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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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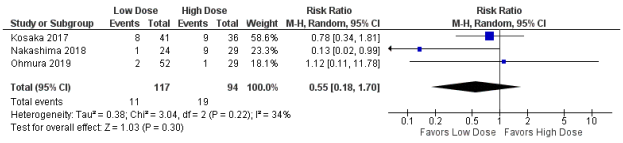
Session: O-28. Innovations and Updates in Mycology

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.

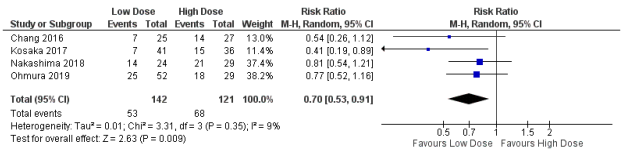
Methods: We conducted a systematic review and meta-analysis according to PRISMA guidelines. Pubmed and Embase databases were searched from inception to January 15, 2020, for studies in English evaluating low-dose SMX-TMP (< 15 mg/kg/day) compared with conventional dosing for the treatment of PJP. Additionally, 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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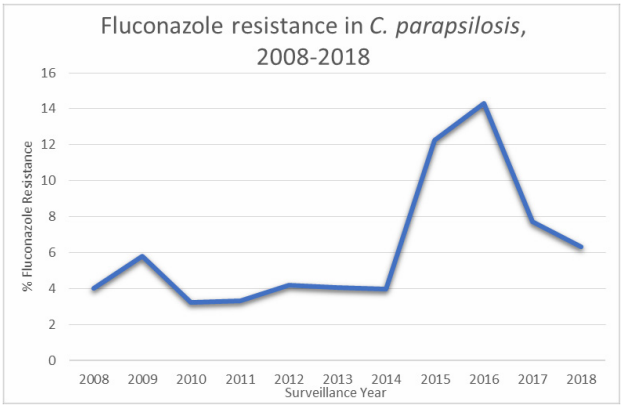
Session: O-28. Innovations and Updates in Mycology

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

within 96 hrs of start of study drug who received at least 1 dose of FMGX were included in the mITT population. The primary efficacy endpoint was outcome at end of study treatment (EOST) as determined by an independent data review committee (DRC). Successful outcome was defined as clearance of *Candida* from blood cultures with no additional antifungal treatment and survival at EOST. All *Candida* isolates were tested for antifungal susceptibility.

Results: A total of 21 subjects were enrolled in the study: 20 were included in the mITT. Median duration of FMGX was 11 days (range 5–14). All subjects received IV FMGX, 48% (10/21) received PO FMGX. The DRC-assessed success rate at EOST was 80% (16/20). Survival at day 30 was 85% (17/20); 3 deaths were not related FMGX. FMGX was well-tolerated with no treatment-related serious adverse events or discontinuations. FMGX had potent *in vitro* activity against all study *Candida* spp. (EUCAST MIC range 0.001–0.03 µg/ml) including those resistant to other antifungal agents.

Conclusion: FMGX was safe, well-tolerated, and demonstrated proof of concept with a high level of treatment success in patients with candidemia.

Disclosures: **Peter Pappas, MD**, **SCYNEXIS, Inc.** (Consultant, Advisor or Review Panel member, Research Grant or Support) **Bart Jan Kullberg, MD, FRCP, FIDSA**, **Amplyx** (Advisor or Review Panel member) **Galia Rahav, MD**, **AstraZeneca** (Scientific Research Study Investigator) **Mickaël Aoun, MD**, **Amplyx Pharmaceuticals** (Scientific Research Study Investigator) **Pierre Bulpa, MD**, **Amplyx Pharmaceuticals** (Scientific Research Study Investigator) **Ricard Ferrer, MD, PhD**, **Shionogi B.V.** (Advisor or Review Panel member) **Todd P. McCarty, MD**, **Amplyx** (Scientific Research Study Investigator)**Cidara** (Scientific Research Study Investigator) **Sara Barbat, BSN, RN**, **Amplyx Pharmaceuticals** (Employee) **Pamela Wedel, BSc**, **Amplyx Pharmaceuticals** (Employee) **Iwonka Oborska, PhD**, **Amplyx Pharmaceuticals** (Consultant, Independent Contractor) **Haran T. Schlamm, MD**, **Amplyx** (Consultant) **Michael Hodges, BSc. MD**, **Amplyx Pharmaceuticals Inc.** (Employee)

148. Fungal Disease Mortality Trends, United States, 1999–2017

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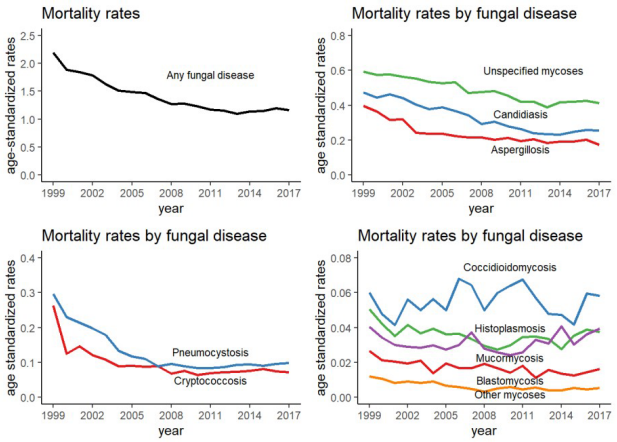
Session: O-28. Innovations and Updates in Mycology

Background: Fungal diseases can lead to substantial morbidity and mortality, although research funding has been disproportionately low compared with other infectious diseases. Despite dramatic changes in immunosuppressive therapy over the past two decades, the U.S. mortality burden of fungal diseases has not been recently assessed.

