



European Committee on Antimicrobial Susceptibility Testing and Clinical and Laboratory Standards Institute breakpoints—the only point that matters in candidemia?

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Candidemia is associated with high mortality of around 46.9% (1). Risk factor for candidemia are sepsis, *Clostridium difficile* infection, diabetes mellitus, total parenteral nutrition, chronic obstructive pulmonary disease, presence of peripherally inserted central catheter, previous antibiotic therapy and immunosuppressive therapy (2). Treatment of candidemia should be guided by local epidemiology and sensitivity pattern. To point out the difference, *Candida albicans* is the predominant candida isolated in Australia, Japan, Korea, Hong Kong, Malaysia, Singapore and Thailand whereas in Pakistan and India *C. tropicalis* is the most frequently encountered species (3). The IDSA recommends using echinocandins for candidemia and fluconazole for step down therapy or fluconazole in patients with low risk of resistant organism (4).

Microbiology labs perform antifungal sensitivity test which are guided by breakpoints given by Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST). The guidelines give us species specific cut offs for management. There was a recent change in the cut-off which was due to increased adverse outcomes with higher minimum inhibitory concentration (MIC) (5). It is important to understand that CLSI and EUCAST have different size of inoculum used for testing and both cannot be compared directly with each other.

Even if the isolate is sensitive *in vivo* to a given antifungal, the successful outcome of the patient depends on multiple factors like local concentration of the antifungal at

the site of infection, biofilm formation, host immune status, drug interactions and burden of organism. The 90:60 rule applies to antifungals as well. This rule states that infections due to susceptible isolates respond to therapy approximately 90% of the time, whereas infections due to resistant isolates respond approximately 60% of the time (6). Change is the only constant, antifungals which were once considered appropriate are now considered inappropriate given the change in breakpoints.

The study by Ghanem *et al.* aimed at studying the association between inappropriate antifungal therapy and mortality taking into consideration different EUCAST and CLSI breakpoint definitions. They also looked at the different breakpoints definition that best discriminates patients who survived *vs.* those who did not. This was a retrospective study with patients from a wide range of backgrounds which included medical, surgical, burns, haematology and bone marrow transplant patients. Most studies restrict themselves to a specific group of patients to have a homogeneity in the background illness and comorbidities. Bacteraemia patients were also included and they were associated with increased 30-day mortality when inappropriately treated with the odds ratio of 3.79 (95% CI: 1.69–8.47).

The CLSI and EUCAST both suggest broth dilution as a method of choice for conducting susceptibility testing which needs resources, expertise and is subjective in interpretation. The study by Ghanem *et al.* used E-test (AB Biodisk, Solna, Sweden) and VITEK 2 AST-YS07 card for susceptibility. Studies have reported Vitek-2

misidentifying candida isolates 4.9–7.5% (7,8).

The study has compared the three different guidelines from different time periods which reflects the changing epidemiology and resistance pattern. The study considered the treatment as appropriate or inappropriate according to breakpoints given by CLSI 2008, 2012 and EUCAST 2017 guidelines. With the change in breakpoints the study reported lesser number of patients receiving definitive treatment which was appropriate, CLSI-2008 93.5% compared to 62.3% if grouped according to EUCAST 2017. The study showed that if the patient has received appropriate antifungal therapy according to any MIC given by CLSI/EUCAST, the patient would have a lesser odd of unfavourable outcome.

The study did not report dose of the antifungal used and renal functions of the patient which has shown to impact the outcome of the patient even if considered to receive appropriate antifungal treatment as per any guidelines (9). The study also showed better 30-day mortality rate with removal of catheter but a similar result was not seen for 90-day mortality. Early central venous catheter (CVC) removal has been shown to be associated with decreased mortality (10). A recent study on individual patient level quantitative review of randomized trials which included 1915 patients showed improved survival with removal of the CVC (11).

The study did not report how many patients received inappropriate treatment according to the 3 different guidelines and their outcomes which would have helped us to understand if inappropriate treatment was associated with worse outcome. A study from Columbia reported no association of fluconazole resistance with mortality despite the change in breakpoints. On the contrary the study reported reduced mortality with fluconazole by 30%, acting as a protective factor (9). A similar study from Japan reported decreased mortality with empirical fluconazole (12). A Spanish study reported no association of high fluconazole MIC values or PK/PD parameters with clinical failure (13). Inappropriate antifungal therapy was given in 16 patients (10.7%) but this was not associated with increased mortality ($P=0.58$) in a study by González-Lara *et al.* (10).

In conclusion the study attempted to understand the impact of the changing breakpoints on clinical outcome taking MIC and clinical breakpoints from bench to bedside and opening new questions for further research. MIC levels should not be the only factor driving the choice of antifungal therapy. Antifungal concentration at the site of infection, side effect profile of the antifungal and prompt source control by surgery or removing catheters/implants

are important for a favourable outcome.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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