Native and prosthetic transcatheter aortic valve infective endocarditis due to *Lactobacillus rhamnosus*

Endocarditis infecciosa nativa y sobre válvula aórtica protésica transcatéter (TAVI) causada por Lactobacillus rhamnosus

Lactobacillus spp. are a heterogeneous group of microaerophilic grampositive rods, commensal of the gastrointestinal and female genitourinary tracts, and often considered contaminants in blood cultures. However, cases of severe infections caused by these microorganisms have been reported.[1] We report a native valve endocarditis and a spondylodiscitis with possible transcatheter aortic valve implantation (TAVI) endocarditis caused by *Lactobacillus rhamnosus*.

Case 1

An 81-year-old male was referred for evaluation of *L. rhamnosus* bacteremia. He had history of TAVI implantation five months earlier and degenerative lumbar vertebra pathology, and complained of fever and one-month course of asthenia, anorexia and acute worsening of lumbar pain. Four sets of blood cultures (1 set: BACTEC™ Plus Aerobic/F and BACTEC™ Anaerobic/F, BD) were drawn on different days (two sets on the 3rd and two more on the 5th day) which were all positive after 29–42 h of incubation. Gram staining showed grampositive rods that were identified as *L. rhamnosus* by MALDI-TOF directly from positive blood culture (score 1.8). After subculturing and incubation under anaerobic conditions, identification was further confirmed by both MALDI-TOF (score > 2) and 16S rRNA gene sequencing. The 16S gene was amplified by PCR using the universal primers (27f and 907r) with conditions previously described.[2] The PCR product was purified and sequenced using a BigDye terminator protocol (Applied Biosystems). Sequences were compared with BLAST (http://www.ncbi.nlm.nih.gov/BLAST) and the identification was confirmed (>99% identity) with the 16S rRNA gene sequence of *L. rhamnosus* LDTM7511 (GenBank accession number CP051227.1). Transesophageal echocardiography was performed and neither vegetations nor valve disfunction was observed. Treatment with ampicillin was initiated. On admission he was afebrile, with holosystolic cardiac murmur and pain at the second lumbar vertebra. Blood cultures after 48 h of antibiotic treatment were negative. Antimicrobial susceptibility testing (AST) was carried out following CLSI recommendations (CLSI M45-A2) which also provides interpretative breakpoints for different antibiotics.[3] MICs were determined using a broth microdilution method, SensititreTM STRHAE2 (ThermoScientific). The *L. rhamnosus* isolate was susceptible to penicillin (MIC 2 μg/mL), ampicillin (MIC 2 μg/mL), erythromycin (MIC < 0.25 μg/mL), clindamycin (MIC < 0.25 μg/mL), daptomycin (MIC 1 μg/mL) and linezolid (MIC < 2 μg/mL). The isolate did not present high-level gentamicin resistance (gentamicin MIC < 500 μg/mL) and was resistant to cefotaxime (MIC > 2 μg/mL) and vancomycin (MIC > 16 μg/mL). Gentamicin was added to the treatment. Positron emission tomography-computed tomography (PET-CT) showed strong 18-F fluorodeoxyglucose uptake at L1-L2 level without heart valves uptake, although performed 15 days after starting antibiotics. Diagnosis of *L. rhamnosus* spondylodiscitis and possible TAVI endocarditis was established (Duke criteria: 1 major microbiological criterium, and 2 minor criteria: predisposing heart condition, fever > 38 °C). Six weeks of treatment with ampicillin were completed, 2 of which in combination with gentamicin. The patient recovered, without relapses after a follow-up of 10 months.

