Large Invasive Aspergillosis (IA) Pseudooutbreak due to an intravenous (i.v.) Formulation of Acetaminophen.

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Introduction.

Serum Galactomannan (GM) is a useful tool for the screening of invasive aspergillosis in high risk haematological patients. However, its usefulness is known to be hampered by false positive results (FP) due to cross reactions with other fungi (i.e: *Penicillium* spp, *Paecilomyces* spp, Fusarium spp, …), bacteria (*Bifidobacterium* spp in cases of disruption of intestinal barrier) or with products that may contain similar fungal antigens (i.e: beta-lactam antibiotics, gluconates).

The aim of this work is to describe a pseudo-outbreak of IA in haematological adult patients in which a high proportion of GM FP (GMindex≥0.5 in 2 consecutive samples without any other evidence of IA) was registered and linked to the i.v. administration of a generic preparate of acetaminophen.

Materials and Methods.

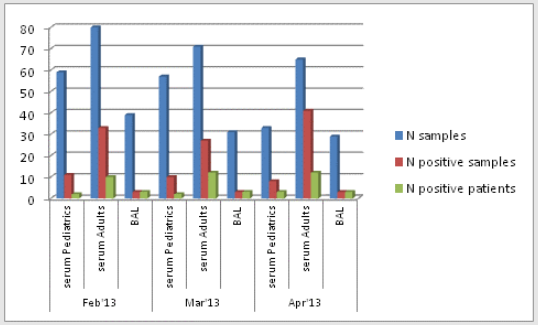
Prospective study carried out in adult hematological patients (n=73) admitted to Vall d'Hebron Hospital between February-October'2013 from whom 630 serum samples were obtained. 12 samples from 2 patients with probable/proved AI were excluded from the analysis.

PERIOD 1 (February-April'13. 213 serum samples, 31 patients). A rise in the precentage of serum GM FP was observed in adult hematological inpatients not related to similar increases in GM results obtained from serum samples of pediatric patients or broncho-alveolar lavages in the same period. The source of the FP was investigated and previously described causes of FP were ruled out (i.e: lab contamination, beta-lactam antibiotics, gluconates, intestinal GVHD, construction works). Recent introduction of any new product or new brand of products to be given to the affected patients was also ruled out, as it is known that different brands of the same product may provide different results in GM testing. Intravenous medications prescribed in common to a sample of 12 patients 24h before GM FP determinations (acetaminophen, ClK, and metoclopramide) were investigated using the Patelia Aspergillus Ag, Bio-Rad. Thereafter, the relationship between acetaminophen prescription and GM FP was retrospectively studied in the other 19 patients of period 1. Their results were compared to those of **PERIOD 2** (May-July'13. 205 serum samples, 35 patients), in which acetaminophen prescription was restricted to patients not candidates to receive other antiinflammatory formulations, and **PERIOD 3** (August-October'13. 38 patients, 200 serum samples), when contaminated acetaminophen was substituted by another acetaminophen brand that tested negative for GM .

Chi^2 and Mann-Whitney Rank U tests were used as statistics. A p<=0.005 was considered significant.

Results.

Fig 1: Number of hematolgic adult serum samples (total/positives) received for GM testing in february-april 2013 non related to an increase in the number of positive samples or patients from Pediatric Oncohematology ward or bronchoalveolar lavages in the same period .



A total of 113 products were given as therapy or supportive care to a sample of 12 patients studied in April. Of them, 41 were administered i.v. but only 3 were consistently prescribed 24 hours before: A generic acetaminophen, metoclopramide and ClK. The GM index of several batches of a generic i.v. acetaminophen formulation in use in our center tested positive, whereas 3 other acetaminophen brands (pointing out the possible role of the citrate used as excipient in the formulation in use in our center) , ClK and metoclopramide rendered negative results. Mean results are shown in table 1

TABLE 1	Mean GMindex
Metoclopramide	0.079 (2 batches)
Acetaminophen 1[1]	>10 (5 batches)
Acetaminophen 2[2]	0.059
Acetaminophen 3[2]	0.080
Acetaminophen 4[2]	0.049
Sterile saline	0.080

[1]Product in use in our center between Feb-Jul'13;
[2]Other brands of acetaminophen i.v.

Number of serum samples and comparison of GM index of inpatients with and without indication of i.v. Acetaminophen prescription 24 hours before GM determination is shown in table 2.

Period	Prescription (n serums)	N FP (% total)	GM index (IC95)
Feb-Apr	Yes (n=144)	87 (60.4)*	1.02 (0.84-1.20)*
	No (n=28)	5 (17.6)	0.47 (0.18-0.75)
May-Jul	Yes (n=23)	10 (43.6)*	0.70 (0.40-1.00)*
	No (n=124)	9 (7.26)	0.22 (0.15-0.30)
Aug-Oct	Yes (n=67)	1 (1.49)	0.12 (0.09-0.15)
	No (n=74)	1 (1.35)	0.11 (0.06-0.15)

*p<0.001 as compared to no-prescription

Conclusions.

False positive results in GN testing may be due to non-previously described sources.

In our case, batches of the citrate used as excipient in the composition of the intravenous formulation of acetaminophen in use in our center was thought to be responsible for the increase of GM FP observed. Since this product was in use since 2010, this episode underlines the importance of a careful investigation not only of products used in patients' care but also of their composition and the different batches used.

The presence of citrate, among other products obtained from *Aspergillus* biofermentation , should be ascertained in products administered to patients whose serum samples are submitted for GM testing in case of FP.