

Prevalence of Colonic and Liver disease in Patients with group D Streptococcus Infection in Tertiary Hospital in Thailand

Piyant Chonmaitree, Worawut Roongsangmanoon, Dittapol Muntham, Piyanch Piyasatit, Prasit Upanan

Piyant Chonmaitree, Worawut Roongsangmanoon, Piyanch Piyasatit, Prasit Upanan, Department of Medicine, Faculty of Medicine, Srinakharinwirot University, Nakhon Nayok, Thailand
Dittapol Muntham, Department of Mathematic, Faculty of Science and Technology, Rajamangala University of Technology Suvarnabhumi, Thailand

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Correspondence to: Piyant Chonmaitree, Department of Medicine, Faculty of Medicine, Srinakharinwirot University, 62 Moo 7, Rangsit Nakhon Nayok Road, Ongkharak, Nakhon Nayok, 26120 Thailand.

Email: piyant_n@yahoo.co.th
Telephone: +66-37-395085

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ABSTRACT

BACKGROUND: Group D Streptococcus (GDS) infection was most often associated with infective endocarditis and bacteremia. GDS formerly named as *Streptococcus bovis*. In addition to an association of GDS with colonic disease, evidence of a correlation with liver disease has been presented. This study aimed to evaluate the prevalence of colonic and liver disease in patients with GDS and to identify factors that increase risk of colonic and liver diseases in patients with GDS infection.

METHODS: A prospective study of all adult patients with GDS

infection at Her Royal Highness Princess Maha Chakri Sirindhorn Medical Center between March 2016 and December 2017 and retrospective chart review between January 2012 and February 2016 were performed.

RESULTS: Sixty-two episodes of GDS infection in 45 patients were included in the study. Thirty-two patients (51.6%) were male and mean age was 64 ± 10.7 years. Two patients (3.2%) was diagnosed colorectal cancer and 49 patients (79%) had liver cirrhosis before GDS infection. Most of patients had bacteremia (93.5%). Subspecies were identified in 48.4% of patients, 25 patients (40.3%) were *S. gallolyticus* and 5 patients (8.1%) were *S. pasteurianus*. Forty-seven percent of patients had colonic evaluation and 19 patients (30.7%) had colonic disease. Prevalence of colonic disease and liver disease in GDS infection was 33.8% and 79%, respectively. Six patients with GDS infection had both colonic and liver disease. Overall median to mortality was 1.28 years (95%CI 0.68-1.86). Mortality rate was 48 person/100 person-year.

CONCLUSION: Prevalence of colonic disease and liver disease was 33.8% and 79%, respectively. Patients with GDS infection should be evaluated for colonic and liver disease. Colonic and liver disease may simultaneous occurs in the patients with GDS infection.

Key words: Group D Streptococcus; Colonic disease; Colonic cancer; Liver disease

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INTRODUCTION

Group D Streptococcus (GDS) is a species of gram positive bacteria which usually found as normal flora of the human. GDS infections are most often associated with infective endocarditis (IE) and bacteremia^[1]. GDS formerly named as *Streptococcus bovis* (SB). In 1951, an association between SB and colorectal cancer (CRC) was first reported^[2]. Recently, an association between SB and liver disease

was also reported^[3]. The aims of the current study were to evaluate prevalence of colonic and liver disease in patients with GDS and to identify factors that increase risk of colonic and liver diseases in patients with GDS infection.

PATIENTS AND METHOD

The prospective study was conducted in Her Royal Highness Princess Maha Chakri Sirindhorn Medical Center from March 2016 to December 2017. All adult patients with GDS infection were enrolled. Patients were excluded if they had contraindication for colonic evaluation. Participants provided written and informed consent. Data about age, sex, weight, underlying disease, site of GDS infection, biotype of GDS, blood tests (CBC, BUN, creatinine, electrolyte, liver function test), and outcome of treatment was recorded. A retrospective chart review of adult patients with GDS infection since January 2012 to February 2016 was also performed. The study protocol was approved by the Ethics Committee of Faculty of Medicine, Srinakharinwirot University.

Evaluation of colonic disease was performed by barium enema, flexible sigmoidoscopy or colonoscopy. Flexible sigmoidoscopy and colonoscopy were performed using Olympus CF 170, Fujinon EC 530 WR or Pentax EC 3490i. Type of polyps and colorectal cancer were confirmed by histopathological examination. Colonic diseases included CRC, polyps and diverticulosis.

Liver diseases comprised of liver cirrhosis and hepatocellular carcinoma (HCC). The diagnosis of liver cirrhosis was based on clinical, biochemical results and imaging (ultrasound, computer tomography or magnetic resonance imaging). Diagnosis of HCC based on CT or MRI finding according to EASL guideline^[4]. Bacteria were identified using culture and subspecies determination was performed using mass spectrometry (MEDITOF) or biochemistry testing (VITEK 2).

