ThermoFisher SCIENTIFIC

Procalcitonin (PCT)

Antibiotic Stewardship implementation Guide

Part 3: Optimization with Biomarkers

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Content

This guide is the third of a three-part series on Antibiotic Stewardship and focuses on optimization. To learn more about getting started and implementing an Antibiotic Stewardship program in your hospital, please be sure to check out part one and part two in the series.

Part 1: The Importance of ABS

Part 2: Implementation

Part 3: Optimization with Biomarkers

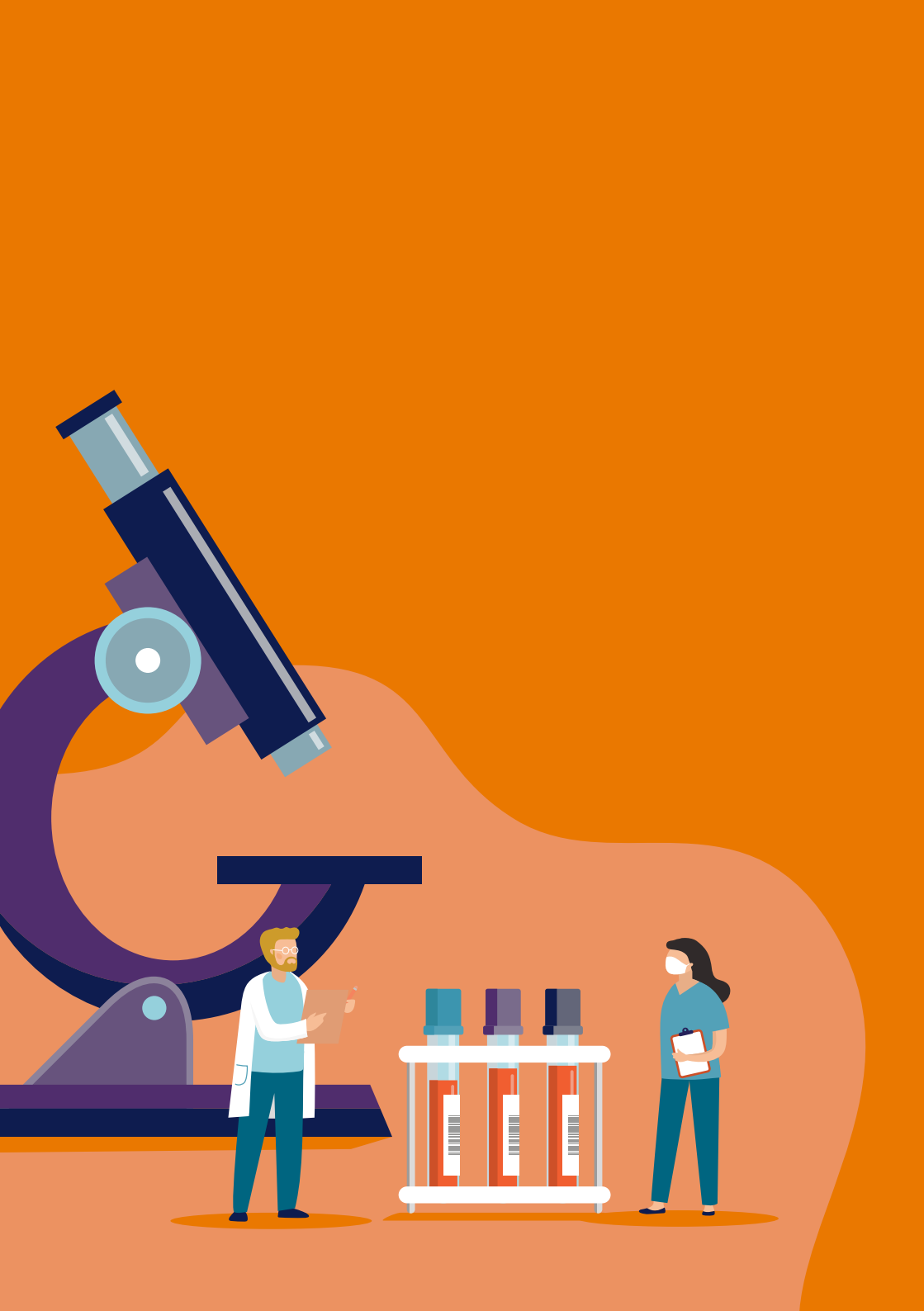
Purpose of this booklet

Evidence from around the world shows a global decline in the effectiveness of antibiotics. Inappropriate use of antibiotics has driven the dramatic increase in resistance seen to all first-line and last-resort antibiotics. Antimicrobial resistance (AMR) has been identified by the WHO as a global healthcare threat as it limits our capacity to fight life-threatening diseases.

Antibiotic stewardship (ABS) is a key strategy used to preserve the effectiveness of antibiotics by promoting and monitoring their responsible use. If used effectively, it can help reduce and optimize the prescription of antibiotics in several healthcare settings.

This booklet serves as a practical guide to support the implementation of an ABS program within a hospital, outlining the key steps needed for successful implementation. Most of the information on ABS implementation have been adopted from recommendations and guidelines from IDSA[1], CDC[2], WHO[3], BSAC[4], and CDDEP.[5] The role of in-vitro diagnostics in an ABS program is discussed, and in particular the role of the biomarker procalcitonin (PCT) is highlighted, as the WHO recognizes the value of PCT for tertiary care facilities and above “to guide antibiotic therapy or its discontinuation in sepsis and lower respiratory tract infection”.[6]

We gratefully acknowledge the help of Dr. Broyles, Prof. Kwa and Prof. Giamarellos-Bourboulis for providing the examples for practical implementations of procalcitonin into an antibiotic stewardship program.



Impact of the biomarker procalcitonin as part of antibiotic stewardship

3

