Q J Med 2014; **107**:355–361
doi:10.1093/qjmed/hct261 Advance Access Publication 24 December 2013

Streptococcus gallolyticus bacteraemia in hepatobiliary–pancreatic and colonic pathologies

S. CHETCUTI ZAMMIT, N. AZZOPARDI and P. ELLUL

From the Department of Medicine, Mater Dei Hospital, Msida, Malta

Address correspondence to S. Chetcuti Zammit, Department of Medicine, Mater Dei Hospital, Malta. email: stf_che@yahoo.com

Received 22 October 2013 and in revised form 14 December 2013

Summary

Background: *Streptococcus gallolyticus* bacteraemia has been associated with several pathologies, including bacterial endocarditis and colorectal cancer.
Aims: In this study, we have analysed whether *Streptococcus gallolyticus* bacteraemia is associated with an increased risk of hepatobiliary and colonic pathology. The association with other pathologies and the antibiotic sensitivities of *Streptococcus gallolyticus* were also analysed.
Design: Observational retrospective study.
Methods: The case notes of patients with documented *Streptococcus gallolyticus* bacteraemia between 2007 and 2012 at Mater Dei hospital (Malta) were reviewed. Demographic and clinical data, including co-morbidities, clinical investigations, antibiotic sensitivities and mortality were analysed.
Results: A total of 42 patients (33 males, 9 females) were recruited. Two patients were pre-term infants and were therefore excluded from the study. Mean age of the cohort population studied was 72 years (SD ± 14). One-year survival rate was 62%. Gastrointestinal (colonic and hepatobiliary–pancreatic) pathologies were present in 59.5% of patients with 16% of this group having more than one gastrointestinal pathology. High incidence rates of underlying diabetes mellitus (28.6%), valvular heart disease (21.4%) and malignancies (21.4%) were noted in this study. Furthermore, we observed that 14.3% of patients had an underlying respiratory pathology. *Streptococcus gallolyticus* was 100% sensitive to cefotaxime and vancomycin but was highly resistant to clindamycin, erythromycin and tetracycline.
Conclusions: *Streptococcus gallolyticus* bacteraemia is commoner in the elderly and in those with multiple underlying co-morbidities. The high incidence of gastrointestinal pathologies among patients with *Streptococcus gallolyticus* bacteraemia (59.5%) suggests that a thorough work-up for colonic and hepatobiliary/pancreatic pathology should be carried out in these patients.

Introduction

In modern literature, *Streptococcus gallolyticus* is used interchangeably with *Streptococcus bovis*. In this study, we decided to use the term *Streptococcus gallolyticus* to refer to all subtypes of *Streptococcus bovis*. *Streptococcus gallolyticus* forms part of the normal flora of the alimentary tract. Faecal carriage of *Streptococcus gallolyticus* in normal colons ranges from 2.3% to 13.0%.[1–3] It is also commonly found in the alimentary tract of cows, sheep and other ruminants.[4–6] Some studies have demonstrated a significantly higher carriage rate of *Streptococcus gallolyticus* in patients suffering from colorectal cancer when compared with controls.[1,2] However, there are also data showing no increase carriage rate when compared with controls in patients suffering from colorectal cancer[3] or colorectal adenomatous polyps.[7] It is a catalase negative and oxidase-negative, non-motile, non-sporulating, non-beta-haemolytic Gram-positive

lactic acid bacterium that grows as pairs or chains of cocci.[8]

The incidence of colorectal cancer with *Streptococcus gallolyticus* endocarditis or bacteraemia has been reported to vary from 6% to 80%.[9–11] Colonic neoplasia may arise years after the presentation of *Streptococcus gallolyticus* bacteraemia or infectious endocarditis.[12] The association between serological positivity for *Streptococcus gallolyticus* and colorectal cancer is still controversial though studies have shown higher levels of IgG antibodies against *Streptococcus gallolyticus* in colorectal cancer patients than in controls.[13–16] However, there has been no difference between *Streptococcus gallolyticus* IgM levels in colorectal cancer patients and controls, thus suggesting the role of chronic bacterial inflammation in colonic cancer.

