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ANTIFUNGAL STEWARDSHIP BASED ON 1,3-BETA-D-GLUCAN IN CRITICAL PATIENTS: A TOOL TO RATIONALISE EMPIRICAL ANTIFUNGAL THERAPY

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Background and aim

The availability of reliable and rapid serological test to confidently exclude the presence of an invasive fungal infection (IFI) is a critical, unmet clinical need, in order to reduce unnecessary exposure to empirical antifungal treatment (*Valerio M. et al., JAC 2014; Martínez-Jiménez MC et al., JAC 2016*). β-D-Glucan (BDG) is a panfungal polysaccharide detected in serum during several IFIs, whose quantification may help to exclude the presence of a in IFI in critical patients, especially from hematological or intensive care units (ICU). We aimed at evaluating the diagnostic performance of a mycological stewardship protocol based on sequential, rapid BDG quantification for an early exclusion of IFI in high-risk critical patients with suspected clinical and/or radiological pictures.

Material and methods

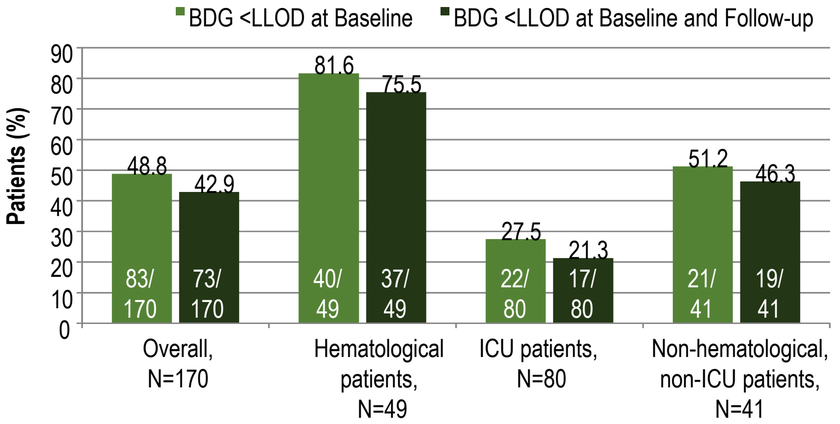
BDG was dosed twice weekly by a rapid turbidimetric assay (ß-Glucan Test kit; FUJIFILM Wako Chemicals Europe GmbH, Germany; lower-limit of detection [LLOD]=2 pg/mL; no batch processing). The classification of IFI was performed based on the revised 2008 EORTC/MSG criteria (*De Pauw et al., 2008*). Empiric or targeted antifungal treatment was started at discretion of clinicians, according to local and international guidelines. Statistical analyses were performed using the SPSS software package (version 19.0) for Windows (SPSS Inc., Chicago, IL).

170 critical patients with possible IFI were included

		Hematological patients, N=49	ICU patients, N=80	Non-hematological, non-ICU patients, N=41
Male N (%)		24 (49.0)	58 (72.5)	28 (68.3)
Age (years), Median (IQR)		56 (51-68)	64 (51-72)	58 (49-66)
Length of hospitalization (days), Median (IQR)		15 (10-26)	13 (7-21)	12 (4-31)
Stratification of patients, N (%)	*Immunosuppressed*	49 (100)	12 (15.0)	19 (46.3)
	Non-surgical	-	5 (6.3)	5 (12.2)
	High-risk digestive tract surgery	-	30 (37.5)	11 (26.8)
	Abdominal surgery	-	16 (20.0)	1 (2.4)
	Non-abdominal surgery	-	17 (21.3)	5 (12.2)
Classification of sepsis, N (%)	*No sepsis*	44 (89.8)	26 (32.5)	22 (53.7)
	Mild to severe sepsis	1 (2.0)	14 (17.5)	17 (41.5)
	Septic shock	3 (6.1)	37 (46.3)	1 (2.4)
	Multi-organ Failure	1 (2.0)	3 (3.8)	1 (2.4)
Antifungal prophylaxis, N (%)		17 (34.7)	-	-

Results

BDG results were reported to the attending physicians within 4 hours maximum since sample collection, and only BDG values < LLOD were defined as negative