3.1 Diagnostics are an integral part of an ABS program

Diagnostics are an integral and essential part of an ABS program. Blood cultures and molecular diagnostics provide information if and which kind of pathogen is present, which can guide appropriate antibiotic prescription. In addition, blood biomarkers can give information on how the host is responding to the infection.

"Essential diagnostics: diagnostics that satisfy the priority healthcare needs of the population and are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and accuracy and comparative cost-effectiveness."[22]

Procalcitonin (PCT) is a rapid-reacting biomarker which indicates the host-response specifically to a bacterial infection. PCT provides information about the likelihood of a clinically relevant bacterial infection and the risk of progression to sepsis and septic shock and aids in antibiotic therapy decisions. The WHO, in their model list of essential in vitro diagnostics (EDL3), recognized the role of PCT for tertiary care facilities and above "to guide antibiotic therapy or its discontinuation in sepsis and lower respiratory tract infection."[6] **PCT is the only biomarker in the EDL that is recognized as an aid in antibiotic therapy decisions.**

Randomized controlled interventional studies have shown that integrating PCT into clinical decision making is beneficial for patients with respiratory tract infections and sepsis as it significantly reduced antibiotic exposure, infection-related adverse events, and mortality.[23,24,25]

Procalcitonin is now mentioned in the WHO model list of essential in vitro diagnostics as an aid for decisions on antibiotic therapy or its discontinuation.[6]

3.2 Algorithm for B·R·A·H·M·S PCT use

Procalcitonin can be safely used for initiation of antibiotic therapy and for monitoring antibiotic treatment efficacy, together with the information given by the medical history, physical examination, and microbiological evaluation. An algorithm using Thermo Scientific™ B·R·A·H·M·S PCT™ for the safe and effective reduction of antibiotic use has been developed for patients with lower respiratory tract infection (LRTI, Figures 1a and d) and sepsis (Figures 1b-d), based on the clinical evidence and practical experience.