The link between *Streptococcus gallolyticus* and adenomatous polyps has been described in the literature, though in small studies, case series and case reports.[16–19] In a study in rats, *Streptococcus infantarius* subsp. *infantarius* or its antigens promoted the progression of pre-neoplastic lesions through increased formation of hyper-proliferative aberrant colonic crypts, enhanced expression of proliferative markers and increased production of IL-8 in the colonic mucosa.[20]

Streptococcus gallolyticus is the second greatest cause of endocarditis from streptococci, being responsible for 5–25% of all patients with bacterial endocarditis.[21–23] The mortality rate of *Streptococcus gallolyticus* endocarditis is estimated to be 2–4%. *Streptococcus gallolyticus* has also been linked mildly to other benign conditions such as diverticulosis and inflammatory bowel disease.[24] Patients with underlying liver cirrhosis may also be at an increased risk of suffering from *Streptococcus gallolyticus* bacteraemia.[25] The most commonly associated organisms include *Streptococcus infantarius* (biotype II/1) and *Streptococcus gallolyticus* subsp. *pasteurianus* (biotype II/2).[26] The reason is possibly due to increased permeability of the intestinal wall, impaired bacterial clearance and decreased motility of the gastrointestinal tract, thus promoting the translocation of bacteria across the intestinal wall.[27]

In this study, we have analysed whether *Streptococcus gallolyticus* bacteraemia is associated with an increased risk of hepatobiliary and colonic pathology. The association with other pathologies and the antibiotic sensitivities of *Streptococcus gallolyticus* were also analysed.

In modern literature, *Streptococcus gallolyticus* is used interchangeably with *Streptococcus bovis*. In this study, we decided to use the term *Streptococcus gallolyticus* to refer to all subtypes of *Streptococcus bovis*.

Methods

All patients with *Streptococcus gallolyticus* bacteraemia admitted to Mater dei Hospital (Malta) between January 2007 and December 2012 were included in the study. The pathology department at our centre identifies *Streptococcus gallolyticus* by carrying out the following tests:

(i) Gram stains on cultures grown on blood agar (*Streptococcus gallolyticus* forms Gram-positive cocci in chains).
(ii) Catalase test (*Streptococcus gallolyticus* is catalase negative).
(iii) Vitek GP (This is a card that helps to identify Gram-positive bacteria and helps identify the subspecies of *Streptococcus gallolyticus*).
(iv) ATB strep (a strip for the antibiogram).

The case notes of patients were reviewed after obtaining data protection clearance and ethical board approval. The following data were retrieved:

- Demographic data;
- Clinical data including underlying medical pathologies, investigations performed and results;
- Length of hospital stay;
- Patient morbidity;
- Mortality;
- Antibiotic sensitivities.

Statistics were calculated using SPSS version 19 and Microsoft Excel 2010.

Results

Forty-two patients (33 males) were recruited. A further two patients (4.76%) were preterm infants and were therefore excluded from the study. The mean age of the cohort studied was 72 years (SD ± 14; interquartile range: 18; range: 41–97 years). Sixteen patients (38.04%) were between 41 and 70 years. Twenty-three (55%) patients were above the age of 71 whereas one patient (2.38%) was above the age of 91 years. Four cases were reported in 2007, 2008 and 2010, respectively, whereas 11 cases were diagnosed in 2009 and 2011. Eight cases of *Streptococcus gallolyticus* bacteraemia were diagnosed in 2012.

Thirty-day survival rate was 83% and 1-year survival rate was 62%. There was 50% survival of patients at 5.35 years as shown in the Kaplan–Meier curve (Figure 1).