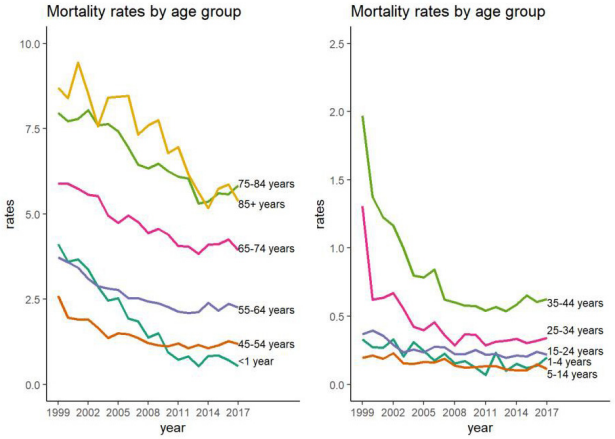
Methods: We analyzed fungal disease-associated mortality trends during 1999–2017 using multiple cause-of-death mortality records from the National Vital Statistics System. We calculated age-standardized rates for aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, pneumocystosis, unspecified mycoses, and other mycoses based on the age distribution of the 2000 U.S. population.

Results: Among over 47 million deaths, 86,058 (0.2%) people had one or more fungal diseases listed on the death certificate as an underlying or contributing cause of death (median 4,431 annually) (Figure 1). The age-standardized mortality rate was 2.2/100,000 population in 1999. By 2017, rates declined by 47% to 1.2. The largest declines occurred for pneumocystosis and cryptococcosis, diseases particularly associated with HIV, by 66–70% from 1999 to 2007 and by 3–6% from 2008 to 2017. During 1999–2017, rates for aspergillosis, candidiasis, and other mycoses declined by 46–56%, although rates for candidiasis and other mycoses increased (10% and 31%, respectively) from 2013 to 2017. Overall, the steepest declines were seen in infants and younger adults (Figure 2).

Age-standardized mortality rates for fungal diseases as underlying and contributing cause of death, per 100,000 people, by year and fungal disease type, United States, 1999–2017



Age-specific mortality rates for fungal diseases as underlying and contributing cause of death, per 100,000 people, by year and age group, United States, 1999–2017



Conclusion: Fungal disease-associated mortality rates declined by half from 1999 to 2017. Improved treatment of HIV and availability of new antifungals likely influenced the decline. However, fungal diseases are still documented in thousands of deaths annually, and rates differed substantially by disease. Better prevention, diagnosis, and treatment are needed to reduce mortality from fungal diseases.

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

149. Efficacy of Cochleated Amphotericin B (CAMB) in Mouse and Human Mucocutaneous Candidiasis

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Session: O-28. Innovations and Updates in Mycology

Background: *Candida albicans* causes debilitating mucosal infections in patients with inherited susceptibility to chronic mucocutaneous candidiasis (CMC), often requiring long-term azole-based treatment. Due to increasing azole resistance, alternative treatments are desirable. Acquired resistance to amphotericin B (AMB) is rare but AMB use is limited by parenteral administration and nephrotoxicity. Cochleated AMB (CAMB) is a new oral formulation of AMB and thus an attractive option for oropharyngeal candidiasis (OPC), esophageal candidiasis (EC) and vulvovaginal candidiasis (VVC). We assessed the efficacy of CAMB in mouse models of OPC and VVC and in 4 patients with azole resistant CMC manifesting as OPC, EC or VVC.

Methods: *Act1-/-* mice were infected with *C. albicans* in models of OPC and VVC and were treated once daily via oral gavage with CAMB or vehicle or intraperitoneal AMB-deoxycholate (AMBd) from day 1 through 4 post-infection (pi). At day 5 pi, the tongue or vaginal tissue was harvested to quantify fungal burden. Patients with azole resistant CMC enrolled in a phase 2A CAMB dose escalation study. The primary endpoint was clinical improvement at 2 weeks based on an efficacy scale, followed by optional extension for long-term suppression of CMC to assess safety and efficacy.

Results: CAMB-treated mice had significantly reduced tongue and vaginal tissue fungal burden compared to vehicle-treated mice, while they exhibited comparable fungal control relative to AMBd-treated mice. Among 4 CAMB-treated patients, 3 reached clinical efficacy by 2 weeks at a dose of 400 mg twice daily and one reached clinical efficacy at 200 mg twice daily. Three of 4 patients continued on the extension phase past 48 months with sustained clinical improvement of OPC and EC; patient #3 had relapse of esophageal symptoms at week 24 and was withdrawn from further study. Clinical response was not seen for onychomycosis or VVC. CAMB was safe and well-tolerated without renal toxicity.

Conclusion: Oral administration of CAMB in IL-17-signaling deficient mice resulted in reduced tongue and vaginal tissue fungal burden during mucosal *C. albicans* infections. A proof-of-concept clinical trial in humans with inherited CMC showed efficacy in OPC and EC with good tolerability and safety.

Disclosures: Benjamin Colton, PharmD, Merck (Shareholder)Pfizer (Shareholder) Ruying Lu, n/a, Matinas BioPharma Inc. (Employee)Matinas BioPharma Inc. (Employee, Shareholder) Theresa Matkovits, PhD, Matinas BioPharma (Employee, Shareholder) Raphael J. Mannino, n/a, Matinas BioPharma Inc. (Employee, Shareholder) Michail Lionakis, MD, ScD, Matinas BioPharma (Research Grant or Support)