Brief report

Javier de Teresa-Alguacil[1]
Miguel Gutiérrez-Soto[2]
Javier Rodríguez-Granger[3]
Antonio Osuna-Ortega[1]
José María Navarro-Marí[3]
José Gutiérrez-Fernández[3,4]

Clinical interest of *Streptococcus bovis* isolates in urine

[1]UGC de Nefrología, Complejo Hospitalario Universitario de Granada-ibsgranada.
[2]Centro de Salud "Polígono Guadalquivir". Córdoba.
[3]Laboratorio de Microbiología, Complejo Hospitalario Universitario de Granada-ibsgranada.
[4]Departamento de Microbiología – Universidad de Granada-ibsgranada.

ABSTRACT

Introduction. *Streptococcus bovis* includes variants related to colorectal cancer and non-urinary infections. Its role as urinary pathogen is unknown. Our objective was to assess the presence of urinary infection by *S. bovis*, analysing the patients and subsequent clinical course.

Material and Methods. Observational study, with longitudinal data collection, performed at our centre between all the cultures requested between February and April 2015. Clinical course of the patients and response to treatment were analysed.

Results. Two thousand five hundred and twenty urine cultures were analysed, of which 831 (33%) had a significant microbial count. *S. bovis* was isolated in 8 patients (0.96%). In 75% of these cases the urine culture was requested because of urinary tract infection symptoms; the remaining 25% because of fever of uncertain source; during the follow-up period no evidence of cancer or endocarditis was detected. *S. gallolyticus* subspecie *pasteurianus* was the only variant observed (100%). The clinical response to initial treatment was favourable in all cases.

Conclusions. *S. bovis* bacteriuria may have clinical significance, especially when *S. gallolyticus* subspecies *pasteurianus* is isolated in cases with underlying urinary tract disease.

Keywords: *Streptococcus bovis*, urinary tract infection, urine culture, *S. gallolyticus* subspecies *pasteurianus*.

Significado clínico de los aislados de *Streptococcus bovis* en orina

RESUMEN

Introducción. *Streptococcus bovis* comprende multitud de variantes de especie relacionados con infecciones no urinarias y cáncer colorrectal. Su papel como patógeno urinario es desconocido. Nuestro objetivo fue valorar la presencia de infección urinaria por *S. bovis*, analizando los pacientes y su evolución clínica posterior.

Material y métodos. Estudio observacional, con obtención de datos longitudinal, realizado en nuestro centro entre todos los urocultivos solicitados durante entre los meses de febrero y abril de 2015. Se analizó la evolución clínica y la respuesta al tratamiento.

Resultados. Se analizaron 2.520 urocultivos, de los que en 831 (33%) hubo un recuento microbiano significativo. Se aisló *S. bovis* en 8 (0,96%) pacientes. En el 75% de estos casos el urocultivo fue solicitado por clínica de infección del tracto urinario. El 25% restante por fiebre sin foco evidente clínicamente, no objetivando historia de cáncer y/o endocarditis durante el periodo seguimiento. La única variante presente fue *S. gallolyticus* subespecie *pasteurianus* (100%). La respuesta clínica al tratamiento inicial fue favorable en todos los casos.

Conclusiones. La bacteriuria por *S. bovis* puede tener significación clínica, sobre todo cuando se aísla *S. gallolyticus* subespecie *pasteurianus*, en pacientes con patología previa del aparato urinario.

Palabras clave: *Streptococcus bovis*, infección del tracto urinario, urocultivo, *S. gallolyticus* subespecie *pasteurianus*.

Correspondencia:
José Gutiérrez-Fernández
Laboratorio de Microbiología. Complejo Hospitalario Universitario de Granada-ibsgranada.
Av. de las Fuerzas Armadas, 2, 18014 Granada
E-mail: josegf@go.ugr.es

INTRODUCTION

Streptococcus bovis bacterial species is a group of bacteria that colonize the intestine of animals and humans. Nowadays, with the application of molecular techniques, this bacterial complex is composed of 3 subtypes (*Streptococcus gallolyticus* subspecies *gallolyticus*, *Streptococcus gallolyticus* subspecies *pasteurianus* and *Streptococcus infantarius* subspecies *infantarius* (or *Streptococcus lutetiensis*). This multitude of genetic variants are associated with human infection, causing bacteraemia, endocarditis, meningitis, or infection of the bile duct, and is most frequently associated with colorectal cancer[1].

The findings of a systematic review[2] showed that 69% of patients infected by *S. bovis* had concomitantly colorectal neoplasia, mostly those infected by the variant *S. gallolyticus* subspecies *gallolyticus* (biotype I). On the other hand, subgroup *S. gallolyticus* subspecies *pasteurianus* has been associated with other infections different from – endocarditis and has not been associated with colorectal cancer[3-10]. However, most studies to date do not differentiate between varieties or subspecies of *S. bovis*[3], which represents a significant limitation for the analysis of the results. Finally, until now, its role as a urinary tract infection (UTI) pathogen is not well known, mainly because it has not been properly studied[11] and more research is needed.