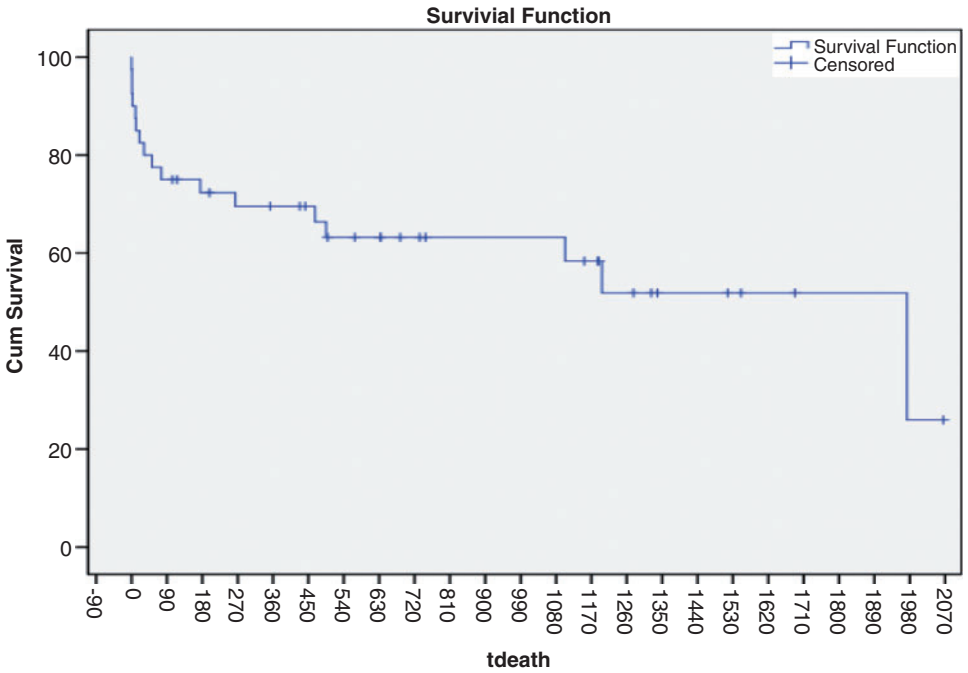

Figure 1. Kaplan–Meier survival curve for patients with *Streptococcus gallolyticus* bacteraemia.

Colonic pathologies

Fifteen patients (35.7%) had significant colonic pathology. Six patients (14.3%) had adenomatous polyps, whereas two patients (4.76%) had colorectal cancer. Thus, 19% of patients had colonic adenomas or colonic adenocarcinoma. The polyps that were included were adenomas with a minimum diameter of 10 mm and had tubulovillous or villous histological findings, with dysplasia. One of these patients also had chronic hepatitis B without evidence of cirrhosis. Seven patients (16.7%) had extensive diverticular disease (in five patients this was the only significant finding present). Two patients had underlying inflammatory bowel disease (ulcerative colitis).

Hepatobiliary–pancreatic pathologies

Eleven patients (27.5%) were diagnosed with hepatobiliary–pancreatic pathologies. Choledocolithiasis or cholelithiasis with cholangitis or cholecystitis was present in four patients. One of these patients also had multiple other pathologies including renal cell carcinoma, congestive heart failure, diverticular disease and myelofibrosis.

Two patients had a pancreatic carcinoma, one patient had chronic hepatitis C and two patients had cirrhosis secondary to autoimmune hepatitis. One of these patients was being treated with azathioprine. Cirrhosis secondary to non-alcoholic steatohepatitis (NASH) and cirrhosis secondary to idiopathic cirrhosis were documented in two other patients.

Immunosuppression

Five patients (12%) were immunosuppressed. One patient had multiple myeloma and was receiving chemotherapy. Another patient had large B-cell lymphoma and another patient had underlying myelofibrosis. Two other patients were being treated with azathioprine for ulcerative colitis and for autoimmune hepatitis, respectively. The latter patient also had congestive cardiac failure as a significant co-morbidity.

Respiratory and *u*rinary pathologies

Four patients (9.52%) with *Streptococcus gallolyticus* bacteraemia were admitted to hospital with a pneumonia. One of these patients had congestive cardiac failure as a medical co-morbidity. Two patients (4.76%) admitted with infective exacerbation of chronic obstructive pulmonary disease were also found to have *Streptococcus gallolyticus* bacteraemia. Another four patients (9.52%) had urinary sepsis. Two of these had congestive cardiac failure.

Other co-morbidities

One patient had an underlying metastatic squamous cell carcinoma of the skin, with diabetes mellitus and congestive heart failure as other co-morbidities. Three patients had underlying haematological

malignancies (one patient—multiple myeloma, one patient—B-cell lymphoma, one patient—myelofibrosis).

Ten patients (24%) had underlying congestive cardiac failure with most of them having several co-morbidities including peripheral vascular disease, cerebrovascular disease and renal impairment.