Caution should be taken in patients with immune-suppression (including HIV), cystic fibrosis, pancreatitis, trauma, pregnancy, and high volume transfusion. B·R·A·H·M·S PCT-aided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis). For *S. aureus* bacteremia and candidemia infection, therapy duration should not be shortened below the minimal duration according to the respective guidelines. Instruction for the use of the in-vitro diagnostic tests should be consulted for correct intended use and interpretation of the results in specific indications.

Clinical suspicion of LRTI

PCT (ng/mL)	<0.10	0.10 - 0.25	0.26 - 0.50	>0.50
Ongoing infection?	Very unlikely	Unlikely	Likely	Very likely
Interpretation	ABx strongly discouraged*	ABx discouraged*	ABx encouraged**	ABx strongly encouraged**

Important considerations

* Antibiotic therapy should be considered regardless of PCT result if the patient is clinically unstable, is at high risk for adverse outcome, has strong evidence of bacterial pathogen, or the clinical context indicates antibiotic therapy is warranted. If antibiotics are withheld, reassess if symptoms persist/worsen and/or repeat PCT measurement within 6-24 hours.

** In order to assess treatment success and to support a decision to discontinue antibiotic therapy, follow up samples should be tested once every 1-2 days, based upon physician discretion taking into account patient's evolution and progress.
PCT levels may not be elevated in patients infected by certain atypical pathogens, such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.

Figure 1a. Initiating antibiotic therapy for patients with suspected or confirmed lower respiratory tract infection (LRTI) (adapted from Schuetz P et al., CHEST 2012)[26]

PCT can be measured on serum or plasma; the liquid chosen should be consistent throughout a patient's clinical course. Do not use citrate plasma tubes for specimen collection.

ABx Antibiotics

Clinical suspicion of sepsis

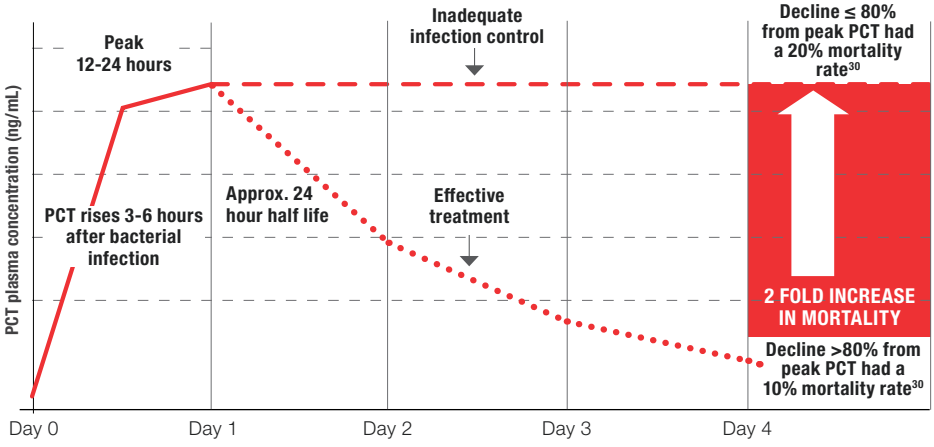


Figure 1b. PCT values rise in relation to sepsis severity, providing clinicians with a valuable tool for assessing patients suspected of sepsis (adapted from Harbarth S et al., Am J Respir Crit Care Med 2001; Meisner M, Bremen 2010; Müller B et al., Crit Care Med 2000)[27-29]

PCT plasma concentration (ng/mL)	Possible interpretations
<0.1	Normal level
<0.5	Low risk for progression to severe sepsis and/or septic shock
0.5 - 2.0	It is recommended to retest PCT within 6-24 hours if any concentrations <2.0 ng/mL are obtained
>2.0	High risk for progression to severe sepsis and/or septic shock

Please note: PCT levels below 0.5 ng/mL do not exclude an infection, because localized infections (without systemic signs) may also be associated with such low levels.