For statistical analysis, continuous variables were reported as mean and standard deviation and discrete variables as numbers and percentage. Differences between frequencies were analyzed using the Chi-square test or Fisher's exact test, a *p* value of < 0.05 is taken to indicate statistical significance. Survival analysis was assessed according to the Kaplan-Meier method and compared by the log-rank test. A cox regression model was applied to estimate the hazard ratios (HR), 95% confidence intervals (CI) and *P* value of mortality. Results were considered statistically significant for *p* < 0.05. All the analyses were conducted with the use of SPSS software (version 23.0, SPSS incorporated).

RESULTS

Sixty-two episodes of GDS infection in 45 patients were included in the study. Thirty-two patients (51.6%) were male. The mean age was 64 ± 10.7 years. Twenty-three patients (23%) had a history of hospitalization within 3 months. Two patients (3.2%) were diagnosed CRC and 49 patients (79%) had liver cirrhosis before GDS infection. Most of patients had bacteremia (93.5%), other sites of infection were gastrointestinal including spontaneous bacterial peritonitis (13%), infected continuous ambulatory peritoneal dialysis (4%) and central nervous system (1.6%). GDS IE was not found. Subspecies was identified in 30 patients (48.4%), 25 patients (40.3%) were *S. gallolyticus* and 5 patients (8.1%) were *S. pasteurianus*. Forty-seven percent of patients had colonic evaluation (colonoscopy 37.1%, flexible sigmoidoscopy 9.7%) and 19 patients (30.7%) had colonic disease. Mean age of patients with colonic disease was 63 ± 10.9

years. One patient (1.6%) had CRC, 10 patients (16.1%) had colonic polyps and 10 patients (16.1%) had diverticulosis. The histopathology of polyps was tubular adenoma in 9 patients and inflammatory polyp in 1 patient. Prevalence of colonic disease was 33.8%. Patients with underlying hematologic disease were associated with colonic disease (Table 1). Univariate logistic regression analysis was performed, odds ratio of underlying hematologic disease was 12.5 (1.4-115.6, *p* 0.02).

Forty-nine patients (79%) had liver cirrhosis and 16 patients (28.1%) had HCC. All liver diseases were diagnosed before GDS infection. Prevalence of liver disease in GDS infection was 79%. Univariate logistic regression analysis was performed, underlying cardiovascular disease, renal failure, solid malignancy, bacteremia, and platelet less than 150,000/mm³ were associated with liver disease in GDS infection (Table 2). In multivariate logistic regression analysis, we found that platelet less than 150,000/mm³ were associated with liver disease in patients with GDS infection (Odds ratio 11.3; 95% CI 1.9-66.7; *p* 0.007).

Five patients had re-infection (2 episodes in 3 patients, 3 episodes in 1 patient and 4 episodes in 1 patient). All patients had cirrhosis with bacteremia. Hypoalbuminemia and thrombocytopenia were found in all patients. One patient had colonic diverticulosis and one patient had colonic polyp.

Twelve of 25 patients with *S. gallolyticus* infection had colonic disease and 22 patients had liver disease. All of patients with *S. pasteurianus* had liver disease and 2 patients had colonic disease. Six patients with GDS infection had both colonic and liver disease.

Average follow-up for all GDS infected patients in this study was 1.34 years. Overall median time to mortality was 1.28 year (95%CI 0.68-1.86). Mortality rate was 48 person/100 person-year. In multivariate cox regression analysis, male sex, underlying solid malignancy and nosocomial infection were identified to be independent risk factors affecting mortality (Table 4).

DISCUSSION

The most commonly reported sites of GDS infection are IE and bacteremia^[1]. Other infections caused by GDS include meningitis, septic arthritis, lateral deep neck abscess, spontaneous bacterial peritonitis, urinary tract infection, osteomyelitis, discitis, neck abscess and infected continuous ambulatory peritoneal dialysis^[5]. By contrast, in this present study, IE caused by GDS was not identified.

Nomenclature of these species is confusing. Previously, GDS named as *Streptococcus bovis*. SB is classified into 2 biotypes, biotype I and II. Biotype II is further divided into subtype II/1 and II/2. Current taxonomy based on genetic analysis classified GDS into *Streptococcus gallolyticus* (SG) (formerly biotype I), *Streptococcus infantarius* (formerly biotype II/1), *Streptococcus lutetiensis* (formerly biotype II/1) and *Streptococcus pasteurianus* (formerly biotype II/2)^[6,7]. An association between enterococcal IE and CRC was first reported by McCoy and Mason in 1951. In 1974, Hoppes and Lerner suggested that enterococci in the previous report were SB^[2]. Six to eight percent of SB bacteremia and 9-67% of SB IE had CRC^[2,5,8-13]. CRC can occur four years after SB infection^[5,14]. Association between SB bacteremia or IE and colonic polyps was also reported, ranging from 35-47%^[2,15]. CRC was more often in SB IE than other sites^[2,13,15,16]. IE or bacteremia from SB biotype I was more frequently associated with CRC than biotype II but studies from Hong Kong showed SB biotype II/2 was dominantly associated with CRC^[2,5,17,18]. Meta-analysis from case reports and case series also demonstrated that SB biotype I increased risk of

