JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2007, p. 676–677 Vol. 45, No. 2
0095-1137/07/$08.00+0 doi:10.1128/JCM.01940-06

Plasmalyte as a Cause of False-Positive Results for *Aspergillus* Galactomannan in Bronchoalveolar Lavage Fluid▽

The detection of galactomannan (GM) in the serum of immunocompromised patients is widely used for the early diagnosis of invasive aspergillosis (6). The test may also be useful when applied to bronchoalveolar lavage (BAL) fluid specimens for clinical diagnosis (5), though not FDA approved for this use. One important limiting factor for GM testing is the potential for false-positive results. Most notably, concomitant administration of piperacillin-tazobactam (1, 8) or amoxicillin clavulanate (4) antibiotics can cause false-positive results. This confounder is clinically important as many patients at risk for invasive aspergillosis receive these antibiotics.

Applying antigen detection strategies to BAL fluid diagnostics can be a potentially powerful tool (3, 5). However, it was unclear if a BAL specimen would have inherent problems with measurement of GM as bronchoscopy is not a sterile technique and contaminating fungal elements are often captured as the bronchoscope passes through the upper airway.

As part of an off-label investigation, we recently noted highly positive *Aspergillus* galactomannan (Platelia aspergillus kit; Bio-Rad) antigen results in 19 consecutive BAL specimens from a single institution from 19 different patients who were treated at a single institution (Table 1). Samples were collected and banked according to institutional review board guidelines for research. The galactomannan index (GMI) was uniformly high (4.1 to 8.2) in these specimens. The BAL fluids were collected for posttransplant surveillance from lung transplant recipients with no evidence of infection, mostly to monitor for allograft rejection. Serum specimens were not tested, however. Fungal cultures yielded no fungal growth in 17 specimens, 1+ *Aspergillus fumigatus* growth from one specimen, and 2+ *Paecilomyces* sp. growth from another. This pattern of positivity was not seen with BAL samples from other institutions tested at this laboratory (MiraVista Diagnostics, Indianapolis, IN); about 10% of these specimens are positive, and GMIs are evenly distributed over the positive range from 0.5 to 5.0. Upon further investigation we learned that Plasmalyte (Baxter) was the solution used to perform bronchoalveolar lavage at that institution. Multiple lots of Plasmalyte were subsequently tested and were highly positive for GM (Table 1). We subsequently tested BAL fluids from procedures that were performed using normal saline, and all samples tested negative for *Aspergillus* galactomannan, as was the saline solution used for lavage.

False-positive tests can lead to improper medical decision making. In the case of *Aspergillus* galactomannan testing, false-positive tests are associated with use of antibiotics produced by fermentation in *Penicillium* (4, 8, 9). *Penicillium* produces a galactomannan that is recognized by the monoclonal antibody used in the Platelia assay (7).

TABLE 1. Samples tested for GM

Test specimen	No. positive/no. tested	Galactomannan index
Human BAL fluid with Plasmalyte for lavage	19/19	4.1–8.2
Human BAL fluid with normal saline for lavage	0/5	0.24–0.34
Plasmalyte solution (four different lots)	4/4	5.4–5.6

Plasmalyte contains sodium gluconate, 503 mg/100 ml, which is produced by fermentation in *Aspergillus niger* (communication with the manufacturer). The false-positive galactomannan antigen results seen with Plasmalyte resemble those observed with piperacillin-tazobactam. In both cases, the false-positive results result from carryover of small amounts of galactomannan during the production of fermentation product, estimated to be about 2 parts/million for sodium gluconate (1 μg galactomannan/503 mg Na gluconate).

We estimated Plasmalyte to contain about 10 ng/ml galactomannan, based upon demonstration that a 1:10 dilution of Plasmalyte yielded a result comparable to the cutoff control (1 ng/ml) provided in the Platelia kit. Thus, 100 ml of Plasmalyte contains about 1 μg of galactomannan. It is unlikely that bronchoalveolar lavage using 100 ml of Plasmalyte (1 μg of galactomannan) causes false-positive antigenemia, especially since more than half of the instilled fluid is recovered during the lavage and the remaining fluid is unlikely to be totally absorbed into the serum.

