Table 2. Antibiotic Duration.

	Days of use	p value
ProHosp PCT intervention group	5.0	0.001; 1 vs 2
ProReal study	6.2	<0.001; 2 vs 3
ProHosp control group (standard care)	7.9	

PCT affected the decision to withhold or initiate antibiotics. Its greatest effect in patients with COPD exacerbation or bronchitis was to reduce initial prescription of antibiotic therapy, whereas for patients with pneumonia, it was most effective in shortening antibiotic duration. No significant increases in adverse medical outcome were detected.

Published evidence on PCT-guided antibiotic therapy to date has been obtained in trials in which physicians knew that they were being monitored, possibly resulting in higher adherence to the PCT algorithm. This study mirrors the use of PCT-guided antibiotic therapy in clinical practice, outside of trial conditions. If algorithm adherence is reinforced, antibiotic exposure can be markedly reduced with subsequent reduction of antibiotic-associated side effects and antibiotic resistance.

Combination Therapy with Flucytosine Improves Survival in AIDS-Related Cryptococcal Meningitis

Written by Noelle Lake, MD

The first randomized, controlled trial to show a survival benefit of an antifungal treatment in HIV-infected patients with cryptococcal meningitis was completed this year in Vietnam [ISRCTN 95123928]. Results were presented by Jeremy N. Day, MD, Oxford University Clinical Research Unit, Wellcome Trust Major Overseas Programme Vietnam, in collaboration with colleagues from the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam.

The study compared three induction-phase treatment strategies that are currently recommended by the Infectious Disease Society of America [Perfect JR et al. *Clin Infect Dis* 2010]. Although combination therapy with flucytosine is considered first-line therapy, a mortality benefit over other regimens has not been shown in a randomized, controlled trial. Also, there are distinct disadvantages to flucytosine use—namely expense, toxicity, and poor availability in areas with high cryptococcal disease rates.

Dr. Day and his colleagues were interested in whether combining antifungal therapies in the induction phase of treatment would offer a survival advantage when compared with amphotericin monotherapy, the standard practice in Vietnam.

Enrolled patients presented with a syndrome that was consistent with cryptococcal meningitis and microbiological evidence of *Cryptococcus* in the CSF and/or blood. All patients were >14 years of age and HIV-positive. Patients with prior history of cryptococcal infection or prior antifungal treatment (>3 days) were excluded. Patients were randomly assigned to receive one of three possible induction treatments: amphotericin B 1 mg/kg/day monotherapy for 4 weeks (Arm I, the standard of care in Vietnam); amphotericin B 1 mg/kg/day plus flucytosine 100 mg/kg/day for 2 weeks (Arm II); or amphotericin B 1 mg/kg/day plus fluconazole 400 mg twice daily for 2 weeks (Arm III; Table 1). The coprimary endpoint was mortality at 2 and 10 weeks. Secondary endpoints included survival to 6 months and disability at 70 days and 6 months.

Table 1. Study Design.

Treatment Arm	Week										
	1	2	3	4	5	6	7	8	9	10	26
I	APT B 1 mg/kg/day				FLCZ 400 mg daily						FLCZ 200 mg/day
II	APT B 1 mg/kg/day + FLTS 200 mg/day		FLCZ 400 mg daily								FLCZ 200 mg/day
III	APT B 1 mg/kg/day + FLCZ 200 mg/day		FLCZ 400 mg daily								FLCZ 200 mg/day

APT=amphotericin; FLCZ=fluconazole; FLTS=flucytosine.
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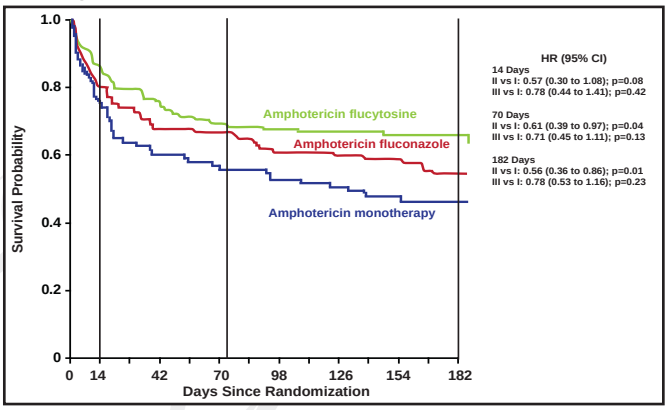
The intent-to-treat (ITT) population comprised 298 patients, predominantly male, with a median age of 28 years. Approximately 30% had some level of impaired consciousness, reflected by a Glasgow coma score of <15. All patients underwent lumbar puncture, which revealed elevated CSF opening pressure (>18 cm/CSF) in over two-thirds of patients and high yeast burdens (median 5.9 log 10 CFU/mL).