Eleven patients (26%) had underlying diabetes mellitus and nine patients (21.4%) had underlying valvular heart disease.

Bacterial endocarditis

Bacterial endocarditis was diagnosed in eight patients (19.0%), three of whom (37.5%) had underlying valvular heart disease, with two patients having undergone prosthetic valve replacements.

Three patients with bacterial endocarditis had underlying adenomatous polyps at colonoscopy and another patient had malignancy of the sigmoid colon. Hepatitis C was an underlying co-morbidity in a patient diagnosed with *Streptococcus gallolyticus* bacteraemia.

A summary of the patients' conditions can be found in (Table 1).

Antibiotic sensitivity profile

In this study, *Streptococcus gallolyticus* was 100% sensitive to cefotaxime and vancomycin, with 88% sensitivity to levofloxacin and chloramphenicol and 79% sensitivity to penicillins. However, we found an increased resistance to clindamycin (33.3%), erythromycin (50.0%) and tetracycline (73.8%) (Table 2).

Discussion

Streptococcus gallolyticus forms part of the normal intestinal microflora. The stool carriage rates in neonates have been reported to be 28%, whereas in adults it varies from 2.3% to 13%.[1,2,3,28]

Our study showed a rising trend of *Streptococcus gallolyticus* in recent years. A rising trend in *Streptococcus gallolyticus* as a cause of infective endocarditis was also reported in France.[21,23]

Gastrointestinal pathologies were present in 59.5% of patients. Significant colonic pathology was present in 35.7% thus emphasizing the need for a colonoscopy or CT colonography in patients with *Streptococcus gallolyticus* bacteraemia. Colonic cancers or adenomatous polyps were present in 19% of patients which is lower than the previously reported rates of 25–80%.[29] Meanwhile, the reported incidence of colon cancer in males in 2012 where Malta has a slightly higher incidence (60.1 in males; 37.6 in females per 100 000 patients) when compared with the rest of Europe (55.7 in males and 34.6 in females per 100 000 patients).[30]

Thus, the diagnosis of underlying *Streptococcus gallolyticus* bacteraemia may provide an early opportunity for screening patients and detecting colonic lesions at a precancerous stage. Colorectal cancer may appear years after the diagnosis of *Streptococcus gallolyticus* bacteraemia.[13]

Mechanisms by which *Streptococcus gallolyticus* can lead to colonic malignancies have been studied. In laboratory experiments, the binding of *Streptococcus bovis* extracted antigens to colon cancer cells stimulated the production of inflammatory cytokines and the overexpression of cyclooxygenase-2 (COX-2). COX-2, via prostaglandins, promotes cellular proliferation and angiogenesis and inhibits apoptosis thus playing a role in cancer formation.[31,32]

Histone-like protein A of *Streptococcus gallolyticus* has been identified to bind to heparan sulphate proteoglycans-expressing colon tumour cell lines.[33] *Streptococcus gallolyticus* can cause bacterial endocarditis by binding to collagen type I most commonly but also collagen type IV, fibrinogen, collagen type V and fibronectin.[34]

Beside the characteristic adhesive traits of *Streptococcus gallolyticus* to the intestinal cells, it is also able to grow in bile.[35] This enables it to bypass the hepatic reticulo-endothelial system and access systemic circulation easily.[12] This might explain the route responsible for colonic pathology. Furthermore, its ability to survive in bile may be responsible for biliary sepsis especially in the presence of pre-existing biliary tract disease. In our study, 9.5% of patients had sepsis secondary to gallstones. *Streptococcus gallolyticus* bacteraemia also tends to affect patients who are elderly and immunocompromised and with multiple underlying co-morbidities.[36]

The incidence of infective endocarditis in those patients with underlying adenomatous polyps or colonic cancer was 50% (four out of eight patients with adenomatous polyps and colorectal cancer). An incidence of between 6% and 80% of infective endocarditis with underlying adenomatous polyps and colorectal cancer is reported in the literature.[10] The incidence of infective endocarditis (11.8%; 4 out of 34 patients) was much higher than in the rest of the cohort (without underlying colonic adenomas and colorectal cancer).[11]