Table 1 Factors associated with colonic disease in GDS infected patients.

	without colonic disease	with colonic disease	p value
Male	22	10	0.65
Age ≥ 50 years	36	21	0.16
Body weight ≥ 60 kg	16	13	0.12
Underlying disease			
Hypertension	20	15	0.09
Cerebrovascular disease	5	2	1
Respiratory disease	2	1	1
Cardiovascular disease	5	2	1
Diabetes mellitus	17	12	0.24
Renal failure	9	7	0.33
Cirrhosis	32	17	1
Hematologic disease	1	5	0.01
Hematologic malignancy	2	0	0.55
Solid malignancy	14	5	0.4
Smoking	7	8	0.07
Alcohol drinking	20	12	0.53
Bacteremia	38	20	1
Central nervous system infection	0	1	0.34
Gastrointestinal infection	9	4	1
Lower respiratory tract infection	1	0	1
Infected continuous ambulatory peritoneal dialysis	3	1	1
Biotype			0.11
S. gallolyticus	3	2	
S. pasteurianus	13	12	

Table 2 Factors associated with liver disease in Patients with GDS infected patients.

	without liver disease	with liver disease	p value
Male	8	24	0.42
Age ≥ 50 years	12	45	1
Body weight ≥ 60 kg	5	24	0.42
Underlying disease			
Hypertension	9	26	0.3
Cerebrovascular disease	2	5	0.63
Respiratory disease	2	1	0.11
Cardiovascular disease	4	3	0.03
Diabetes mellitus	4	25	0.19
Renal failure	7	9	0.03
Hematologic disease	2	4	0.6
Hematologic malignancy	2	0	0.04
Solid malignancy	1	18	0.05
Smoking	5	10	0.27
Alcohol drinking	7	25	0.86
Bacteremia	10	48	0.03
Central nervous system infection	1	0	0.21
Gastrointestinal infection	1	12	0.27
Lower respiratory tract infection	0	1	1
Infected continuous ambulatory peritoneal dialysis	4	0	0.001
Biotype			1
S. gallolyticus	5	20	
S. pasteurianus	1	4	

Table 3 Factor associated with mortality in GDS-infected patients

character	Number	mortality rate	95% CI	p value
Male	29	0.72	0.17-1.42	0.01
Age ≥ 50 years	48	0.5	0.67-1.83	0.39
Body weight ≥ 60 kg	23	0.5	0.18-1.07	0.76
Underlying disease				
Hypertension	29	0.47	0.59-2.00	0.95
Cerebrovascular disease	6	1.38	0.49-	0.06
Respiratory disease	3	0.37	0.96-	0.85
Cardiovascular disease	7	0.7	0.49-2.00	0.36
Diabetes mellitus	23	0.47	0.28-2.13	1
Renal failure	13	0.87	0.95-2.00	0.17
Cirrhosis	40	0.5	0.67-1.86	0.62
Hematologic disease	3	0.67	1.08-	0.76
Hematologic malignancy	2	6.35	0.084-	0.01
Solid malignancy	16	1.05	0.17-1.53	0.01
Smoking	13	0.55	0.16-1.83	0.57
Alcohol drinking	26	0.53	0.67-1.74	0.61
Type of infection				0.000
Community-acquired	49	0.42	1-1.99	
Noncommunity-acquired	4	6.29	0.084-	
Bacteremia	49	0.48	0.67-1.83	0.52
Central nervous system infection	1	0		
Gastrointestinal infection	11	1.2	0.06-1.83	0.02
Infected continuous ambulatory peritoneal dialysis	4	0.61	1.06-	0.9
Biotype				0.07
S. gallolyticus	14	0.79	0.24-1.43	
S. pasteurianus	1	0.06	1.53-	
Hct < 37%	47	0.48	0.08-	0.98
WBC count				0.61
WBC < 4,000/mm ³	2	0.85	0.23-	
WBC > 12,000/mm ³	26	0.37	0.69-	
Platelet < 150,000/mm ³	27	0.46	0.77-2.13	0.73
Serum sodium < 135 mEq/L	32	0.55	0.28-2.00	0.42
Albumin < 3.5 g/dl	51	0.5	0.67-1.83	0.39
Total bilirubin ≥ 2 mg/dl	26	0.54	0.22-	0.63
AST ≥ 35 U/L	38	0.46	0.77-1.86	0.85
ALT ≥ 35 U/L	23	0.47	0.23-	0.81
ALP ≥ 150 U/L	17	0.53	0.1-1.74	0.41

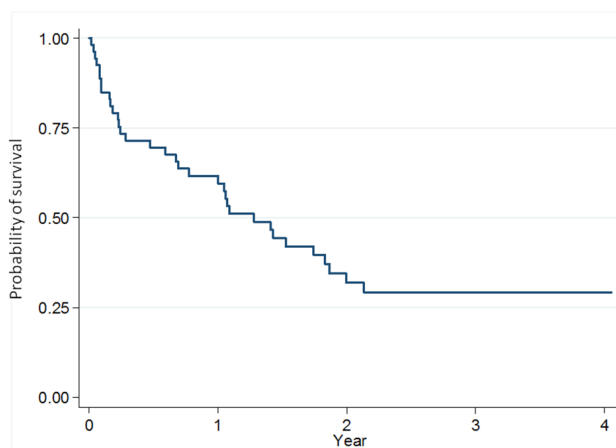


Figure 1 Kaplan-Meire estimates of survival in patients with SB/SG infection.

