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145. the Efficacy and Safety of Low Dose Trimethoprim-sulfamethoxazole for the Treatment of Pneumocystis Pneumonia: A Systematic Review and Meta-analysis

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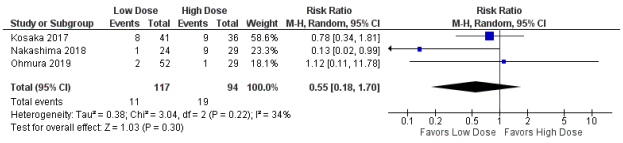
Session: O-28. Innovations and Updates in Mycology

Background: *Pneumocystis jirovecii* pneumonia (PJP) is an opportunistic fungal infection causing significant morbidity and mortality in immunocompromised patients. The conventional treatment of PJP is sulfamethoxazole-trimethoprim (SMX-TMP) dosed at 15–20 mg/kg/day of the trimethoprim component. This high-dose regimen is associated with severe adverse reactions that result in patient harm or treatment discontinuation. Studies have suggested similar mortality and an improved adverse effect profile using lower dose (< 15 mg/kg/day) SMX-TMP. Our objective of this meta-analysis was to evaluate the safety and efficacy of lower dose SMX-TMP for PJP pneumonia.

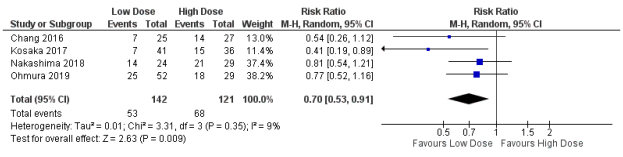
Methods: We conducted a systematic review and meta-analysis according to PRISMA guidelines. Pubmed and Embase databases were searched from inception to January 15, 2020, for studies in English evaluating low-dose SMX-TMP (< 15 mg/kg/day) compared with conventional dosing for the treatment of PJP. Additionally, conference proceedings were reviewed to address potential publication bias. Outcomes evaluated in our meta-analysis include survival and adverse reactions. We performed a sensitivity analysis using E-values to determine the robustness of our results.

Results: After excluding studies that did not meet our inclusion criteria, four studies were analyzed for adverse reaction rates and three for mortality rates. Overall, there was no significant difference in mortality between low-dose and conventional-dose SMX-TMP groups (relative risk [RR]: 0.55, 95% confidence interval [CI], 0.18 -1.70). There was a significant decrease in the rate of adverse reactions for the low-dose group compared with the conventional-dose group (RR: 0.70, 95% CI, 0.53 - 0.91). Sensitivity analyses using E-Values reflect a confounder with RR 2.2 or greater could explain away the estimate on adverse events leading to no difference while mortality would require RR 5.6 to reflect worse outcomes with low dose.

Mortality Forest Plot



Adverse Effects Forest Plot



Conclusion: This meta-analysis shows a significant decrease in adverse reactions and similar mortality rates with lower-dose SMX-TMP compared with conventional dosing. A low-dose SMX-TMP regimen in the treatment of PJP should be considered a viable option with the potential to decrease treatment discontinuation and reduce harm.

Disclosures: **All Authors**: No reported disclosures

146. antifungal Susceptibility Patterns of candida Parapsilosis Bloodstream Isolates in the US, 2008–2018