Whether intravenous administration of Plasmalyte would cause false-positive antigenemia requires further study. One liter of Plasmalyte contains about 10 μg of galactomannan, which would be diluted into the total plasma volume. Assuming that the 10 μg of galactomannan is diluted into 3 to 4 liters of plasma volume (average 70-kg patient), this would yield a concentration greater than 2.5 ng/ml, which is above the sensitivity (0.5 ng/ml) of the galactomannan assay. Furthermore, with repeated infusion, as occurs in fluid replacement therapy, sufficient galactomannan may accumulate to cause false antigenemia, as with piperacillin-tazobactam (2). Furthermore, the mechanism for elimination of galactomannan is unknown, and conditions affecting elimination could facilitate accumulation following repeated administration. Studies with patients are required to address these issues.

In conclusion, Plasmalyte contains small amounts of *Aspergillus* galactomannan and can cause false-positive results in BAL specimens. Although not demonstrated, intravenous administration of Plasmalyte should also be considered a potential cause for false antigenemia.

REFERENCES

1. **Adam, O., A. Auperin, F. Wilquin, J. H. Bourhis, B. Gachot, and E. Chachaty.** 2004. Treatment with piperacillin-tazobactam and false-positive Aspergillus galactomannan antigen test results for patients with hematological malignancies. Clin. Infect. Dis. **38:**917–920.
2. **Aubry, A., R. Porcher, J. Bottero, S. Touratier, T. Leblanc, B. Brethon, P. Rousselot, E. Raffoux, J. Menotti, F. Derouin, P. Ribaud, and A. Sulahian.** 2006. Occurrence and kinetics of false-positive *Aspergillus* galactomannan test results following treatment with β-lactam antibiotics in patients with hematological disorders. J. Clin. Microbiol. **44:**389–394.
3. **Hage, C. A., T. E. Davis, L. Egan, M. Parker, D. Fuller, A. M. Lemonte, M. Durkin, P. Connelly, L. J. Wheat, D. Blue-Hnidy, and K. S. Knox.** 2007. Diagnosis of pulmonary histoplasmosis and blastomycosis by detection of antigen in bronchoalveolar lavage fluid using an improved second-generation enzyme-linked immunoassay. Respir. Med. **101:**43–47.
4. **Mattei, D., D. Rapezzi, N. Mordini, F. Cuda, C. Lo Nigro, M. Musso, A. Arnelli, S. Cagnassi, and A. Gallamini.** 2004. False-positive *Aspergillus* galactomannan enzyme-linked immunosorbent assay results in vivo during amoxicillin-clavulanic acid treatment. J. Clin. Microbiol. **42:**5362–5363.

5. **Musher, B., D. Fredricks, W. Leisenring, S. A. Balajee, C. Smith, and K. A. Marr.** 2004. *Aspergillus* galactomannan enzyme immunoassay and quantitative PCR for diagnosis of invasive aspergillosis with bronchoalveolar lavage fluid. J. Clin. Microbiol. **42:**5517–5522.
6. **Pfeiffer, C. D., J. P. Fine, and N. Safdar.** 2006. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin. Infect. Dis. **42:**1417–1427.
7. **Stynen, D., J. Sarfati, A. Goris, M.-C. Prévost, M. Lesourd, H. Kamphuis, V. Darras, and J. P. Latgé.** 1992. Rat monoclonal antibodies against *Aspergillus* galactomannan. Infect. Immun. **60:**2237–2245.
8. **Walsh, T. J., S. Shoham, R. Petraitiene, T. Sein, R. Schaufele, A. Kelaher, H. Murray, C. Mya-San, J. Bacher, and V. Petraitis.** 2004. Detection of galactomannan antigenemia in patients receiving piperacillin-tazobactam and correlations between in vitro, in vivo, and clinical properties of the drug-antigen interaction. J. Clin. Microbiol. **42:**4744–4748.
9. **Wheat, L. J.** 2003. Rapid diagnosis of invasive aspergillosis by antigen detection. Transplant. Infect. Dis. **5:**158–166.

Chadi A. Hage*
Indiana University School of Medicine and Roudebush VA Medical Center
1481 W. 10th St., 111P-IU
Indianapolis, Indiana 46202

John M. Reynolds
Methodist Hospital
Indianapolis, Indiana

Michelle Durkin
L. Joseph Wheat
MiraVista Diagnostics
Indianapolis, Indiana

Kenneth S. Knox
Indiana University School of Medicine and Roudebush VA Medical Center
Indianapolis, Indiana

*Phone: (317) 988-3811
Fax: (317) 988-3976
E-mail: chage@iupui.edu

▽ Published ahead of print on 13 December 2006.