Table 4 Multivariate analysis for survival.

Variable	Hazard ratio	P value	95% CI
Sex	2.3	0.025	1.1-4.7
Underlying solid malignancy	2.6	0.007	1.3-5.3
Nosocomial infection	7.1	0.001	2.2-23.6

CRC comparing with SB biotype II but the authors suggested that inconsistent naming of SB may be biased the result^[16]. Studies using recent taxonomy demonstrated that SG bacteremia or IE was associated with underlying CRC^[5,10,17-19]. SG bacteremia or IE was strong correlated with CRC when compared with *Enterococcus* and *Bacteroides fragilis*^[2,7,20]. Chance of SG bacteremia or IE in CRC patient is much lower than chance of CRC in SG bacteremia or IE^[5]. DNA of SG was found in 49% of CRC^[21]. Association of SG and adenoma was more evident than CRC^[5,12,14,15,22]. Prevalence of colonic disease in GDS infected patients was 33.8% in this study. Only 3 patients had colorectal cancer, 2 patients with SG and 1 patient with *S. pasteurianus*. Prevalence of CRC and colonic polyps in GDS infection was lower than the previous report which may cause by small sample size, low prevalence of CRC in Thai population and no GDS IE in the current study. CRC in patients with SB bacteremia/IE may depend on geographic and ethnic group. There is only 2 subspecies in this study, SG and *S. pasteurianus*. SG bacteremia was more common than *S. pasteurianus* bacteremia. CRC and colonic polyps can be found in both subspecies with no statistically significant difference.

SB carriage rate was low in normal population^[2,23]. Fecal carriage rate of SB increased in CRC compared with healthy control^[5,16,24]. SB/SG carriage in CRC was higher than polyps and normal population, respectively^[25]. SB/SG colonization inside tumor lesions was higher than on mucosal surface of CRC and normal. Patients with bacteremia have an increased risk of colonization^[21]. Patients with CRC had median IgG titer to SB higher than controls but IgM titer was similar^[2,16]. SB/SG antibody by immunoblot and immunofluorescence was not found in CRC^[20]. IgG to SG by ELISA was significantly higher in CRC than control^[3,20]. IgG to SB and *E.fecalis* in patient with CRC was higher than control^[20]. In adenoma, SB/SG IgG was higher than in CRC and control^[3].

Pathogenesis of CRC in SB/SG patient is not completely understood. It is questionable that bacteria originates or facilitates carcinogenesis or preexisting colonic polyp or CRC facilitates bacteremia. SG can survive in the gut and produces enzymes that utilize diverse carbohydrate in the gut^[8]. Virulence factors of SG are polysaccharide capsule glycan mucopolysaccharides, 3 types of pili and collagen-binding proteins^[5,26]. SG can colonize in a paracellular fashion across malignant intestine by expressing collagen-binding adhesins and 3 types of pili^[5,8,27]. SB/SG adheres to host via extracellular matrix proteins, collagen type I, II, IV, fibrinogen, tenascin, laminin and forms biofilms but does not enter epithelium^[5,8,27]. Another study demonstrated SG highly efficient adhere extracellular matrix using collagen type I, IV, V, fibrinogen and fibronectin^[28]. Histone-like protein A is the adhesins of SG which binding to heparan sulfate proteoglycans of colonic tissue^[29]. SG disrupts capillary channels and enters blood circulation leading to bacteremia or IE. Protein of cell wall of SB induced neoplastic transformation more potent than intact bacteria^[30]. Cell wall antigen of SB can bind human colonic cancer cell (CaCo-2) in vitro and increase production of inflammatory cytokines (TNF- α , IL-1B, IL-6, IL-8)^[5,11,21,30-33]. Cytokines and chemical mediators promote vasodilation and enhance capillary permeability that facilitates

