



Letter to the Editor

False-positive results in the galactomannan Platelia™ *Aspergillus* assay with generic piperacillin/tazobactam



Resultados falsos positivos con el ensayo Platelia *Aspergillus*® para la determinación de galactomanano con el uso de formulaciones genéricas de piperacilina/tazobactam

Dear Editor,

Invasive aspergillosis (IA) is a highly lethal disease that mostly affects immunocompromised patients.⁶ Galactomannan (GM), a component of the genus *Aspergillus* cell wall, can be detected in clinical samples early in the course of the disease by the Platelia™ *Aspergillus* assay (Bio-Rad, Marnes-la-Coquette, France). One of the main reported disadvantages of this test is the false-positive results in patients receiving some beta-lactam antibiotics, especially piperacillin/tazobactam (TZP).¹ According to recent reports, newer TZP formulations have been free of this effect.^{5,9} Nevertheless, this false-positive reaction may remain a problem with the use of some generic formulations.²

Twelve TZP vials from three different manufacturers available in Mexico (PiSA™, Mexico; Vitalis™, Colombia; and Pfizer™, USA) and other beta-lactam antibiotics were analyzed for the GM antigen by the Platelia™ *Aspergillus* assay. The antibiotics were diluted with saline 0.9% at the maximum concentration recommended for their intravenous administration. We used as negative controls saline 0.9% and the solution included in the kit. The results were presented

as the GM index (GM-I). All tests were performed in duplicate by trained personnel blinded to the samples. Among the beta-lactam antibiotics tested, three TZP vials from one lot manufactured by PiSA (PIPTABAC™) yielded the highest GM-I (median [range]: 9.34 [9.26–9.41], 11.04 [9.69–12.39], and 9.58 [9.48–9.67]), Table 1. The other beta-lactam antibiotics examined, including the TZP manufactured by Vitalis™, Pfizer™, and the remainder lots from PiSA™, as well as the negative controls, consistently showed negative GM-I.

The standard methods for diagnosing IA (i.e., histopathology and culture) have low sensitivity and a long turn-around time, leading to treatment delays and poor outcomes.⁶ In consequence, the indirect evidence of IA through diagnostic methods such as GM has a significant role in IA diagnosis.⁷ False positive reactions can lead to unnecessary morbid therapeutic and diagnostic procedures.⁸ Although there is evidence that some brand and generic TZP formulations available around the world are no longer associated with false positive results in GM detection (USA, Italy, Brazil and Republic of Korea), concern remains about some generic TZP formulations may still present a problem in some countries (France and Turkey).^{2–5,9,10} Here, we demonstrated the presence of high GM-I in one lot of the generic TZP formulation manufactured by PiSA (PIPTABAC™). Previous studies that have analyzed generic TZP formulations for GM contamination have also found variation even between batches of the same brands.¹⁰ Our results highlight the importance of maintaining an active surveillance for the possibility of GM contamination in generic TZP formulations.

In conclusion, a widely used generic TZP available in Mexico may still be cause of GM cross reactions by the Platelia™ *Aspergillus*

Table 1

In vitro analysis of beta-lactams available in Mexico with the Platelia™ *Aspergillus* enzyme-linked immunosorbent assay.

Drug	Dosage form (mg)	Manufacturer	Lot. no.	Vial	GM-I	Median (range)
Piperacillin/tazobactam (PIPTABAC™)	4000/500	PiSA™	I15S019	1	9.34	(9.26–9.41)
				2	11.04	(9.69–12.39)
				3	9.58	(9.48–9.67)
			I17S125	1	0.09	(0.07–0.11)
				1	0.06	(0.05–0.06)
				1	0.08	(0.06–0.09)
Piperacillin/tazobactam (Tazocin™EF)	4000/500	Pfizer™	AKLA/13	1	0.19	(0.18–0.19)
Piperacillin/tazobactam	4000/500	Vitalis™	B150033	2	0.13	(0.13–0.13)
				1	0.27	(0.20–0.33)
				2	0.17	(0.09–0.24)
				3	0.18	(0.17–0.18)
Amoxicillin/sulbactam (Trifamox™)	1000/500	Armstrong™	B170220	1	0.10	(0.07–0.13)
				1	0.18	(0.14–0.22)
				1	0.08	(0.07–0.08)
Ampicillin (Meprizina™)	1000	PiSA™	I156966	1	0.13	(0.12–0.14)
Dicloxacillin (Penclox™)	500	PiSA™	I16A303	1	0.04	(0.04–0.04)
Ceftriaxone	1000	PiSA™	I16A303	1	0.04	(0.03–0.04)
Cephalothin	1000	PiSA™	J16F088	1	0.04	(0.04–0.04)
Imipenem/cilastatin (Tienam™)	500/500	MSD™	1505093	1	0.03	(0.03–0.03)
Ertapenem (Invanz™)	1000	MSD™	2182560	1	0.19	(0.16–0.22)
Meropenem (Merrem™)	1000	AstraZeneca™	15006B	1		