Ten (23.8%) of our patients had underlying solid organ (non-colonic) and haematological malignancies. In the literature, this was reported to vary between 15% and 32%.[37,38] In a study by Corrediora *et al.*, the association of *Streptococcus*

Table 1 A summary of patient observations in this study

Observation	Number of patients	% of patients
Colonic pathologies		
Adenomatous polyps	6	14.30
Colorectal cancer	2	4.76
Diverticular disease	7	16.70
Inflammatory bowel disease	2	4.76
Hepatobiliary/pancreatic pathologies		
Choledocolithiasis/cholelithiasis	4	9.52
Pancreatic carcinoma	2	4.76
Chronic hepatitis C	1	2.38
Cirrhosis secondary to autoimmune hepatitis	2	4.76
Cirrhosis secondary to NASH	1	2.38
Cirrhosis secondary to idiopathic cirrhosis	1	2.38
Immunosuppressed patients	5	12.00
Respiratory pathologies		
Pneumonia	4	9.52
Infective exacerbation of chronic obstructive pulmonary disease	2	4.76
Urinary sepsis	4	9.52
Malignancies		
Squamous cell carcinoma	1	2.38
Haematological malignancies	3	7.14
Pancreatic carcinoma	2	4.76
Cardiac pathologies		
Underlying valvular heart disease	9	21.40
Congestive heart failure	10	24.00
Bacterial endocarditis	8	19.00
Diabetes mellitus	11	26.00

Table 2 Antibiotic sensitivity profile

Type of antibiotic	Sensitive	Resistant	Intermediate
Penicillin	33 (78.6)	0	9 (21.4)
Chloramphenicol	37 (88.1)	0	5 (11.9)
Cefotaxime	42 (100)	0	0
Vancomycin	42 (100)	0	0
Clindamycin	28 (66.7)	14 (33.3)	0
Levofloxacin	37 (88.1)	1 (2.38)	4 (9.52)
Erythromycin	21 (50.0)	21 (50.0)	0
Tetracycline	11 (26.2)	31 (73.8)	0

Values in parentheses are percentages.

gallolyticus with non-colonic cancer was 6% vs. 57% for *Streptococcus infantarius* ($P < 0.0001$).[39]

Out of five patients who were immunosuppressed and developed the infection, two of them were being administered azathioprine. This is an immunosuppressive pro-drug that is converted into 6-mercaptopurine in the body thus blocking purine metabolism and DNA synthesis. It is known to increase the risk of fungal, protozoal, viral and uncommon bacterial infections.[40]

We had an incidence of 14.3% of respiratory pathologies in those with underlying *Streptococcus gallolyticus* bacteraemia. This value was not significantly different from the presence of colorectal cancer and colorectal adenomas in our study group, which to date has been more of an established association. These are the first data in the literature showing this occurrence. Future studies may be aimed to determine if there is a true association between respiratory pathologies and *Streptococcus gallolyticus* bacteraemia.

In our study, the incidence of diabetes mellitus was 26% similar to 24% reported in the literature.[41] Patients with underlying diabetes mellitus have a higher incidence of infection and a worse outcome.[42,43] Rising trends in the incidence of diabetes mellitus in Malta might be responsible for the rising trends in *Streptococcus gallolyticus* bacteraemia in over recent years.

High incidence rates of valvular heart disease (21.4%) and underlying malignancies (21.4%) were also noted in this study. Malignancies included colonic (two patients), renal cell (one patient), pancreatic (two patients) and haematological

malignancies (three patients) and one metastatic squamous cell cancer.

The retrospective nature of this study is an important limitation. However, our cohort represents one of the largest group of patients which have been extensively investigated and followed up for different pathologies. Furthermore, our study also gives important information about antibiotic susceptibility and resistance.

Conclusions

Streptococcus gallolyticus bacteraemia is more common in the elderly and in those with multiple underlying co-morbidities. The high incidence of gastrointestinial pathologies (59.5%) in these patients suggests that all patients with *Streptococcus gallolyticus* should undergo a thorough colonic and hepatobiliary–pancreatic assessment. The presence of any underlying malignancy should also be sought. The association of respiratory pathologies needs to be further evaluated in future studies.

Conflict of interest: None declared.

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