Galactomannan in Piperacillin-Tazobactam: How Much and to What Extent?

The detection of *Aspergillus* galactomannan antigen (GM) with the Platelia *Aspergillus* (PA) enzyme-linked immunosorbent assay (Bio-Rad) is a method widely used for the diagnosis of invasive aspergillosis (IA), a life-threatening fungal infection (3, 7). In the last 2 years, several authors found GM in patients treated with piperacillin-tazobactam (TZP) and in TZP vials (1, 6, 8, 10, 11) while others did not (5).

In order to find an explanation for this discordance, we assayed a larger number of TZP vials with the PA test to evaluate the proportion of positive batches and vials and the amount of GM in the drug.

Ninety TZP vials from 30 randomly selected batches were tested with the PA test (median number of vials per batch, three; range, one to four). The drug was diluted as for clinical use (45 mg/ml NaCl [0.9%]), and the test was performed as for serum samples following the manufacturer's instructions. NaCl (0.9%) alone was tested as a negative control. The results were tabulated as an index (GM-I) between the optical density of the sample tested and the optical density of the threshold control (1 ng/ml) provided in the PA kit. All samples and controls were tested in duplicate, and they were considered to be positive if the GM-I was ≥0.7.

Twenty-six batches (86%) tested positive (all 79 vials), with a median GM-I of 1.99 (range, 0.77 to 6.98), while four batches (11 vials) tested negative (median GM-I, 0.28; range, 0.19 to 0.3). There is an apparently bimodal distribution of GM-I in the 79 positive vials. Indeed, 40 vials had GM-Is of 0.77 to 2.87, while 27 vials had GM-Is of 3.86 to 6.98. Twelve additional vials had GM-Is of >7. Division of the positive results into two groups was supported by analysis of frequency distribution (Fig. 1).

In each batch, the mean coefficient of variation (9) (the respective standard deviation divided by the overall mean, expressed as a percentage) of the GM-I was 8.88% (median, 9.21%; range, 1.20 to 20.33%), a value well below the mean intra-assay coefficient of variation in our laboratory (11.08%; median, 9.18%; range, 0.45 to 31.22%). This suggests a low intrabatch variability of GM.

The rate of TZP batches testing positive with the PA test is in agreement with previous reports (75 to 100%). The presence of negative batches and the very wide range of GM-Is of positive TZP batches, with a bimodal distribution, may explain the great variability of the false-positive results and also why some authors did not find any false positivity (5). A recent study indicates that a positive PA test with TZP is likely due to the presence of GM in TZP rather than to a cross-reaction with the antibiotic (4). The origin of the TZP-GM remains unclear, and the only hypothesis made so far suggests something happening during the production process, which likely includes at some point the use of *Penicillium* spp. *Penicillium* GM is similar to *Aspergillus* GM (2). However, if this is true, we are unable to explain why some batches have no GM and why there is such a great variability between the GM contents of different batches.

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FIG. 1. Frequency distribution of GM indexed in 90 TZP vials.


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