If the PCT measurement is done very early after the systemic infection process has started (usually <6 hours), these values may still be low.

See page 35 for additional notes.

Figure 1c. PCT plasma concentrations (adapted from Harbarth S et al., Am J Respir Crit Care Med 2001; Meisner M, Bremen 2010; Müller B et al., Crit Care Med 2000, Morgenthaler NG et al., Clin Lab 2002)[27-29,33]

When to stop antibiotics

Important considerations: If clinical picture has not improved and PCT remains high, re-evaluate and consider treatment failure or other causes.

Figure 1d. Figure 1d. Discontinuing antibiotics for patients with lower respiratory tract infection (LRTI), or suspected or confirmed sepsis (adapted from Schuetz P et al., Jama 2009; Bouadma L et al., Lancet 2010)[31,32]

PCT values may be elevated in certain conditions independent of bacterial infection. These include, but are not limited to:[28]

- Injuries including major trauma, burns and heat stroke
- Acute medical conditions such as biliary pancreatitis, chemical pneumonitis, viral hepatitis and/or decompensated severe cirrhosis (Child-Pugh Class C), prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, and post-cardiac arrest
- Active medullary C-cell carcinoma, small cell lung carcinoma, and bronchial carcinoid
- Invasive fungal infections and acute *Plasmodium falciparum* malaria
- Following interventions such as surgery with extra-corporeal circulation, treatment with drugs stimulating release of pro-inflammatory cytokines or resulting in anaphylaxis, peritoneal or hemodialysis

The PCT reference ranges are valuable guidelines for the clinician but they should always be interpreted in context of the patient's clinical condition. PCT serum concentrations are elevated in clinically relevant bacterial infections and continue to rise with the increasing severity of the disease. However, as an expression of individually different immune responses and different clinical situations, the same focus of infection may be associated with varying individual elevations in PCT concentrations. Antibiotic treatment should be started/continued on suspicion of infection, particularly in high-risk patients.

B·R·A·H·M·S PCT results should be evaluated in context of all clinical and laboratory findings. If results do not agree with clinical finding, additional testing should be performed.

3.3 Example of successful implementation of PCT within an ABS program in the USA

A single-center, pre-post, retrospective cohort study was conducted at the Five Rivers Medical Center, a community hospital in Arkansas, to evaluate the impact of adding PCT to existing ABS practices.[34] Four years of data were collected before and after PCT implementation and were compared in critical and acute care patients of all ages. After implementation, a baseline PCT was obtained on admission in patients with suspected bacterial infection and serial PCT measurement were repeated daily to evaluate effectiveness of therapy.

"The goal is to provide leading thought processes in patient management and use technology to enhance clinicians' ability to have the best options in their patients' clinical status, decision support, and improve outcomes through better clinical care."

Mike Broyles, PharmD
Pharmacy Director at the Five River Medical Center in Pocahontas, Arkansas (USA) at the time of study publication

Dr. Broyles has more than 30 years of experience as a Hospital Pharmacy and Laboratory Director providing patients with current concepts in the clinical use of drugs with a focus on antimicrobial stewardship.

He has consulted for more than 25 of the 40 largest Integrated Healthcare Networks in the U.S. He has served on advisory boards and regularly speaks to industry, serving hospitals ranging from 35 to 1200 beds in size. Most recently, he served as a global expert consensus member on PCT-aided antibiotic therapy in hospitals and presented to the FDA in the most recent claim approval for use of PCT in sepsis and LRTI.

The addition of PCT to the existing anti-microbial stewardship practices at Five Rivers Medical Center contributed to significant reductions in median days on antibiotic therapy, all-cause readmission, adverse events from antimicrobials, all-cause hospital mortality and *Clostridioides difficile* infections (Figure 2).