bacterial entrance and adherence to various cells^[3,30,32]. Inflammatory cytokines stimulate nitric oxide and free radicals formation^[30]. NF- κ B and IL-8 are important mediators for progression of adenoma to cancer. NF- κ B promotes carcinogenic effect and IL-8 induces angiogenic effect on colorectal mucosa^[33]. Phosphorylation of mitogen activated host kinases 3 (MAPK 3) is enhanced. Cell proliferation, transformation and genetic mutation are increased. MAPKs also induce COX-2 which promotes cellular proliferation, angiogenesis and inhibit apoptosis^[2,5]. In vitro study, SB wall extracted antigen induced overexpression of COX-2^[31,32]. SG increases tumor burden, dysplasia grade, cell proliferation and β -catenin staining in colonic crypts of mice^[34]. Increase of β -catenin c-myc and proliferating cell nuclear antigen (PCNA) in colonic cancer cells following incubation of SG knockdown or inhibitor of β -catenin abolished effect of SG. Hyperplastic colonic crypts are not occurred in normal rats receiving SB wall extracted antigen, while 50% of rats receiving both chemocarcinogen and SB wall extracted antigen developed neoplastic lesions^[30]. Development of CRC may occur only in patient with preneoplastic lesions. From the latest scientific evidence, SB/SG promotes carcinogenesis rather than CRC facilitates bacteremia. SB/SG can trigger severe inflammatory reaction in colorectal mucosa, induce inflammation and angiogenic cytokines leading to free radical formation and cancer development.^[3,21,30,33]

Nineteen to sixty-one percent of SB bacteremia or IE had underlying liver disease^[5,7,14,15,35]. Majority of liver disease is cirrhosis. SB/SG IE had chronic liver disease significantly higher than IE from other organism^[15]. SB bacteremia with or without liver disease had the same mortality (46% VS 33%)^[35]. In patients with SB bacteremia or IE, simultaneous liver disease and CRC can occurred^[5,14]. In patients with SB bacteremia who has advanced liver disease would not exclude colonic disease^[35,36]. SB biotype I commonly associated with liver disease^[8,15,24]. *S. pasteurianus* is associated with cirrhosis and SG is associated with non-cirrhosis^[37]. In SB sepsis, patients with or without liver disease had similar mortality^[35]. SB bacteremia in advanced liver disease had very poor prognosis^[35]. From this study, the prevalence of liver disease was similar to previous study. Liver diseases were found in both subspecies (SG and *S. pasteurianus*). Simultaneous liver disease and colonic disease was also found.

In cirrhosis, intrahepatic blood shunting, impaired bacteria clearance from portal blood, altered hepatic secretion of bile salts or immunoglobulin (IgG) and compromised hepatic reticuloendothelial system may promote SB overgrowth and translocation into portal venous system. Thus cirrhotic patients are susceptible to develop bacteremia^[5,14,15,35].

Mortality of GDS-infected patients in current study was high. Male, underlying solid malignancy and nosocomial infection were associated with higher mortality.

SB infection was also reported in other malignancy including multiple myeloma, metastatic melanoma, esophageal cancer, duodenal cancer, gallbladder cancer, pancreatic cancer, squamous cell cancer of mouth, lung cancer, endometrial cancer, ovarian cancer, lymphosarcoma, Kaposi sarcoma, gastric lymphoma^[5,38-42]. Association of SB with other diseases was documented including diverticulosis, inflammatory bowel disease, cecal volvulus, perirectal abscess, hemorrhoids, cholecystitis, cholangitis, biliary tract disease, *Klebsiella pneumoniae* liver abscess, gastric ulcer, dental problems and adenoma of oropharynx, pancreas, liver and stomach^[5,11,24]. In current study, two patients had history of breast cancer, one patient had multiple myeloma, and one patient was diagnosed with esophageal cancer 6 months after GDS infection.

In western countries, SG infection usually presents with IE, whereas in other geographic regions such as Hong Kong SG infection usually causes cholangitis, cholecystitis and biliary tract disease.^[43] In current study, most of GDS infection was bacteremia.

Evaluation of colonic and hepatic disease should be performed in patient with SB bacteremia or IE regardless of subspecies^[14]. Colonoscopy is recommended for evaluate colonic disease^[2,14,35]. Surveillance should be considered because CRC can occur a few years later. To evaluate liver disease, liver function test, hepatitis screen, ultrasound or computer tomography should be done^[14,35]. Liver biopsy is considered in selected case.

CONCLUSION

The prevalence of colonic disease and liver disease in individuals with GDS were 33.8% and 79%, respectively. Patients with GDS infection should be evaluated for colonic and liver disease regardless of subspecies. Colonic and liver disease may occur simultaneously in patients with GDS infection.

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Author contributions: Piyanant Chonmaitree conducted the research, designed the research, analyzed the data, performed statistical analysis, wrote the manuscript and approved the final manuscript. Worawut Roongsangmanoon revised the manuscript and approved the final manuscript. Dittapol Muntham analyzed the data and performed statistical analysis. Piyanuch Piyasatit was involved in the data acquisition. Prasit Upapan designed the research and approved the final manuscript.