Case 2

An 83-year-old woman without relevant background was brought to the emergency department due to syncope. She complained of constitutional symptoms for the past six months. Physical examination showed a holosystolic murmur in mitral focus. Transthoracic echocardiogram showed a vegetation in the posterior mitral leaflet with possible valve rupture and severe mitral regurgitation. Six sets of blood cultures were positive at 26-44 h of incubation (four sets the first day and two more, two days after). Microbiological diagnosis, identification and antimicrobial susceptibility testing was performed as described above in case 1. Identification by MALDI-TOF directly from the positive blood culture was unsuccessful, and *L. rhamnosus* was identified by MALDI-TOF (score > 2) directly from colonies after subculturing, and by 16S rRNA gene analysis. The *L. rhamnosus* isolate was susceptible to penicillin (MIC 2 μg/mL), ampicillin (MIC 4 μg/mL), erythromycin (MIC < 0.25 μg/mL) and clindamycin (MIC < 0.25 μg/mL). Furthermore, the isolate did not show high-level resistance to gentamicin (gentamicin MIC < 500 μg/mL) as was resistant to cefotaxime (MIC > 2 μg/mL) and vancomycin (MIC > 16 μg/mL). She was admitted with the definitive diagnosis of subacute *L. rhamnosus* endocarditis on mitral native valve (according to Duke criteria, 2 major criteria: microbiological evidence and imaging plus 1 minor criteria: fever) and intravenous penicillin 3 MU every 4 h was initiated. A whole-body PET-CT showed no pathological uptakes. Transoesophageal echocardiogram showed rupture of the posterior leaflet of mitral valve. Follow-up blood cultures at 72 h of treatment were negative. The patient was considered not suitable for surgery due to advanced age and fragility. Four weeks of penicillin were completed. The patient remained asymptomatic, without relapse after 6 months of follow-up.

Although *L. rhamnosus* is considered a barely virulent pathogen, cases of endocarditis have been reported.[1,4–8,10–20] Infective endocarditis due to *Lactobacillus* spp. is rare, accounting for less than 0.5% of all episodes. We only found 16 cases of *L. rhamnosus* endocarditis published since 1980, nevertheless some reported cases of *Lactobacillus* spp. endocarditis not identified at the species level could also correspond to *L. rhamnosus* episodes.[4] After excluding a pediatric patient and two cases without available information, the 13 remaining cases are detailed in Table 1. Underlying valve disease is the most common predisposing factor, as well as prior gastrointestinal o dental manipulations.[5,6] Consumption of probiotics is also considered a potential risk factor,[7,8] as specifically described in 6 cases (46.2%). The most frequently affected valve is the aortic (n = 9, 69.2%), followed by mitral (n = 3, 23.1%). Whereas only three cases (23.1%) involved prosthetic valves, most native valves were anatomically or functionally abnormal.

Closely related, *Lactobacillus* species are difficult to identify by conventional methods, including MALDI-TOF MS. Therefore, molecular techniques such as 16S rRNA sequencing might be used in combination to achieve a more reliable identification. We suggest that the lack of genus-specific clinical breakpoints for *Lactobacillus* spp. is a challenge for interpretation of antimicrobial susceptibility testing. For example, EUCAST categorizes this gender into a global grampositive anaerobes group[9] and CLSI only defines breakpoints for a few antimicrobials against *Lactobacillus* spp. In this sense, further studies are required in order to develop reproducible and definitive standards to interpret susceptibility results.

Even though there is no standard treatment, most reports suggest the combination of ampicillin with aminoglycosides. Com-

Table 1
Infective endocarditis (IE) due to *Lactobacillus rhamnosus*: summary of case reports.

