Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis (PROGRESS)[1]

BACKGROUND[1,2]

- Procalcitonin (PCT) is a biomarker that showcases better specificity than other inflammatory markers (C-reactive protein or cytokines) in identifying bacterial infections.[2]
- The use of PCT to guide discontinuation of antibiotic therapy was demonstrated to reduce antibiotic exposure and the risk for adverse outcomes in lower respiratory tract infections (LRTI).[1]
- Previous trials have shown that use of PCT to guide discontinuation of antibiotic therapy has been shown to have survival benefits, but the mechanism and extent of these benefits has yet to be clarified.[1]

Methods[1]

Study design	Randomized, parallel group, multicenter trial conducted in Greece	
Objective	To investigate if procalcitonin guided therapy duration may reduce the incidence of long-term infection-associated adverse events in sepsis	
Intervention	• Procalcitonin guided antibiotic discontinuation when PCT drops below <0.5mcg/L or is reduced by 80% from baseline (measured on day 1, day 5, and everyday thereafter until antibiotic discontinuation) and if medically stable/afebrile • Standard of care (SOC) antibiotic duration (per international guidelines)	

Study participants	**Inclusion**
	• 18 years or older
	• Hospitalized with
	  ○ Lower respiratory tract infection (community, hospital acquired, or ventilator associated)
	  ○ Acute pyelonephritis
	  ○ Primary bloodstream infection
	• Meeting Sepsis-3 definitions
		Exclusion
		• Need for prolonged treatment
		• Viral or parasite infections
		• Tuberculosis
		• Cystic fibrosis
		• Neutropenia
		• HIV infection with low CD4 count
		• Pregnancy or lactation

Endpoints	**Primary**
	• Rate of infection-associated adverse events until day 180 composed of the following:
	  • New case of *Clostridioides difficile*
	  • New case of multidrug resistant organism (MDRO) infection
	(Stool samples were collect on day 7, 28, and 180 to help assess the presence of *C. difficile* and MDRO colonization.)
	  • Death associated with either a MDRO or *C. difficile* baseline infection
		Secondary
		• Time until first new infection
		• Length of antibiotic therapy (LOT)
		• 28-day and 180-day mortality
		• Cost of hospitalization

Follow up	Data collection was completed by individuals blinded to the allocation groups. Discharged patients were followed up monthly by phone and were brought in for labs if any changes were identified in their health status. Final labs/stool samples were collected on day 180 for study participants.	
Statistical Analysis	Predefined analysis was done among the intention-to-treat population using the Fisher's exact test and confirmatory forward stepwise Cox analysis. Sensitivity analyses were conducted for the effect of early death, protocol compliance, and extreme LOT. Any two-sided P value <0.05 was statistically significant.	

RESULTS[1]

Enrollment	266 individuals were randomized and 131 in the standard of care and 125 in the PCT guidance group were analyzed

Population demographics

	SOC (N=131)	PCT Guidance (N=125)
Age, mean	78	80
Sex, Male	45.8%	40.8%
SOFA score, mean	4.1	4.1
Community-acquired pneumonia	43.5%	44%
Healthcare-associated pneumonia	20.6%	12.8%
Acute pyelonephritis	33.6%	40.8%
Primary bloodstream infection	0.8%	1.6%
Hospital-acquired pneumonia	1.5%	0.8%
Empiric treatment per ESCMID* guidelines	85.5%	82.4%
Overall compliance with PCT stopping rule	N/A	76.8%

*ESCMID-European Society of Clinical Microbiology and Infectious Diseases

Primary Endpoint

N (%)	SOC (N=131)	PCT Guidance(N=125)	Odds Ratio (95% CI)	P value
Composite adverse events until day 180	20 (15.3)	9 (7.2)	0.43	0.045
New infection by MDRO	8 (6.1)	5 (4.0)	0.64	0.57
New *C. difficile* infection	12 (9.2)	6 (4.8)	0.50	0.22
Mortality associated with baseline infection	5 (3.8)	1 (0.8)	0.20	0.21

Secondary Endpoints

N (%)	SOC (N=131)	PCT Guidance (N=125)	Odds Ratio (95% CI)	P value
28-day mortality	37 (28.2)	19 (15.2)	0.46	0.02
180-day mortality	50 (38.2)	38 (30.4)	0.71	0.24
Antimicrobial treatment duration days, median (Q1-Q3)	10 (7-15)	5 (5-7)	N/A	<0.001
Cost of hospitalization euros, median	1183.49	956.99	N/A	0.05

Safety

PCT guidance was associated with a significant decrease in adverse events compared to the SOC for diarrhea, acute kidney injury, and nonserious organ-threatening adverse events (electrolyte disorders, elevated liver enzymes, and arrhythmia).

AUTHOR'S CONCLUSIONS[1]

The use of PCT guidance for early discontinuation of antimicrobials in medically stable and afebrile patients with sepsis demonstrated significant clinical benefits. These benefits included lower infection-associated adverse events, lower 28-day mortality, shorter LOT, early hospital discharge, and decreased costs of hospitalization.

DISCUSSION

Strengths

- Multicenter, randomized trial
- Of any current study assessing PCT's role in discontinuing antibiotics, the PROGRESS trial had the highest compliance with PCT guided discontinuation at 76.8%
- Addresses possible mechanisms for mortality benefits
- Includes infections outside of LRTIs

Limitations

- Infrequent stool sampling between days 28-100, which allows for decreased assessment of changes in microbiota
- Patients included, although septic, were not necessarily treated in ICU wards. This was attributed to the shortage of ICU beds within the country at the time of the study. This makes it more difficult to compare between previous procalcitonin sepsis studies.

Conclusion and Applicability	• The use of PCT, along with assessment of clinical stability, showed significant decrease in the 28-day mortality, the time to discharge from hospital, and hospitalization costs (this reduction in cost was primarily associated with a decrease in antibiotic costs). • The PROGRESS study demonstrates that PCT guided therapy for individuals with sepsis prevents infection caused by MDROs or *C. difficile.* It also provided a clear explanation for the decrease in 28 day survival seen in the PCT arm with a significant decrease in the adverse events (like diarrhea or electrolyte disturbances) that predispose patients with sepsis to organ dysfunction. • Procalcitonin is currently FDA approved for use in LRTI to help discontinue antibiotics. With this study and may similar studies, PCT may receive further indication in other infectious disease states to help determine therapy duration.

Citations:

1. Kyriazopoulou E, Liaskou-Antoniou L, Adamis G, et al. Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis. A Randomized Trial. *Am J Respir Crit Care Med*. 2021;203(2):202-210. doi:10.1164/rccm.202004-1201OC
2. Rhee C. Using Procalcitonin to Guide Antibiotic Therapy. *Open Forum Infect Dis*. 2016;4(1):ofw249. Published 2016 Dec 7. doi:10.1093/ofid/ofw249