REFERENCES

- Corredoira J, Rabuñal R, Alonso MP. Streptococcus bovis: 100 Years of an Intriguing Pathogen. *Clinical Microbiology Newsletter*. 2017; 39(1): 1-9. [DOI: 10.1016/j.clinmicnews.2016.12.001]
- Burnett-Hartman AN, Newcomb PA, Potter JD. Infectious agents and colorectal cancer: a review of Helicobacter pylori, Streptococcus bovis, JC virus, and human papillomavirus. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2008; 17(11): 2970-9. [PMID: 18990738]; [PMCID: PMC2676114]; [DOI: 10.1158/1055-9965.epi-08-0571]
- Abdulmir AS, Hafidh RR, Mahdi LK, Al-jeboori T, Abubaker F. Investigation into the controversial association of Streptococcus gallolyticus with colorectal cancer and adenoma. *BMC cancer*. 2009; 9: 403. [PMID: 19925668]; [PMCID: PMC2785837]; [DOI: 10.1186/1471-2407-9-403]
- EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Journal of hepatology*. 2012; 56(4): 908-43. [PMID: 22424438]; [DOI: 10.1016/j.jhep.2011.12.001]
- Abdulmir AS, Hafidh RR, Abu Bakar F. The association of Streptococcus bovis/gallolyticus with colorectal tumors: the nature and the underlying mechanisms of its etiological role. *Journal of experimental & clinical cancer research: CR*. 2011; 30: 11. [PMID: 21247505]; [PMCID: PMC3032743]; [DOI: 10.1186/1756-9966-30-11]
- Ruoff KL BAPapoid. Classification of Streptococci. In: Mandell GL BJ, Dolin R, editor. 7 ed. Philadelphia: Elsevier; 2010. p. 2591-3.
- Romero B, Morosini MI, Loza E, Rodriguez-Banos M, Navas E, Canton R, Campo RD. Reidentification of Streptococcus bovis isolates causing bacteremia according to the new taxonomy criteria: still an issue? *Journal of clinical microbiology*. 2011; 49(9): 3228-33. [PMID: 21752968]; [PMCID: PMC3165630]; [DOI: 10.1128/jcm.00524-11]
- Hensler ME. Streptococcus gallolyticus, infective endocarditis, and colon carcinoma: new light on an intriguing coincidence. *The Journal of infectious diseases*. 2011; 203(8): 1040-2. [PMID: 21450993]; [DOI: 10.1093/infdis/jiq170]
- Tsai CE, Chiu CT, Rayner CK, Wu KL, Chiu YC, Hu ML, Chuah SK, Tai WC, Liang CM, Wang HM. Associated factors in Streptococcus bovis bacteremia and colorectal cancer. *The Kaohsiung journal of medical sciences*. 2016; 32(4): 196-200. [PMID: 27185602]; [DOI: 10.1016/j.kjms.2016.03.003]
- Giannitsioti E, Chirouze C, Bouvet A, Beguinot I, Delahaye F, Mainardi JL, Celard M, Mihaila-Amrouche L, Moing VL, Hoen B, Group AS. Characteristics and regional variations of group D streptococcal endocarditis in France. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2007; 13(8): 770-6. [PMID: 17501973]; [DOI: 10.1111/j.1469-0691.2007.01753.x]
- Shanan S, Gumaa SA, Sandstrom G, Abd H. Significant Association of Streptococcus bovis with Malignant Gastrointestinal Diseases. *International journal of microbiology*. 2011; 2011: 792019. [PMID: 22121365]; [PMCID: 3205774]; [DOI: 10.1155/2011/792019]
- Alazmi W, Bustamante M, O'Loughlin C, Gonzalez J, Raskin JB. The association of Streptococcus bovis bacteremia and gastrointestinal diseases: a retrospective analysis. *Digestive diseases and sciences*. 2006; 51(4): 732-6. [PMID: 16614996]; [DOI: 10.1007/s10620-006-3199-7]
- Antonic V, Stojadinovic A, Kester KE, Weina PJ, Brucher BL, Protic M, Avital I, Izadjoo M. Significance of infectious agents in colorectal cancer development. *Journal of Cancer*. 2013; 4(3): 227-40. [PMID: 23459622]; [PMCID: PMC3584836]; [DOI: 10.7150/jca.5835]
- Zarkin BA, Lillemoe KD, Cameron JL, Effron PN, Magnuson TH, Pitt HA. The triad of Streptococcus bovis bacteremia, colonic pathology, and liver disease. *Annals of surgery*. 1990; 211(6): 786-91; discussion 91-2. [PMID: 2357141]; [PMCID: PMC1358139]
- Tripodi MF, Adinolfi LE, Ragone E, Durante Mangoni E, Fortunato R, Iarussi D, Ruggiero G, Utili R. Streptococcus bovis endocarditis and its association with chronic liver disease: an underestimated risk factor. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2004; 38(10): 1394-400. [PMID: 15156477]; [DOI: 10.1086/392503]
- Boleij A, van Gelder MM, Swinkels DW, Tjalsma H. Clinical Importance of Streptococcus gallolyticus infection among colorectal cancer patients: systematic review and meta-analysis. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2011; 53(9): 870-8. [PMID: 21960713]; [DOI: 10.1093/cid/cir609]
- Ruoff KL, Miller SI, Garner CV, Ferraro MJ, Calderwood SB. Bacteremia with Streptococcus bovis and Streptococcus salivarius: clinical correlates of more accurate identification of isolates. *Journal of clinical microbiology*. 1989; 27(2): 305-8. [PMID: 2915024]; [PMCID: 267297]
- Corredoira JC, Alonso MP, Garcia JF, Casariego E, Coira A, Rodriguez A, Pita J, Louzao C, Pombo B, Lopez MJ, Varela J. Clinical characteristics and significance of Streptococcus salivarius bacteremia and Streptococcus bovis bacteremia: a prospective 16-year study. *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology*. 2005; 24(4): 250-5. [PMID: 15902530]; [DOI: 10.1007/s10096-005-1314-x]
- Corredoira-Sanchez J, Garcia-Garrote F, Rabunal R, Lopez-Roses L, Garcia-Pais MJ, Castro E, Gonzalez-Soler R, Coira A, Pita J, Lopez-Alvarez MJ, Alonso MP, Varela J. Association between