Our objective was to analyse the clinical significance of the presence of significant *S. bovis* counts in urine, as well as the clinical response after receiving antibiotic treatment.

MATERIAL AND METHODS

It was an observational study, with longitudinal data collection, between the months of February and April 2015, from Granada University Hospital Complex Microbiology Lab. (Hospital Virgen de las Nieves). This hospital is a reference centre in Andalusia, which serves a population of about 440,000 subjects. During this-period of time urine specimens, from hospitalized patients and followed-up in the outpatient clinic were processed, following the previously described criteria[12]. The sample was first inoculated on CHROMagar Orientation® medium (Becton Dickinson, Franklin Lakes, NJ, USA) in a quantitative manner using a 1-µl calibrated loop (COPAN, Brescia, Italy); in cases with underlying urinary tract disease, an additional 10 µl was inoculated on Columbia blood agar (Becton Dickinson). *S. bovis* suspicious colonies were identified using Gram stain, routine biochemical tests (MicroScan; Siemens Healthcare, Rockville, MD, USA) and mass spectrophotometry, using system Biotyper® (Bruker Daltonics, Coventry, UK). This allows the identification of subspecies. We investigated the sensitivity of isolates to penicillin, levofloxacin, fosfomycin and nitrofurantoin by microdilution (MicroScan). The isolates were classified as sensitive, intermediate or resistant to each antibiotic in accordance with the recommendations of the European Committee for Antimicrobial Susceptibility Testing[13].

Clinical data. Once patients were identified with a *S. bovis* isolation in urine they were classified as symptomatic or asymptomatic. The presence of UTI was recorded as lower (defined by the existence of dysuria, urinary frequency and/or urinary urgency) or upper (if it was accompanied by fever and/or back or flank pain). Demographic and clinical data were collected and analysed: age, sex, race, underlying pathology (*diabetes melli-*

Table 1 | **Patient's characteristics and strains of *Streptococcus bovis***

Patients	Age	Sex	Urine culture (microorganism)	Blood culture	Charlson' co-morbidity index	Underlying condition	Antibiotic treatment	Clinical course and outcome
1	63	F	*S. gallolyticus* spp. *pasteurianus*	Negative	6.3	High blood pressure (HBP), Stroke, AVB (auricular-ventricular blockade)	Amoxicillin clavulanic	ICU admission-Favourable
2	48	F	*S. gallolyticus* spp. *pasteurianus*	Not performed	0.8	Unknown	Amoxicillin	Favourable
3	49	F	*S. gallolyticus* spp. *pasteurianus*	Not performed	4.9	Amyloidosis, Still disease, CKD-Kidney transplant recipient, OSA.	Fosfomycin	Favourable
4	37	F	*S. gallolyticus* spp. *pasteurianus*	Not performed	1.7	None	Ciprofloxacin	Favourable
5	38	F	*S. gallolyticus* spp. *pasteurianus*	Not performed	3.8	Transplant Kidney recipient , Acute Pulmonary embolism (APE)	Ciprofloxacin	Favourable
6	65	M	*S. gallolyticus* spp. *pasteurianus*	Not performed	2.5	BPH (Benign Prostatic Hyperplasia)	Unknown	Favourable
7	78	F	*S. gallolyticus* spp. *pasteurianus*	Not performed	9.8	HBP, Hypertensive cardiomyopathy , Type II Diabetes, Diabetic nephropathy, Hydronephrosis	Cefuroxime	Favourable
8	85	F	*S. gallolyticus* spp. *pasteurianus*	Not performed	6.5	UTI, Metrorragy	Cefuroxime	Favourable

Table 2 **Susceptibility of *Streptococcus bovis* strains.**

Patients	Subespecies	CFU/ml	Levofloxacin MIC (mg/L)	Penicillin Susceptibility level / MIC (mg/L)	Fosfomycin MIC (mg/L)	Nitrofurantoin MIC (mg/L)
1	*Gallolyticus* spp. *pasteurianus*	>10.000	2	S/≤ 0,03	≤ 32	≤ 32
2	*Gallolyticus* spp. *pasteurianus*	10.000-100.000	≤ 1	S/≤ 0,03	≤ 32	≤ 32
3	*Gallolyticus* spp. *pasteurianus*	>100.000	>4	I / 2	≤ 32	≤ 32
4	*Gallolyticus* spp. *pasteurianus*	>100.000	≤ 1	S/≤ 0,03	≤ 32	≤ 32
5	*Gallolyticus* spp. *pasteurianus*	>100.000	≤ 1	S/≤ 0,03	≤ 32	≤ 32
6	*Gallolyticus* spp. *pasteurianus*	>100.000	2	S/≤ 0,03	≤ 32	≤ 32
7	*Gallolyticus* spp. *pasteurianus*	>100.000	2	S/≤ 0,03	≤ 32	≤ 32
8	*Gallolyticus* spp. *pasteurianus*	>10.000	2	S/≤ 0,03	≤ 32	≤ 32