In addition, implementation of the PCT protocol significantly reduced the costs per patient with sepsis and lower respiratory tract infections (LRTI) (Figure 3).

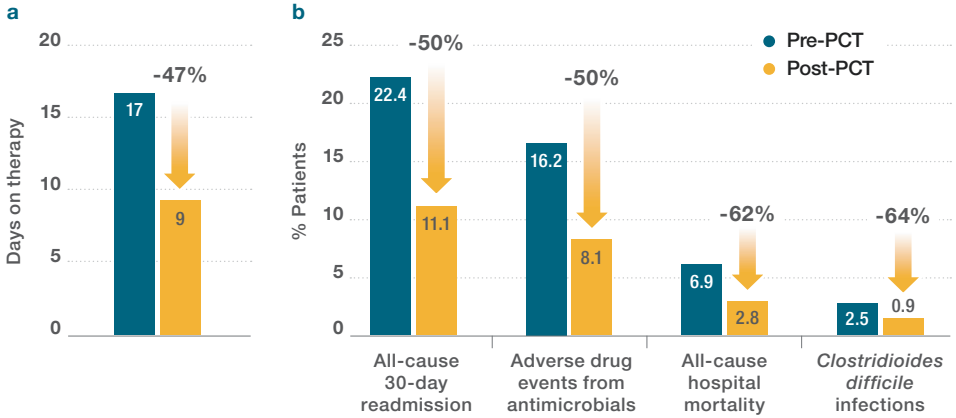


Figure 2. (a) Median days on therapy four years before PCT implementation (pre-PCT, 985 patients) and four years after PCT implementation (post-PCT, 1167 patients). (b) Percentage of patients suffering complications pre-PCT and post-PCT (adapted from Broyles MR et al., Open Forum Infect Dis 2017)[34]

	Pre-PCT	Post-PCT	Difference post-pre
Cost per sepsis patient	$52,055	$26,433	$-25,611
Cost per LRTI patient	$15,738	$12,109	$-3,629

Figure 3. Hospital costs per patient in the four years preceding PCT implementation (pre-PCT) and four years after PCT implementation (post-PCT) (adapted from Voermans AM et al., OMICS 2019)[34]
A negative value for the difference indicates cost savings in the post peaked phase.

To get the most out of the PCT-aided algorithm, the following need to be considered in order to integrate PCT into the hospital workflow:

- There should be clear protocols to start, revise and stop antibiotic therapy, approved by medical staff and pharmacy
- The PCT protocol should be placed in the top admission diagnoses that required or may require the use of antibiotics
- For suspected infections, PCT should be a pre-checked box on the admission order sets and listed as a priority item
- PCT-aided ABS starts with the admission order sets for the emergency department (where the majority of admissions enter) and continues with all hospital admissions using the electronic medical record system order sets
- The pharmacy reviews all antibiotic use or potential diagnoses for appropriate antibiotic use
- The PCT protocol can be ordered and followed by the pharmacist if omitted or unchecked by clinician or for a less common diagnosis that was not in order sets

Figure 4. Considerations before the integration of PCT in an ABS program (adapted from Broyles MR et al., Open Forum Infect Dis 2017)[34]

3.4 Example of successful implementation of PCT within an ABS program in Singapore

Singapore General Hospital has been running a multidisciplinary ABS program since 2006. The success of this program has mainly been due to the support received from the senior hospital administration, the government, and the clinical teams of the participating departments. Successfully implementing the ABS program was based on involving stakeholders from the top-down and bottom-up together. Giving timely prospective feedback and engaging regularly and frequently with clinical departments on further improvements has been very important for adoption. PCT was introduced in 2008 as part of the ABS program. It is used as an aid, in conjunction with clinical judgement, as an objective marker for the decisions on the safe discontinuation of antibiotics.

Andrea Kwa, PharmD
Pharmacy Clinician Scientist with the Singapore General Hospital, and an Associate Professor with the Duke-National University of Singapore, Emerging Infectious Diseases Program, Singapore.

