Procalcitonin-Guided Antibiotic Therapy In Patients with Lower Respiratory Tract Infections

Written by Eric Butterman

To date, evidence regarding the effectiveness of procalcitonin (PCT)-guided antibiotic therapy has been obtained in randomized, controlled trials (RTCs), which may not be representative of routine clinical settings. Werner Albrich, MD, University of Basel, Kantonsspital Aarau, Aarau, Switzerland, presented data from a quality control survey [ISRCTN40854211] that monitored PCT-guided antibiotic therapy and algorithm adherence in simulated "real-life" conditions. The PCT algorithm effectively reduced antibiotic exposure without increasing complications. Regional and cultural differences did not affect outcomes. The integration of the PCT algorithm into daily practice requires ongoing reinforcement and involves a learning process by prescribing physicians [Schuetz P et al. *Eur J Clin Microbiol Infect Dis* 2010].

This was an observational, prospective, multicenter, international survey of consecutive patients with community-acquired lower respiratory tract infections (LRTIs) in emergency departments or physicians' offices in Switzerland (n=10), France (n=3), and the United States (n=1) from September 2009 to February 2011. PCT was measured using a rapid, sensitive immunoassay with a functional assay sensitivity of 0.06–0.09 ug/L (KRYPTOR®, Brahms or (Mini-)Vidas®, BioMérieux). Diagnostic workup, antibiotic choice(s), and management were at the physician's discretion.

The algorithm was based on the level of circulating PCT, which correlates with the likelihood for a bacterial infection, and was as follows:

- <0.1 µg/L - antibiotic therapy strongly discouraged
- 0.1 to 0.25 µg/L - antibiotic therapy discouraged
- 0.26 to 0.5 µg/L- antibiotic therapy recommended
- >0.5 µg/L - antibiotic therapy strongly recommended

The primary endpoint was duration of antibiotic treatment within 30 days (effectiveness). Compliance with the PCT algorithm, adverse medical outcomes (safety), and influence of PCT on antibiotic decision were secondary endpoints. A total of 1810 patients were enrolled (1520 with LRTI and 1425 with 30-day follow-up information). The majority presented with community-acquired pneumonia, followed by acute exacerbations of chronic obstructive pulmonary disease (COPD) and bronchitis.

There was good overall algorithm compliance (68.2%), which was affected by treatment site, country, experience, and diagnosis. Good compliance led to significantly shorter antibiotic duration (-43% or 3.8 fewer antibiotic days; HR, 1.27; 95% CI, 1.13 to 1.43; p<0.0001) but did not increase the risk of complications (adj. OR, 1.40; 95% CI, 0.78 to 2.52; p=0.26; Table 1).

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Table 1. Compliance Does Not Increase Risk for Complications.

	Compliant*	Noncompliant*	p value
In-hospital complications	20.5%	16.6%	0.07
30-day mortality	7.7%	6.0%	0.23
Recurrences	6.4%	7.6%	0.20
Antibiotic side effects	3.8%	6.0%	0.05

*only patients with low PCT value could be in the noncompliant group

Antibiotic duration in the ProReal study was shorter than that seen for standard care but longer than that seen in the PCT intervention group of the ProHosp RCT (Table 2) [Schuetz P et al. *JAMA* 2010].

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