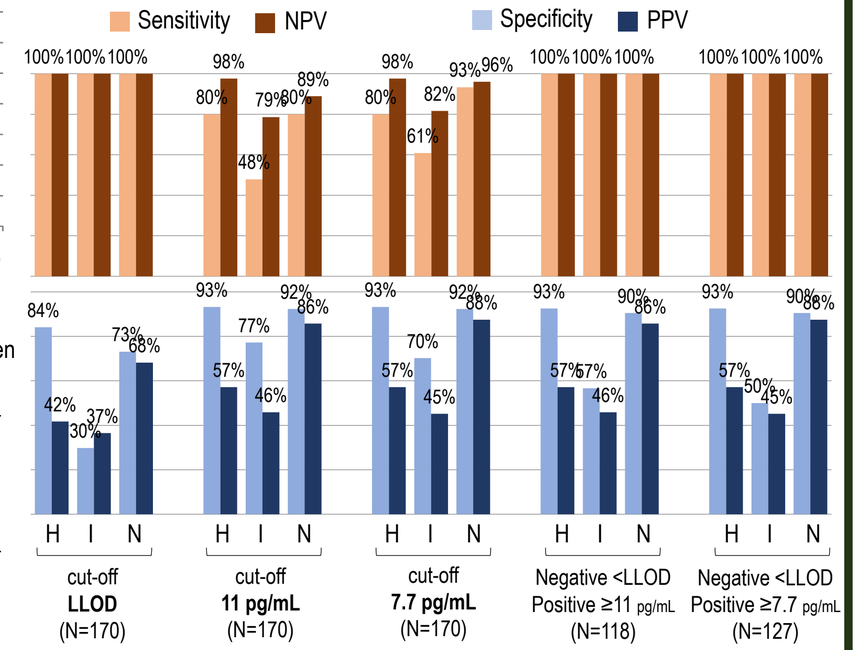
None of the patients with a double BDG quantification <LLOD was diagnosed with a proven IFI, nor contextually to BDG sampling nor during the following month of hospitalization.

		Hematological patients, N=49	ICU patients, N=80	Non-hematological, non-ICU patients, N=41
Classification of invasive fungal infection, N (%)	Proven	5 (10.2)	23 (28.8)	15 (36.6)
	Probable	3 (6.1)	13 (16.3)	2 (4.9)
	No IFI	41 (83.7)	44 (55.0)	24 (58.5)
IFI episode, N (%)	IC without candidaemia	2 (40.0)	15 (65.2)	6 (40.0)
	Only candidaemia	1 (20.0)	3 (13.0)	4 (26.7)
	IC with candidaemia	-	3 (13.0)	2 (13.3)
	IA	1 (20.0)	3 (13.0)	-
	PJP	1 (20.0)	-	3 (20)
Mortality, N (%)	Proven IFI	4 (80.0)	6 (26.1)	6 (40.0)
	Probable IFI	1 (33.3)	3 (23.1)	-
	No IFI	7 (17.1)	8 (18.2)	5 (20.8)

IA, invasive aspergillosis; IC, invasive candidiasis; IFI, invasive fungal infections; PJP, Pneumonia by *Pneumocystis jirovecii*

When 2 consecutive BDG values < LLOD are used to define the negativity of the test, both sensitivity and negative predictive value reach 100%

For all analyzed populations, the reduction of positivity cut-off from 11 pg/mL to 7.7 pg/mL allowed a limitation of patients with BDG results within the grey-zone (from 52 patients to 43), without apparently affecting sensitivity and NPVs.



Conclusions

Our study showed that a double negative BDG result, defined by BDG values strictly below the LLOD of the test, is a very effective diagnostic tool able to exclude with 100% sensibility and 100% NPV the diagnosis of an IFI in high risk clinical settings. In daily practice, the short turnover time to results, the high sensitivity and versatility in IFI diagnosis, and the low cost for single test are particularly relevant characteristics for a diagnostic-based therapeutic approach, along with a careful interpretation of results made possible by a close collaboration among microbiologists and clinicians, as all these are necessary for making prompt decisions on proper antifungal treatments in complex clinical care settings.