Dr. Kwa specializes in critical care medicine and infectious diseases. She has a huge passion for research involving antimicrobial resistance (in-vitro and in-vivo) and health services research on antimicrobial stewardship. To-date, she has authored more than 90 peer-reviewed publications and delivered more than 150 presentations.

As an avid reviewer, she has contributed to many scientific journals including Clinical Infectious Disease and Clinical Microbiology & Infections.

"The success of any ABS program is that it must ultimately have a continuous positive impact on patient care in terms of safety."

The impact of implementing PCT into the ABS program was significant. As shown in Figure 5 below, when physicians accepted the ABS program recommendations aided by PCT and clinical judgement, it led to a significant reduction in antibiotic exposure and a shorter length of stay, without negatively impacting patient outcomes measured by 14-day all-cause mortality and 14-day readmission due to infection.[20] The algorithm used for the audit concurrent feedback from Singapore General Hospital is shown in Part 2, Figure 8.

794 patients

identified by ABS committee
for stopping of empiric antibiotics

	In **579** patients the attending physician **accepted** to stop antibiotics	In **215** patients the attending physician **rejected** to stop antibiotics	
Mean PCT* (µg/L)	**0.18**	**0.16**	n.s.
ABx duration (days)	**2.72**	**5.33**	-2.61**
LOS (days)	**7.98**	**15.39**	-7.41**

Figure 5. Outcome analysis for patients where the ABS committee recommended discontinuation of empiric antibiotics within 24 h of prescribing based on a ABS protocol including PCT (adapted from Loo LW et al., International Journal of Antimicrobial Agents 2019)[20]

* PCT was available for >70% of patients
** $p<0.01$ accepted vs rejected intervention

ABS Antibiotic stewardship **ABx** Antibiotic **LOS** Length of stay **NS** Not significant

3.4 Example of successful implementation of PCT within an ABS program in Greece

Long-term use of antibiotics can increase the risk of infections caused by *Clostridioides difficile* (CDI) and multidrug-resistant organisms (MDRO) in critically-ill patients, which can lead to poor clinical outcomes.

The PROGRESS[25] study, a multi-center, real-world pragmatic trial in Greece, showed that using PCT as an aid for the decision for early discontinuation of antibiotic therapy in sepsis patients reduced the duration of antibiotic treatment compared to standard of care. The incidence of infection-associated adverse events like infections by CDI, MDRO or associated deaths was reduced in the PCT-group, while 28-day survival was significantly improved. This indicates that PCT-aided decision-making in sepsis is safe and provides long-term benefits with a potentially substantial public health impact.

> The benefits of PCT-aided decision-making "may have substantial impact on public health, particularly for countries with high antimicrobial consumption."[25]

Evangelos J. Giamarellos-Bourboulis, MD, PhD
Professor of Internal Medicine at the National and Kapodistrian University of Athens, Medical School; Supervisor of Immunology of Infectious Diseases Section at ATTIKON University Hospital

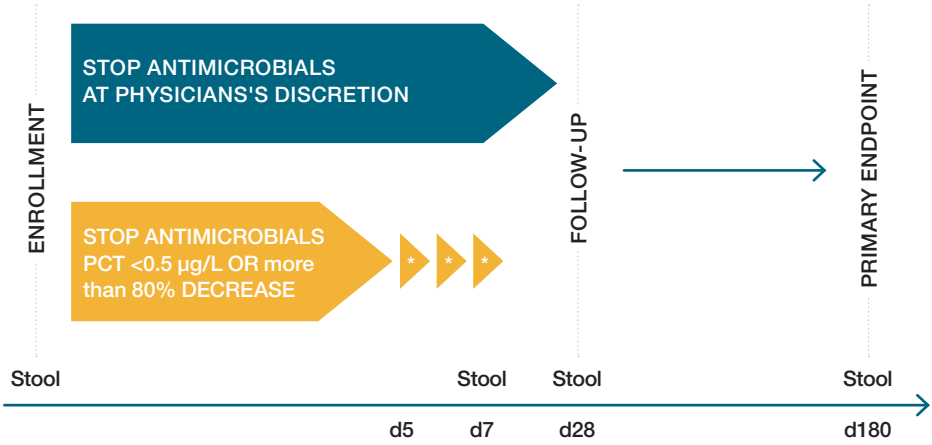
Prof. Giamarellos-Bourboulis' research interests include the pathogenesis of sepsis with emphasis on immunoparalysis, innate immunity, and in-vitro activities as well as pharmacokinetics of antimicrobials and their interactions on multidrug resistance species.

