer compared to cases with colorectal adenomas, however it is essential to monitor the presence of preneoplastic lesions

in patients with a history of *S. gallolyticus* bacteremia, since through the analysis of several reports it was determined that preneoplastic lesions can increase in size over time and become malignant, since 50 to 70% of patients with bacteremia already have or will develop colorectal cancer.<sup>2</sup> Likewise, a hypothesis is presented that explains the possible etiological mechanisms in the colorectal cancer that *S. gallolyticus* poses, based on the evidence found, which suggests that they could be related to the activation of oncogenes by mutations that promote the altered proliferation of the mucosa of the colon, accompanied by the inhibition of genes suppressing tumor genesis

## Conclusion

It was concluded that the association between colorectal tumors with *S. gallolyticus* seems to be of an aetiological nature. The evidence presented through 15 case reports evaluated retrospectively from the period of 1974 to 2017 shows that there is a fundamental relationship between a *S. bovis* bacteremia and colorectal cancer. Therefore, a diagnosis of bacteraemia due to *S. gallolyticus* should be considered as a silent signal, and a minimum follow-up of 2 to 4 years of follow-up with colonoscopy in these patients for prophylaxis purposes is suggested.<sup>2,22</sup>

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## Conflict of interest

The author declares no conflict of interest.

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