EUCAST Technical Note on fluconazole

The European Committee on Antimicrobial Susceptibility Testing—Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST)*

**Keywords** Breakpoints, EUCAST Technical Note, fluconazole, susceptibility testing


**INTRODUCTION**

Fluconazole is an azole antifungal agent active against _Candida_ spp. and _Cryptococcus_ spp. It can be administered orally or intravenously. It has been used for treating _Candida_ infections, and is effective in treating infections caused by strains of _Candida albicans_, _Candida tropicalis_ and _Candida parapsilosis_ without acquired resistance mechanisms. The drug is ineffective for treating infections caused by _Candida krusei_, which is naturally resistant. The response of infections caused by _Candida glabrata_ is variable, as the wild-type MIC distribution straddles most reasonable MIC breakpoints. Every attempt should be made to identify _Candida_ isolates to the species level before or in conjunction with antimicrobial susceptibility testing.

The EUCAST-AFST (European Committee on Antimicrobial Susceptibility Testing—Subcommittee on Antifungal Susceptibility Testing) has determined breakpoints of fluconazole for _Candida_ spp. This Technical Note is based on the EUCAST fluconazole rationale document (available on the EUCAST website: http://www.eucast.org). The rationale document includes more detail and published references related to the selection of EUCAST-AFST breakpoints.

**DOSAGE**

The EUCAST-AFST has determined clinical breakpoints for a fluconazole dose of 400–800 mg/day, given orally or parenterally.

**MIC DISTRIBUTIONS**

The MIC values for wild-type _Candida_ spp. are shown in Table 1. The MIC distributions are based on large collections of MIC values from several investigators, obtained using the EUCAST-AFST, CLSI and Etest methods. Wild-type isolates of _C. albicans_, _C. tropicalis_ and _C. parapsilosis_ exhibit MICs of ≤2 mg/L, whereas MICs for _C. glabrata_ are higher at 32 mg/L, and those for _C. krusei_ are higher still at up to 128 mg/L. Updates on wild-type MIC distributions can be found at http://www.eucast.org.

**ESTABLISHED BREAKPOINTS**

Only Norway and Germany have established national breakpoints for fluconazole, at sensitive (S) ≤4/resistant (R) >32 mg/L and S ≤4/R >16 mg/L respectively.

**PHARMACOKINETIC DATA**

The pharmacokinetic data used to evaluate fluconazole were based on standard doses of 400 and 800 mg (Table 2).

**PHARMACODYNAMIC DATA**

Fluconazole is thought to be fungistatic when given in lower doses, and fungicidal when given in higher doses. The pharmacodynamic index best related to outcome is the fAUC/MIC. This is virtually the same as the dose/MIC, since the AUC and the dose are highly correlated. Hence, dose provides a good surrogate for the AUC. The
pharmacokinetic/pharmacodynamic target was explored using Monte Carlo simulations to estimate the likelihood that a target fAUC/MIC of 50–100 could be attained. Most cases of candidosis involve immunocompromised patients; hence, fungicidal levels are considered to be a prerequisite for success. Therefore, an fAUC/MIC target of at least 100 is desirable. Classification and regression tree (CART) analysis supports this target, since >90% of patients given at least 100 mg of fluconazole daily are likely to respond.

**CLINICAL EFFICACY**

There is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct, albeit imperfect, relationship between the AUC (or dose) and a successful clinical response in cases of oral candidosis and, to a lesser extent, in cases of candidaemia. Similarly, cure is less likely for infections caused by strains with higher MICs.

The EUCAST-AFST considers that fluconazole is appropriate therapy for candidaemia in neutropenic and non-neutropenic patients, chronic disseminated candidosis, disseminated cutaneous neonatal candidosis, urinary tract infections, lower respiratory tract infections, osteomyelitis, arthritis, infections of the gallbladder, pancreas and peritoneum, endocarditis, pericarditis, suppurative phlebitis, myocarditis, meningitis and endophthalmitis caused by Candida spp., non-genital mucocutaneous candidosis and genital candidosis.

The EUCAST-AFST considers that fluconazole is appropriate prophylaxis for neutropenic patients, particularly those colonised with C. tropicalis, as well as for allogeneic haematopoietic stem-cell transplant recipients and recipients of liver transplants, who are considered to be at high risk for infection.

**BREAKPOINTS**

Breakpoints are summarised in Table 3.

### Non-species-related breakpoints

These have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data, and are independent of the MIC distributions for specific species. The column ‘non-species-related breakpoints’ is reserved for those species not indicated separately in Table 3. These breakpoints...
should not be applied to species for which susceptibility testing is not recommended (marked with ‘−’ or ‘IE’ in EUCAST breakpoint tables).

**Species-related breakpoints**

The in-vitro activity of fluconazole against *Candida* spp. is not uniform. The species associated most frequently with human infections include *C. albicans*, *C. parapsilosis* and *C. tropicalis*, and these exhibit MIC values of ≤2 mg/L when mechanisms of resistance to fluconazole are absent.

**Species without breakpoints**

*C. krusei* is considered to be inherently resistant, exhibiting high MIC values. A significant number of infections involve *C. glabrata*, which exhibits fluconazole MICs of 2–32 mg/L. Any reasonable breakpoint would divide wild-type *C. glabrata* isolates, thereby frustrating reliable and reproducible susceptibility testing. For these reasons, the EUCAST-AFST has refrained from assigning breakpoints for fluconazole to *C. krusei* and *C. glabrata*, and advises that alternative drugs be employed to manage infections caused by these species. One exception would be urinary tract infections caused by *C. glabrata*, since fluconazole is concentrated in the urine to levels that are likely to exceed the MIC for this species. This fact also serves to emphasise the need to correctly identify yeast isolates recovered from urine and other clinical specimens.