S= susceptible, I= intermedia, R= resistant

tus - DM-, renal, urologic, hepatic or cardiovascular disease) and if receiving chronic immunosuppressive therapy. The existence of gastrointestinal disease (malignancy or not), cardiac disease and antibiotic treatment received was recorded as well as the observed clinical response. The baseline condition of each patient was classified according to the Charlson' Comorbidity Index (CCI)[14]. Finally, *S. bovis* subspecies associated with UTI as well as the probability of subsequent complications were examined. The data were analysed using the statistical package SPSS 15.0 .

RESULTS

During the study period a total of 2,520 samples of urine were analysed, of which 831 (33%) had a significant microbial count, with identification and antibiotic susceptibility study. *S. bovis* was isolated in 8 (0.96%) patients (table 1). Table 2 contains the antibiogram for each case. The median age of the patients was 56 years, being the majority of them women (87.5%). 50% had some underlying nephro-urologic condition: two patients had received a kidney transplant, one patient was carrying a percutaneous nephrostomy catheter and a double "J" for chronic hydronephrosis and another patient had benign prostatic hyperplasia.

The mean value of CCI was 4.53. In 75% (6/8) cases the urine culture was requested by symptoms compatible with UTI; the remaining 25% by fever without evident clinically focus; no evidence of cancer or endocarditis history was detected during the follow-up period. Microhaematuria was present in 37.5% (3/8) of the cases and pyuria in 25% (2/8). Also 25% of the patients were deceased donor kidney transplant recipients with functioning graft and chronic immunosuppressive treatment. 25% had co-infections with *Escherichia coli*. The *S. bovis* variant isolated was *S. gallolyticus* subspecies *pasteurianus* (100% of the cases), being all susceptible to penicillin. The clinical course during the follow-up was favourable in 87% (7/8) of the patients, but one patient was admitted to the ICU for ischemic stroke. The survival rate was 100% during the study period.

DISCUSSION

To date the importance of *S. bovis* as producer of UTI is unknown, and its pathogenesis is not well known. So, we set ourselves the objective of go further in this sense. Our research is useful to bring our experience, providing more data on this topic.

Matesanz et al.[11] have recently described the involvement of the *S. bovis* as genitourinary pathogen, mainly the subspecies *S. pasteurianus*, informing that the infection is most commonly acquired in the community and affects women more frequently. Given that our population corresponds to hospitalized patients and patients followed-up at our outpatient clinic we cannot compare this fact and only describe their presence on patients attending at the hospital. In addition, *S. bovis* colonies shared phenotypic microbiological characteristics with *Enterococcus* spp. and *Streptococcus viridans* group[11,15], as well as in the macroscopic and microscopic morphology and biochemical tests, and may be confused with these in the laboratory. Due to the fact that *Enterococcus* spp. is frequently a causal pathogen of UTIs[11,16] and sometimes we can be confused with *S. viridans* group this problem is especially important since the

frequency of UTI by *S. bovis* could have been underestimated in epidemiological studies.

It has been published that bacteraemia caused by *S. bovis* and *Enterococcus* spp. could have a urinary origin[11,15]. In our series blood culture was only taken in one patient, which was negative, so we cannot compare this fact and only refer that patients did not need it.

Different studies[11,17-19] highlight the role as uropathogen of the variant of *S. bovis* called *S. gallolyticus* subspecies *pasteurianus*, and similarly all our isolates corresponded to this subspecies. Other subspecies of *S. bovis*, such as *S. infantarius* and *S. gallolyticus*, have been less isolated in urine[11]. Therefore, our findings confirm the importance of *S. pasteurianus* as urinary pathogens, mainly by being present in symptomatic patients and for a meaningful count. In the literature episodes of renal failure in patients with endocarditis by *S. bovis* has been published, although they do not specify the subspecies, including cases of acute tubular necrosis associated with sepsis, immune complexes glomerulonephritis, crescentic glomerulonephritis and kidney failure associated with antibiotic treatment[20].

