27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: OS173 Challenges in antifungal treatment

Category: 6c. Antifungal drugs & treatment

25 April 2017, 10:00 - 10:10
OS0851

Comparison of treatment appropriateness defined by previous, current CLSI and EUCAST breakpoints and their association with mortality in candidaemia

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Background: Antifungal susceptibility breakpoints changed dramatically in the last decade; yet uncertainty on the optimal breakpoints persists. We assessed the association between appropriate antifungal treatment (AAT) and survival using different breakpoints defined by CLSI-2008, CLSI-2012 and EUCAST-2014.

Material/methods: Retrospective study including adult patients (>18 years) with candidemia diagnosed between 2009-2015 in a primary and tertiary 960-bed hospital. Empirical antifungal treatment (EAT) was defined as that given within 48 hours after the first positive blood culture was taken. Definitive antifungal treatment (DAT) was defined as the main antifungal administered in the first two weeks after the first positive blood culture. We applied the three breakpoint definitions according to MIC values determined by E test to EAT and DAT. Susceptibility-dose-dependent (CLSI) was defined as covering and intermediate (EUCAST and CLSI) as non-covering. For EAT, all patient-episodes separated by at least 3

months were included in an analysis of 30-day mortality. Univariate odds ratios (OR) were calculated using the Mantel Haeszel test and adjusted ORs using bivariate regression analysis. For DAT, only patient-unique >7 day survivors were included in a survival analysis. Univariate and multivariate Cox regression analyses were conducted to compute hazard ratios (HR).

Results: We included 308 episodes of clinically-significant candidemia among 302 patients. The mean age was 63.3±18.8; 95/308 (30.8%) were *C. albicans*. The 30-day mortality was 54.5% (164/308) and 82.8% (250/302) died by the end of follow-up. Inappropriate treatment rates changed dramatically with the different definitions (Table). For EAT, AAT was significantly associated with 30-day mortality with all definitions, with the largest association observed for EUCAST. On multivariate analysis, adjusting to functional capacity, malignancy, presence of vascular catheter, hypotension and acute mental status change at onset, only EUCAST-defined AAT was significantly associated with survival (OR 0.47, 95% confidence interval 0.27-0.82). For DAT, AAT was significantly associated with survival with all definitions. On multivariate analysis, adjusted to functional capacity, Charlson score, polymicrobial candidemia and hemodynamic instability at onset, AAT was significantly associated with survival only when CLSI-2012 and EUCAST definitions were applied (Table).

Conclusions: We show better associations between AAT and mortality for patients with candidemia, when appropriateness was defined by the newer CLSI or EUCAST definitions.

Table

	Deaths/ inappropriate	Deaths/ appropriate	Inappropriate rate	Unadjusted OR/HR (95% CI)	Multivariate OR/HR (95% CI)
Empirical treatment	30 day mortality (N=308)				
CLSI-2008	94/150 (62.7%)	74/158 (46.8%)	48.7%	**0.53 (0.33-0.83)**	0.66 (0.39-1.11)
CLSI-2012	107/175 (61.1%)	61/133 (43.2%)	56.8%	**0.54 (0.34-0.85)**	0.66 (0.4-1.09)
EUCAST-2014	134/223 (60.1%)	34/85 (40%)	72.4%	**0.44 (0.27-0.74)**	**0.47 (0.27-0.82)**

Definitive treatment	Mortality at end of follow-up (N=215)				
CLSI-2008	8/12 (66.7%)	71/203 (35%)	5.6%	**0.51 (0.28-0.94)**	0.61 (0.32-1.17)
CLSI-2012	25/52 (48.1%)	54/163 (33.1%)	24.2%	**0.68 (0.48-0.97)**	**0.7 (0.49-0.99)**
EUCAST-2014	48/109 (44%)	31/106 (29.2%)	50.7%	**0.76 (0.56-1.03)**	**0.68 (0.5-0.94)**