Author, publication date	Age, sex	Predisposing factors for bacteremia or IE	Consumption of probiotics	Valve/vertebra involved	Antibiotics	Surgery	Outcome
Davies et al., 1986[12]	55, M	UK	No	Aortic valve	Penicillin, gentamicin	Yes	Cured
Holliman et al., 1988[13]	71, F	Prosthetic aortic valve	UK	Prosthetic aortic valve	UK	UK	Death
Griffiths et al., 1992[14]	45, M	Bicuspid aorta; Dental manipulation	No	Bicuspid aorta	Ampicillin, gentamicin	Yes	Cured
Mackay et al., 1999[7]	67, M	Mitral valve prolapse with regurgitation	Yes	Mitral valve	Ampicillin, gentamicin	No	Cured
Presterl et al., 2001[15]	23, M	Bicuspid aorta	Yes	Bicuspid aorta	Penicillin	Yes	Cured
Avlami et al., 2001[6]	65, M	Colonoscopy	No	Aortic valve	Penicillin, gentamicin	No	Cured
Wallet et al., 2002[16]	73, M	Prosthetic aortic valve	No	Mitral valve	Amoxicillin, rifampin	Yes	Cured
Kochan et al., 2011[8]	24, F	Prosthetic aortic valve	Yes	Prosthetic aortic valve	UK	Yes	Cured
Felekos et al., 2014[17]	74, M	Myxomatous mitral valve	No	Myxomatous mitral valve	Penicillin, gentamicin	Yes	Cured
Aaron et al., 2017[5]	80, M	Upper endoscopy	No	Aortic and mitral valve	Penicillin, gentamicin	Yes	Cured
Noreña et al., 2017[18]	28, M	Bicuspid aorta	Yes	Bicuspid aorta	Ampicillin, gentamicin	Yes	Cured
Boumis et al., 2018[19]	65, M	Hereditary hemorrhagic telangiectasia	Yes	Prosthetic aortic valve	Amoxicillin/clavulanate, gentamicin	No	Cured
Naqvi et al., 2018[20]	36, F	Cirrhosis	Yes	Aortic valve	Penicillin, gentamicin	Yes	Death

UK: unknown, not specified in this manuscript.

bination treatment was reported in 10 out of the 13 reviewed cases (76.9%), and surgical intervention was required in 9 cases (69.2%), 8 native and 1 prosthetic valve episodes, most of them operated not during the active phase of treatment (e.g. early valve surgery) but rather to correct the mechanical sequelae with valve dysfunction after finishing antibiotics.

Strains with decreased susceptibility to ampicillin have been found, emphasizing that minimal inhibitory concentration of beta-lactam antibiotics as well as the exclusion of high-level resistance to aminoglycosides are relevant investigations. Eleven patients (84.6%) were cured and 2 (15.4%) died during hospitalization. Only 2 cases of spondylodiscitis have been reported, and one of them was a polymicrobial infection secondary to esophagus perforation. Both cases presented epidural abscess, one requiring surgery and no endocarditis association was described.[10,11]

No previous cases of TAVI endocarditis and spondylodiscitis have been published up to now. Our report underscores the potential clinical significance of *L. rhamnosus* bacteremia, highlighting the need for further investigations in patients with an elusive source of the infection.

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Utilidad del test de antígenos SARS-COV-2 de LumiraDx™ en centros residenciales

Usefulness of the Lumiradx™ SARS-COV-2 antigen test in nursing home

La detección de ácido ribonucleico (ARN) viral mediante la reacción en cadena de la polimerasa con transcriptasa inversa (RT-PCR) es el método de referencia en la detección de SARS-CoV-2, pero su alto precio y la saturación de muchos laboratorios hizo necesario implementar técnicas que ofrezcan resultados rápidos y fiables fuera del laboratorio, como los test rápidos de antígenos. Su aprobación para el diagnóstico de esta infección ha supuesto un cambio en la estrategia frente a la COVID-19[1] por su gran utilidad para detectar individuos infecciosos y reducir la propagación del virus[1]. Su rapidez, sencillez y posibilidad de realización en el punto de atención han hecho que tengan un papel importante en centros alejados del medio hospitalario como las residencias sociosanitarias.