In conclusion, *S. bovis*, mainly the subspecies *S. pasteurianus*, can cause UTIs in cases with underlying urinary tract disease. However, it is advisable to continue studying the relationship of the UTI with this agent analysing populations.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

FUNDING

None to declare

REFERENCES

1. Corredoira-Sánchez J, García-Garrote F, Coira A, López-Agreda H, Alonso-García MP. Colorectal neoplasia associated with *Streptococcus gallolyticus* subspecies *pasteurianus*. Lancet Infect Dis 2014; 14: 272-3.
2. Boleij A, van Gelder MM, Swinkels DW, Tjalsma H. Clinical importance of *Streptococcus gallolyticus* infection among colorectal cancer patients: systematic review and meta-analysis. Clin Infect Dis 2011; 53:70–8.
3. Corredoira J, Grau I, García-Rodríguez JF, Alonso-García P, García-Pais MJ, Rabuñal R, et al. The clinical epidemiology and malignancies associated with *Streptococcus bovis* biotypes in 506 cases of bloodstream infections. J Infect 2015; 71: 317-25.
4. Ruoff K, Miller S, Garner C, Ferraro M, Calderwood S. Bacteriemia with *Streptococcus bovis* and *Streptococcus salivarius*: clinical correlates of more accurate identification of isolates. J Clin Microbiol 1989; 27:305-8.
5. Corredoira JC, Alonso MP, García JF, Casariego E, Coira A, Rodriguez A, et al. Clinical characteristics and significance of *Streptococcus salivarius* bacteriemia and *Streptococcus bovis* bacteriemia: a prospective 16 year study. Eur J Clin Microbiol Infect Dis 2005; 24:250-5.
6. Vaska V, Faoagali J. *Streptococcus bovis* bacteriemia: identification within organism complex and association with endocarditis and colonic malignancy. Pathology 2009; 41:183-6.
7. Lee R, Woo P, To A, Lau S, Wong S, Yuen K. Geographical difference of disease association in *Streptococcus bovis* bacteriemia. J Med Microbiol 2003; 52:903-8.
8. Jean S, Teng L, Hsueh P, Ho S, Luh K. Bacteriemic *Streptococcus bovis* infections at a university hospital. 1992-2001. J Formos Med Assoc 2004; 103:118-23.
9. Corredoira J, Alonso P, Coira A, Varela J. Association between *Streptococcus infantarius* (Formerly *S. bovis* II/1) bacteriemia and noncolonic cancer. J Clin Microbiol 2008; 16:1570.
10. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler Jr VG, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century. The International collaboration on endocarditis-prospective cohort study. Arch Intern Med 2009;169: 463-73.
11. Matesanz M, Rubal D, Iñiguez I, Rabuñal R, García-Garrote F, Coira A, et al. Is *Streptococcus bovis* a urinary pathogen?. Eur J Clin Microbiol Infect Dis. 2015; 34:719-25.
12. Gutiérrez-Fernández J, Rojo Martín MD, Bautista Marín, MF. Procedimiento normalizado de trabajo. Cultivo cuantitativo de orina para estudio de microorganismos aerobios/facultativos de crecimiento rápido. 2015. http://dx.doi.org/10.6084/m9.figshare.1317411 Retrieved, Aug 27, 2015.
13. European Committe for Antimicrobial Susceptibility Testing. URL:http://www.eucast.org. Retrieved, Aug 27, 2015.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987; 40: 373-83.
15. Hoppes WL, Lemer Pl. Non enterococal group-D streptococcal endocarditis caused by *Streptococcus bovis*. Ann Intern Med 1974; 81:588-93.
16. Sorlózano A, Jiménez-Pacheco A, Luna JD, Sampedro A, Martínez-Brocal A, Miranda-Casas C, Navarro-Marí JM, Gutiérrez-Fernández J. Evolution of the resistance to antibiotics of bacteria involved in urinary tract infections: A 7-year surveillance study. Am J Infect Control 2014; 42:1033-8.
17. Lazarovitch T, Shango M, Levine M. The relationship between the new taxonomy of *Streptococcus bovis* and its clonality to colon cancer, endocarditis and biliary disease. Infection 2013; 41:329-37.
18. Klatte JM, Claridge JE 3rd, Bratcher D, Selverangan R. A longitudinal case series description of meningitis due to *Streptococcus gallolyticus* subsp. *pasteurianus* in infants. J Clin Microbiol 2012: 50; 57-60.
19. Thatrimontrichai A, Chanvitan P, Janjindamai W, Dissaneevate S, Maneeil G. Early onset neonatal bacterial meningitis caused by *Streptococcus gallolyticus* subs. *pasteurianus*. Southeast Asian J Trop Med Public Health 2012; 43:145-51.
20. Thongprayoon Ch, Cheungpasitporn W, Srivali N, Kittanamongkolchai W, Ungprasert P. Renal involvements in reported cases of *Streptococcus bovis* endocarditis. Intern J Cardiol 2015;181:179.