He is a guest professor at the Center for Sepsis Control and Care of the Jena University Hospital in Germany and president of the European Shock Society and chairman of the European Sepsis Alliance. He has published 400 peer-reviewed articles with more than 17,000 citations.

The use of the PCT algorithm in the study protocol (Figure 6) led to an approximate 50% shorter median duration of antibiotic therapy independent of the cause of the infection (Figure 7).

This led to a reduction of infection-associated adverse events (15.3% vs 7.2%, *p*:0.045) and in-hospital and 28-day mortality (28.2% vs. 15.2%, *p*:0.02), both by almost 50%. For the PCT-aided arm, the odds ratio for infection-associated adverse events was shown to be independent from fecal colonization, but not so in the standard of care arm. This indicated that although there was some initial colonization, after exposure to antimicrobials in the PCT-aided arm, early discontinuation did not allow development of clinical infection. The increased incidence of infections by MDRO and *Clostridioides difficile* in the standard-of-care arm could be explained by the effect of long-term antibiotic exposure on the gut microbiota.

Study design



* Daily repeat until cut-off achieved

Figure 6. Study design of the PROGRESS trial (adapted from Kyriazopoulou E et al., Am J Respir Crit Care Med 2020)[25]

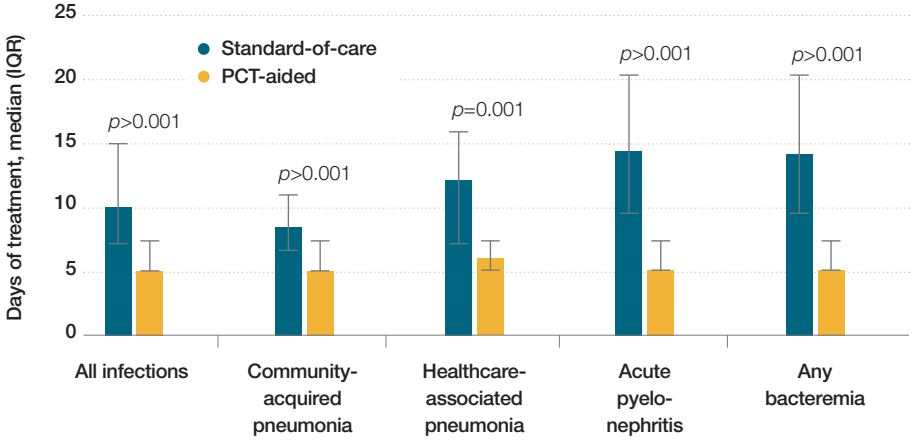


Figure 7. Median length of antibiotic therapy in 266 patients (adapted from Kyriazopoulou E et al., Am J Respir Crit Care Med 2020)[25]

