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*.

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.

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. Combination 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

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.

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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Alba Bergas [a], Samuel Rivera [a], Miriam Torrecillas [b], Guillermo Cuervo [a,*]

[a] Infectious Disease Department, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain
[b] Microbiology Department, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain

* Corresponding author.
E-mail address: guillermo.cuervo@bellvitgehospital.cat (G. Cuervo).

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

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

The detection of viral ribonucleic acid (RNA) by reverse transcriptase-polymerase chain reaction (RT-PCR) is the reference method for the detection of SARS-CoV-2, but its high price and the overburdening of many laboratories made it necessary to implement techniques that offer fast and reliable results outside the laboratory, such as rapid antigen tests. Their approval for the diagnosis of this infection has meant a change in the strategy against COVID-19[1] due to their great usefulness in detecting infectious individuals and reducing the spread of the virus[1]. Their speed and simplicity, as well as it being it possible to perform them at the point of care, have led to them playing an important role in centres outside the hospital environment, such as nursing homes.

The LumiraDx™ SARS-CoV-2 antigen test is a rapid microfluidic immunofluorescence assay that, through the use of test strips, allows direct and qualitative detection of the viral nucleocapsid protein in nasal and nasopharyngeal samples. The usefulness of this technique is based on its high sensitivity and specificity (97.6% and 96.6%, respectively)[2]. In addition, in symptomatic patients, the concordance with RT-PCR in the first 12 days after the onset of symptoms is 100%. The time to result of this test is about 12 min and the result is interpreted by a reading instrument, eliminating the inter-individual interpretation bias of the observer.

The objective of this study was to evaluate the sensitivity and specificity of the LumiraDx™ antigen test in care homes. To do this, a nasal sample was collected from each participant with symptoms compatible with COVID-19 or who were close contacts of patients with COVID-19 in order to perform the LumiraDx™ antigen test (LumiraDx™ Limited, London, United Kingdom) and a nasopharyngeal sample was collected to perform an RT-PCR test, using Allplex™ SARS-CoV-2 reagents (Seegene, Seoul, South Korea). In order to assess whether the negative results obtained using this technique can be used as a criterion when discontinuing isolation, samples were collected from asymptomatic patients already diagnosed with COVID-19 and who had completed the isolation period.

In 46 cases, the antigen test was used for diagnostic purposes. Its sensitivity and specificity were 87.5% and 100%, respectively, with a positive predictive value of 100% and a negative predictive value of 88%. In the symptomatic cases, the sensitivity was 93.33%. In the three cases in which there was discordance (positive RT-PCR and negative antigen), the RT-PCRs showed cycle threshold (Ct) values >33 (Table 1). Previous studies have shown a sensitivity of antigen tests of between 82.2% and 97.6%[3–7], figures similar to those reported by the test analysed in this study. In addition, a recent study indicates the LumiraDx™ antigen test to be one of the most sensitive antigen tests[3].

In our study, this test was used in a small sample (24 cases) to assess its usefulness in deciding to end isolation. The sensitivity was 52.63% and the specificity 100%. Both tests coincided in 15 cases: 10 positive and five negative. In the nine cases in which there was disagreement, RT-PCR showed a Ct value >31 after a mean of 16.66 days of infection. Although its sensitivity was low, it should be noted that the antigen test was negative when the RT-PCR showed an elevated Ct value, which, according to the available evidence, would be equivalent to a non-infectious viral load[1,8]. Therefore, a negative result could support the end of isolation together with compliance with the days of isolation and the absence of symptoms in this vulnerable group, in which access to molecular tests is more difficult.

In short, the LumiraDx™ rapid antigen test has high specificity and good sensitivity in nasal samples from symptomatic and asymptomatic patients. It is an optimal diagnostic tool for SARS-CoV-2 infection and it may be interesting to assess its use in other situations in subsequent studies, such as when deciding to end isolation.

Table 1
LumiraDx™ rapid antigen test compared with RT-PCR for the diagnosis of SARS-CoV-2 according to the reason for performing the test.

		RT-PCR				TOTAL
		Positive		Negative		
		Symptomatic	Close contact	Symptomatic	Close contact	
LumiraDx™ Ag	Positive	14	7	0	0	21
	Negative	1	2	4	18	25
TOTAL		15	9	4	18	46

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