- bacteremia due to *Streptococcus gallolyticus* subsp. *gallolyticus* (*Streptococcus bovis* I) and colorectal neoplasia: a case-control study. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2012; **55**(4): 491-6. [PMID: 22563018]; [DOI: 10.1093/cid/cis434]
20. Darjee R, Gibb AP. Serological investigation into the association between *Streptococcus bovis* and colonic cancer. *Journal of clinical pathology*. 1993; **46**(12): 1116-9. [PMID: 8282836]; [PMCID: Pmc501723]
 21. Abdulmir AS, Hafidh RR, Bakar FA. Molecular detection, quantification, and isolation of *Streptococcus gallolyticus* bacteria colonizing colorectal tumors: inflammation-driven potential of carcinogenesis via IL-1, COX-2, and IL-8. *Molecular cancer*. 2010; **9**: 249. [PMID: 20846456]; [PMCID: PMC2946291]; [DOI: 10.1186/1476-4598-9-249]
 22. Hoen B, Briancon S, Delahaye F, Terhe V, Etienne J, Bigard MA, Canton P. Tumors of the colon increase the risk of developing *Streptococcus bovis* endocarditis: case-control study. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 1994; **19**(2): 361-2. [PMID: 7986925]
 23. Noble CJ. Carriage of group D streptococci in the human bowel. *Journal of clinical pathology*. 1978; **31**(12): 1182-6. [PMID: 107199]; [PMCID: PMC1145528]
 24. Beebe JL, Koneman EW. Recovery of uncommon bacteria from blood: association with neoplastic disease. *Clinical microbiology reviews*. 1995; **8**(3): 336-56. [PMID: 7553569]; [PMCID: 174628]
 25. Burns CA, McCaughey R, Lauter CB. The association of *Streptococcus bovis* fecal carriage and colon neoplasia: possible relationship with polyps and their premalignant potential. *The American journal of gastroenterology*. 1985; **80**(1): 42-6. [PMID: 3966453]
 26. Rusniok C, Couve E, Da Cunha V, El Gana R, Zidane N, Bouchier C, Poyart C, Leclercq R, Trieu-Cuot P, Glaser P. Genome sequence of *Streptococcus gallolyticus*: insights into its adaptation to the bovine rumen and its ability to cause endocarditis. *Journal of bacteriology*. 2010; **192**(8): 2266-76. [PMID: 20139183]; [PMCID: PMC2849448]; [DOI: 10.1128/jb.01659-09]
 27. Boleij A, Muytjens CM, Bukhari SI, Cayet N, Glaser P, Hermans PW, Swinkels DW, Bolhuis A, Tjalsma H. Novel clues on the specific association of *Streptococcus gallolyticus* subsp. *gallolyticus* with colorectal cancer. *The Journal of infectious diseases*. 2011; **203**(8): 1101-9. [PMID: 21451000]; [DOI: 10.1093/infdis/jiq169]
 28. Sillanpaa J, Nallapareddy SR, Singh KV, Ferraro MJ, Murray BE. Adherence characteristics of endocarditis-derived *Streptococcus gallolyticus* ssp. *gallolyticus* (*Streptococcus bovis* biotype I) isolates to host extracellular matrix proteins. *FEMS microbiology letters*. 2008; **289**(1): 104-9. [PMID: 19054100]; [DOI: 10.1111/j.1574-6968.2008.01378.x]
 29. Boleij A, Schaeps RM, de Kleijn S, Hermans PW, Glaser P, Pancholi V, Swinkels DW, Tjalsma H. Surface-exposed histone-like protein modulates adherence of *Streptococcus gallolyticus* to colon adenocarcinoma cells. *Infection and immunity*. 2009; **77**(12): 5519-27. [PMID: 19752027]; [PMCID: PMC2786452]; [DOI: 10.1128/iai.00384-09]
 30. Ellmerich S, Scholler M, Duranton B, Gosse F, Galluser M, Klein JP, Raul F. Promotion of intestinal carcinogenesis by *Streptococcus bovis*. *Carcinogenesis*. 2000; **21**(4): 753-6. [PMID: 10753212]