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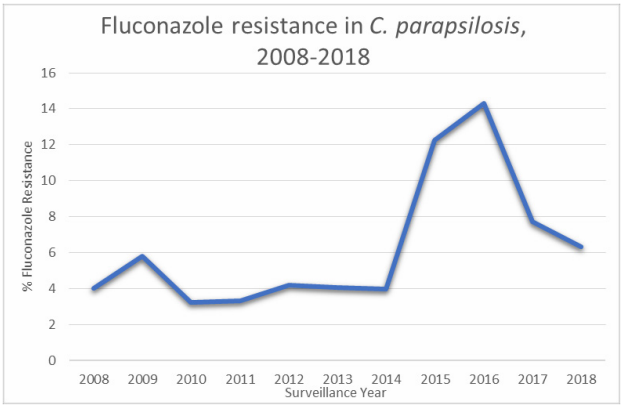
Background: Multidrug resistant *Candida* is an increasing concern. *C. parapsilosis* in particular has decreased *in vitro* susceptibility to echinocandins. As a result, fluconazole had been favored for *C. parapsilosis* treatment. However, there is growing concern about increasing azole resistance among *Candida* species. We report on antifungal susceptibility patterns of *C. parapsilosis* in the US from 2008 through 2018.

Methods: Active, population-based surveillance for candidemia through the Centers for Disease Control and Prevention's (CDC) Emerging Infections Program was conducted between 2008–2018, eventually encompassing 9 states (GA, MD,OR, TN, NY, CA, CO, MN, NM). Each incident isolate was sent to the CDC for species confirmation and antifungal susceptibility testing (AFST). Frequency of resistance was calculated and stratified by year and state using SAS 9.4

Results: Of the 8,704 incident candidemia isolates identified, 1,471 (15%) were *C. parapsilosis*; the third most common species after *C. albicans* and *C. glabrata*. AFST results were available for 1,340 *C. parapsilosis* isolates. No resistance was detected to caspofungin (MIC_{50} 0.25) or micafungin (MIC_{50} 1.00) with only one (< 1%) isolate resistant to anidulafungin (MIC_{50} 1.00). In contrast, 84 (6.3%) isolates were resistant to fluconazole and another 44 (3.3%) isolates had dose-dependent susceptibility to fluconazole (MIC_{50} 1.00). Fluconazole resistance increased sharply from an average of 4% during 2008–2014 to a peak of 14% in 2016 with a subsequent decline to 6% in 2018 (see figure). Regional variation is also observed with fluconazole resistance ranging from 0% (CO, MN, NM) to 42% (NY) of isolates by site.



Conclusion: The recent marked increase in fluconazole resistance among *C. parapsilosis* highlights this pathogen as an emerging drug resistant pathogen of concern and the need for ongoing antifungal resistance surveillance among *Candida* species. Our data support the empiric use of echinocandins for *C. parapsilosis* bloodstream infections and underscore the need to obtain AFST prior to fluconazole treatment. Furthermore, regional variation in fluconazole resistance emphasizes the importance of understanding local *Candida* susceptibility patterns.

Disclosures: **Lee Harrison, MD**, **GSK** (Consultant)**Merck** (Consultant)**Pfizer** (Consultant)**Sanofi Pasteur** (Consultant)

147. Clinical Safety and Efficacy of Novel Antifungal, Fosmanogepix, in the Treatment of Candidemia: Results from a Phase 2 Proof of Concept Trial

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Background: Fosmanogepix (FMGX) is a first-in-class antifungal agent, with a unique MOA targeting the fungal enzyme Gwt1, that has broad-spectrum activity against both yeasts, molds, and dimorphic fungi, including fungi resistant to other antifungal agents. FMGX has a favorable safety profile, reduced potential for clinically significant drug-drug interactions, and is formulated for IV and oral administration.

Methods: This global, multicenter, open-label, non-comparative study evaluated the safety and efficacy of FMGX for first-line treatment of candidemia. Patients with a recent diagnosis of candidemia defined as positive blood culture for *Candida* spp. within 96 hrs prior to study entry, with ≤2 days of prior antifungal treatment were eligible. Patients with neutropenia, *C. krusei* infection, or deep-seated *Candida* infections were excluded. Patients were treated with FMGX for up to 14 days: 1000 mg IV BID for 1 day, then 600 mg IV QD for at least 2 days, followed by either 600 mg IV QD or 700 mg PO QD. Short-term fluconazole (or appropriate alternative) could follow if treatment was required beyond 14 days. Patients with a diagnosis of candidemia