El test de antígeno LumiraDx™ SARS-CoV-2 es un ensayo de inmunofluorescencia microfluídica rápida que mediante el uso tiras reactivas permite la detección directa y cualitativa de la proteína de nucleocápside viral en muestras nasales y nasofaríngeas. La utilidad de esta técnica se basa en su elevada sensibilidad y especificidad (del 97,6 y del 96,6%, respectivamente)[2]. Además, en pacientes sintomáticos la concordancia con la RT-PCR en los primeros 12 días tras el inicio de los síntomas es del 100%. El tiempo de respuesta del resultado de este test es de unos 12 minutos y el resultado es interpretado por un instrumento de lectura, eliminando el sesgo de interpretación interindividual del observador.

El objetivo del presente estudio es evaluar la sensibilidad y especificidad del test de antígeno LumiraDx™ en centros residenciales. Para ello, a cada participante con sintomatología compatible con COVID-19 o que eran contactos estrechos de pacientes con COVID-19, se le retiró una muestra nasal para realizar el test de antígeno LumiraDx™ (LumiraDx™ Limited, Londres, Reino Unido) y una muestra nasofaríngea para realización de RT-PCR, empleando los reactivos Allplex™ SARS-CoV-2 (Seegene, Seúl, Corea del Sur). Por otro lado, con la finalidad de valorar si los resultados negativos obtenidos mediante esta técnica pueden emplearse como criterio a la hora de discontinuar el aislamiento, se recogieron muestras de pacientes asintomáticos ya diagnosticados de COVID-19 y que habían cumplido el tiempo de aislamiento.

En 46 casos se utilizó el test de antígeno con finalidad diagnóstica. Su sensibilidad y especificidad fue del 87,5% y del 100%, respectivamente, con un valor predictivo positivo del 100% y un valor predictivo negativo del 88%. Centrándonos en los casos sintomáticos, la sensibilidad fue del 93,33%. En los tres casos en los que hubo discordancia (RT-PCR positiva y antígeno negativo) las RT-PCR presentaron ciclos de umbral (Ct) > 33 (tabla 1). Estudios previos han demostrado una sensibilidad de los test de antígenos de entre el 82,2 y 97,6%[3–7], cifras similares a las que arroja el test analizado en este estudio. Además, un reciente estudio señala el test de antígeno LumiraDx™ como uno de los test antigénicos más sensibles[3].

En el presente estudio se utilizó este test en una pequeña muestra (24 casos) para valorar su utilidad a la hora de decidir finalizar el aislamiento. La sensibilidad fue del 52,63% y la especificidad del 100%. Ambas pruebas coincidieron en 15 casos: 10 positivos y cinco negativos. En los nueve casos en los que hubo discordancia, la RT-PCR ofreció Ct > 31 tras una media de 16,66 días de infección. Aunque su sensibilidad fue baja, es necesario destacar que el test de antígeno fue negativo cuando la RT-PCR mostró Ct elevados lo que, según la evidencia disponible, equivaldría a una carga viral sin capacidad infectiva[1,8]. Por tanto, un resultado negativo podría apoyar la finalización del aislamiento junto con el cumplimento de los días de aislamiento y la ausencia de sintomatología en este colectivo vulnerable, en el cual la accesibilidad a las pruebas moleculares es más difícil.

En definitiva, el test rápido de antígenos LumiraDx™ presenta una elevada especificidad y una buena sensibilidad en muestras nasales de pacientes sintomáticos y asintomáticos. Se trata de una óptima herramienta diagnóstica de infección por SARS-CoV-2 y puede ser interesante valorar en estudios posteriores su utilización en otras situaciones como a hora de decidir la finalización del aislamiento.

Tabla 1
Test rápido de antígeno LumiraDx™ comparado con RT-PCR para diagnóstico de SARS-CoV-2 en función del motivo de realización de la prueba

		RT-PCR				TOTAL
		Positivo		Negativo		
		Sintomático	Contacto estrecho	Sintomático	Contacto estrecho	
LumiraDx™ Ag	Positivo	14	7	0	0	21
	Negativo	1	2	4	18	25
TOTAL		15	9	4	18	46