 31. Nguyen IS, Biarc J, Pini A, Gosse F, Richert S, Thierse D, Van Dorsseleer A, Leize-Wagner E, Raul F, Klein JP, Scholler-Guinard M. *Streptococcus infantarius* and colonic cancer: Identification and purification of cell wall proteins putatively involved in colorectal inflammation and carcinogenesis in rats. *International Congress Series*. 2006; **1289**: 257-61. [DOI: 10.1016/j.ics.2005.11.081]
 32. Biarc J, Nguyen IS, Pini A, Gosse F, Richert S, Thierse D, Van Dorsseleer A, Leize-Wagner E, Raul F, Klein JP, Scholler-Guinard M. Carcinogenic properties of proteins with pro-inflammatory activity from *Streptococcus infantarius* (formerly *S.bovis*). *Carcinogenesis*. 2004; **25**(8): 1477-84. [PMID: 14742316]; [DOI: 10.1093/carcin/bgh091]
 33. Ellmerich S, Djouder N, Scholler M, Klein JP. Production of cytokines by monocytes, epithelial and endothelial cells activated by *Streptococcus bovis*. *Cytokine*. 2000; **12**(1): 26-31. [PMID: 10623439]; [DOI: 10.1006/cyto.1999.0521]
 34. Kumar R, Herold JL, Schady D, Davis J, Kopetz S, Martinez-Moczygemba M, Murray BE, Han F, Li Y, Callaway E, Chapkin RS, Dashwood WM, Dashwood RH, Berry T, Mackenzie C, Xu Y. *Streptococcus gallolyticus* subsp. *gallolyticus* promotes colorectal tumor development. *PLoS pathogens*. 2017; **13**(7): e1006440. [PMID: 28704539]; [PMCID: PMC5509344]; [DOI: 10.1371/journal.ppat.1006440]
 35. Gonzalez-Quintela A, Martinez-Rey C, Castroagudin JF, Rajo-Iglesias MC, Dominguez-Santalla MJ. Prevalence of liver disease in patients with *Streptococcus bovis* bacteraemia. *The Journal of infection*. 2001; **42**(2): 116-9. [PMID: 11531317]; [DOI: 10.1053/jinf.2001.0799]
 36. Chirouze C, Patry I, Duval X, Baty V, Tattevin P, Aparicio T, Pagenault M, Carbonnel F, Couetdic G, Hoen B. *Streptococcus bovis*/*Streptococcus equinus* complex fecal carriage, colorectal carcinoma, and infective endocarditis: a new appraisal of a complex connection. *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology*. 2013; **32**(9): 1171-6. [PMID: 23558362]; [DOI: 10.1007/s10096-013-1863-3]
 37. Chayakulkeeree M NP, Leelaporn A. Clinical Characteristics of Group D Streptococcal Bacteremia in a University Hospital in Thailand. *Open Forum Infectious Diseases*. 2015(2(suppl1)): 831.
 38. Gold JS, Bayar S, Salem RR. Association of *Streptococcus bovis* bacteremia with colonic neoplasia and extracolonic malignancy. *Archives of surgery (Chicago, Ill: 1960)*. 2004; **139**(7): 760-5. [PMID: 15249410]; [DOI: 10.1001/archsurg.139.7.760]
 39. Gelfand MS, Alford RH. *Streptococcus bovis* endocarditis and squamous-cell carcinoma of the mouth. *The New England journal of medicine*. 1981; **305**(5): 284-5. [PMID: 7242623]
 40. Corredoira J, Alonso MP, Coira A, Varela J. Association between *Streptococcus infantarius* (formerly *S. bovis* II/1) bacteremia and noncolonic cancer. *Journal of clinical microbiology*. 2008; **46**(4): 1570. [PMID: 18256231]; [PMCID: PMC2292944]; [DOI: 10.1128/jcm.00129-08]
 41. Anaf V, Noel JC, Thys JP, Simon P, Buxant F. A first case of *Streptococcus bovis* bacteremia and peritonitis from endometrial cancer origin. *Acta chirurgica Belgica*. 2001; **101**(1): 38-9. [PMID: 11301947]
 42. Glaser JB, Landesman SH. *Streptococcus bovis* bacteremia and acquired immunodeficiency syndrome. *Annals of internal medicine*. 1983; **99**(6): 878. [PMID: 6651037]
 43. Lee RA, Woo PC, To AP, Lau SK, Wong SS, Yuen KY. Geographical difference of disease association in *Streptococcus bovis* bacteraemia. *Journal of medical microbiology*. 2003; **52**(Pt 10): 903-8. [PMID: 12972586]; [DOI: 10.1099/jmm.0.05199-0]

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