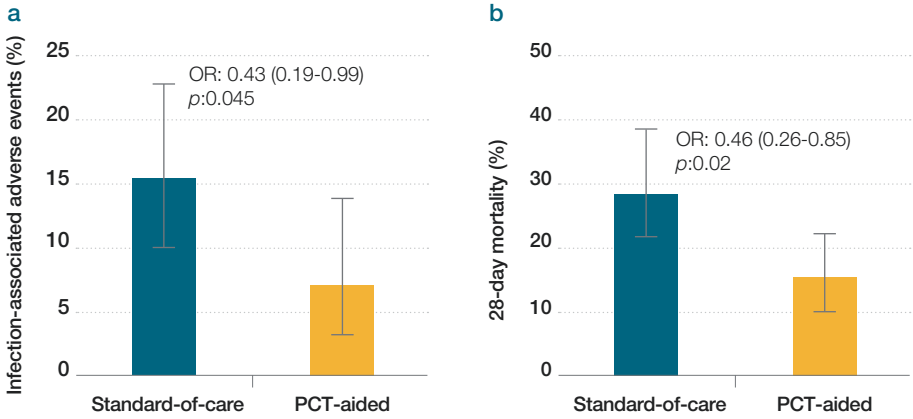


Figure 8. (a) primary endpoint of the study, infection-associated adverse events at six months (composite endpoint consisting of incidence of new CDI, incidence of new MDRO infection and infection-associated death by baseline CDI or MDRO), and (b) secondary endpoint, 28-day mortality (adapted from Kyriazopoulou E et al., Am J Respir Crit Care Med 2020)[25]

IQR Interquartile range **OR** Odds ratio **CDI** *Clostridioides difficile* infection
MDRO Multi drug resistant organism

3.6 Further evidence in selected indications

Lower respiratory tract infections (LRTI)
Schuetz P et al., Lancet Infect Dis 2018 [36]

- PCT-aided decision-making has been shown to significantly reduce antibiotic exposure in patients with LRTI through reduced antibiotic prescription in low-risk settings and low-risk patients, and by shorter duration and earlier discontinuation of antibiotics in high-risk patients

- PCT-aided antibiotic treatment resulted in significantly lower antibiotic side-effects and mortality

Intensive care unit
de Jong E et al.,
The Lancet Infectious Diseases 2016 [9]

- PCT-aided antibiotic therapy significantly reduced treatment duration by 2 days and antibiotic consumption by 19% when compared to standard of care in a setting that already had comparatively short antibiotic therapy regimes

- PCT-aided antibiotic therapy among critically-ill patients was associated with a significant reduction in mortality at 28 days and 1 year when compared to standard of care

3.7 Key messages

Diagnostics are an integral part of an ABS program. In addition to blood cultures and molecular diagnostics, the host-response biomarker PCT can aid in the clinical management of patients.

PCT can be safely used to monitor antibiotic treatment efficacy, together with the information given by the medical history, physical examination, and microbiological evaluation.

Evidence from multicenter studies and meta-analyses have shown the PCT algorithm to be safe and effective in reducing antibiotic prescriptions and reducing adverse events in adults across multiple settings globally.

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Please note, this guide is part three in a three-part series. The references below are a culmination of the references for all three guides in the series.

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Want to learn more?

Find out more on ABS

BSAC https://bsac.org.uk/education/
CDC https://www.cdc.gov/antibiotic-use/healthcare/evidence.html
IDSA https://academy.idsociety.org/course-catalog-table?f%255B0%255D=field_course_format%3A19&f%5B0%5D=field_course_format%3A19
WHO https://www.who.int/activities/raising-awareness-and-educating-on-antimicrobial-resistance

Find out more on hospital ABS programs

CDC https://www.cdc.gov/antibiotic-use/training

Find out more on local resistance

CDDEP https://resistancemap.cddep.org/

Find out more on antimicrobial prescribing guidelines

NICE https://www.nice.org.uk/guidance/health-protection/communicable-diseases/antimicrobial-stewardship

Find out more on infection prevention and control

ECDC https://www.ecdc.europa.eu/en/publications-data/directory-guidance-prevention-and-control/training/training-courses-infection

Find out more on the use of procalcitonin in ABS

thermoscientific.com/procalcitonin

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