GM-I: galactomannan optical density index.

<https://doi.org/10.1016/j.riam.2018.07.004>

1130-1406/© 2018 Asociación Española de Micología. Published by Elsevier España, S.L.U. All rights reserved.

assay. Prospectively testing for GM false-positive results in TZP formulations vials from new batches from PiSA and generic formulations from other manufacturers seems to be necessary in order to avoid IA over-diagnosis. Moreover, an inspection and improvement of the manufacturing process of PIPTABAC™ might be needed given that recent TZP products from other manufacturers did not show galactomannan false-positive reactions.

References

1. Alhambra A, Cuétara MS, Ortiz MC, Moreno JM, del Palacio A, Pontón J, et al. False positive galactomannan results in adult hematological patients treated with piperacillin–tazobactam. *Rev Iberoam Micol.* 2007;24:106–12.
2. Demiraslan H, Atalay MA, Eren E, Demir K, Kaynar L, Koc AN, et al. Assessing the risk of false positive serum galactomannan among patients receiving piperacillin/tazobactam for febrile neutropenia. *Med Mycol.* 2017;55:535–40.
3. Gerlinger MP, Rousselot P, Rigauadeau S, Billon C, Touratier S, Castaigne S, et al. False positive galactomannan Platelia due to piperacillin–tazobactam. *Med Mal Infect.* 2012;42:10–4.
4. Ko JH, Peck KR, Lee WJ, Lee JY, Cho SY, Ha YE, et al. Generic piperacillin/tazobactam is not associated with galactomannan false-positivity in adult patients with cancer: a case–control study. *Eur J Clin Microbiol Infect Dis.* 2015;34:1437–41.
5. Mikulska M, Furfaro E, Del Bono V, Raiola AM, Ratto S, Bacigalupo A, et al. Piperacillin/tazobactam (Tazocin™) seems to be no longer responsible for false-positive results of the galactomannan assay. *J Antimicrob Chemother.* 2012;67:1746–8.
6. Pemán J, Quindós G. State of the art in invasive diseases by filamentous fungi. *Rev Iberoam Micol.* 2014;31:213–8.
7. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. *Clin Infect Dis.* 2006;42:1417–27.
8. Sulahian A, Touratier S, Ribaud P. False positive test for *Aspergillus* antigenemia related to concomitant administration of piperacillin and tazobactam. *N Engl J Med.* 2003;349:2366–7.
9. Vergidis P, Razonable RR, Wheat LJ, Estes L, Caliendo AM, Baden LR, et al. Reduction in false-positive *Aspergillus* serum galactomannan enzyme immunoassay results associated with use of piperacillin–tazobactam in the United States. *J Clin Microbiol.* 2014;52:2199–201.
10. Xavier MO, Pasqualotto AC, Aquino VR, Sukiennik TC, Severo LC. Galactomannan detection from piperacillin–tazobactam brands available in the Brazilian market. *Braz J Infect Dis.* 2009;13:353–5.

Edgar Ortiz-Brizuela^a, Andrea Rangel-Cordero^b,
Alfredo Ponce-de-León^{a,b}, Juan Sierra-Madero^{a,*}

^a *Department of Infectious Diseases, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Avenida Vasco de Quiróga No. 15, Colonia Belisario Domínguez Sección XVI, Del. Tlalpan, C.P.14080 Mexico City, Mexico*

^b *Department of Laboratory of Clinical Microbiology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Avenida Vasco de Quiróga No. 15, Colonia Belisario Domínguez Sección XVI, Del. Tlalpan, C.P.14080 Mexico City, Mexico*

* Corresponding author.

E-mail address: jsmadero@yahoo.com (J. Sierra-Madero).