Compared with amphotericin monotherapy, the amphotericin+flucytosine combination was associated with a significantly reduced hazard of death by both Day 70 [HR, 0.61; 95% CI, 0.39 to 0.97; p=0.04] and Day 182 [HR, 0.56; 95% CI, 0.36 to 0.89; p=0.01] (Figure 1). Amphotericin B, combined with fluconazole, offered

no survival advantage compared with amphotericin monotherapy. After adjusting for fungal burden and Glasgow coma score at study entry, the hazard of death by 6 months was also significantly higher among amphotericin-fluconazole-treated patients versus those who received amphotericin-flucytosine (adjusted HR for all-cause mortality, 1.81; 95% CI, 1.14 to 2.88; p=0.01). The death rate at 70 days was 30% for patients who were on combination therapy with flucytosine versus 44% for those who were on monotherapy. Rates of adverse events between the two combination regimens were comparable and included anemia, neutropenia, and renal impairment.

Figure 1. Kaplan-Meier Curve of Survival Outcomes Among ITT Population.



Significantly improved survival noted among patients treated with flucytosine-containing combination therapy (Arm II, green line) compared with amphotericin monotherapy (Arm I, blue line) at 70 days and 182 days.
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Dr. Day concluded by saying that in light of this research, improving access to amphotericin and flucytosine in regions where cryptococcal disease is prevalent, such as southeast Asia and Africa, has the potential to significantly reduce the global burden of deaths due to this devastating disease.

CXA-201 Effective Against Common ICU Pathogens, Including MDR Gram-Negative Pathogens and *Pseudomonas aeruginosa*

Written by Eric Butterman

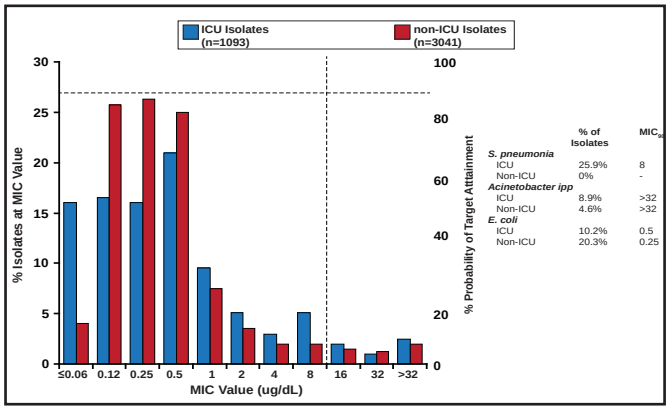
Using a pharmacokinetic/pharmacodynamic (PK/PD) target algorithm, the *in vitro* potency of CXA-201 (CXA101/tazobactam), a novel cephalosporin and β-lactamase inhibitor combination that is being developed to treat serious bacterial infections, was reported to be lower in isolates from the intensive care unit (ICU) compared with non-ICU isolates. This is largely driven by the differences in pathogen incidence in the two environments. Judith Steenbergen, PhD, Cubist Pharmaceuticals, Lexington, Massachusetts, USA, presented data from a study that evaluated the CXA-201 potency for pathogens that were isolated from ICU and non-ICU patients. In addition, the potency of CXA-201 against isolates from different sources of infection was evaluated.

CXA-201 is active against gram-negative pathogens, including *Pseudomonas aeruginosa* and *Enterobacteriaceae*, and select gram-positive organisms. The PK/PD parameter that was used in this study to predict efficacy was the time that was necessary to maintain concentrations of CXA-201 above the minimum inhibitory concentration (MIC) for approximately 40% to 50% of the time between dose administrations (T>MIC).

CXA-201 was tested by broth microdilution against 4134 isolates that were collected in 2008 from both ICU (n=1093) and non-ICU (n=3041) patients. A population PK model that was derived from healthy volunteers and infected patients was used to perform the Monte Carlo simulations (taking into account variability between subjects, residual variability, demographic covariates, and MIC). Target attainment rates were obtained for 1-hour infusion of 1500 mg CXA-201 every 8 hours. For pathogens with an MIC of 8 µg/mL (cutoff target), the target attainment rate was 98.2% for 40% T>MIC.

MIC_{90} was higher for isolates from the ICU (MIC_{90} =8 µg/mL) than non-ICU isolates (MIC_{90} =2 µg/mL). This was largely driven by differences in the percentage of *Streptococcus pneumoniae*, *Acinetobacter spp.*, and *Escherichia coli* isolates in the ICU versus non-ICU patients (Figure 1).

Figure 1. Potency of CXA-201 for ICU and Non-ICU Isolates.



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More than 95% of all isolates had an MIC ≤8 µg/mL (8 µg/mL being the provisional breakpoint), with a