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PROCALCITONIN GUIDANCE FOR OPTIMAL ANTIBIOTIC THERAPY IN CRITICALLY ILL PATIENTS

Ph.D. Thesis

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“He who fights, can lose. He who doesn’t
fight has already lost.”

Bertold Brecht

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1. LIST OF ABBREVIATIONS

AB: Antibiotic

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease

AG: Absolute group

APACHE: Acute Physiology and Health Evaluation

CAP: Community-acquired pneumonia

VAP: Ventilator-associated pneumonia

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease

CI: Confidence interval

DAMP: Damage-associated molecular pattern

ED: Emergency department

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ICU: Intensive care unit

KG: Kinetics group

LOS: Length of stay

LRTI: Lower respiratory tract infection

MA: meta-analysis

MD: Mean difference

MDRO: Multidrug-resistant organism

OR: Odds ratio

PAMP: Pathogen-associated molecular pattern

PCR: Polymerase chain reaction

PCT: Procalcitonin

RCT: Randomised controlled trial

ROB: Risk of bias

SC: Steering committee

SD: Standard deviation

SE: Standard error

SOC: Standard of care

SOFA: Sequential organ failure assessment or Sepsis-related organ failure assessment

UTI: Urinary tract infection

VAP: Ventilator-associated pneumonia

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is that most critically ill patients will receive appropriate antibiotic (AB) therapy: necessary, sufficiently narrow, and not too broad. My mission is to protocolize and individualise antimicrobial therapy using procalcitonin (PCT), the best-known inflammatory biomarker. My specific goals are to investigate the efficacy and safety of procalcitonin-guided antibiotic therapy in critically ill patients using a systematic review and meta-analysis, and to compare a PCT kinetics- and absolute PCT value-guided AB initiation protocol in a randomised controlled trial.



2.2. Scientometrics

Number of all publications:	6
Cumulative IF:	22.6
Av IF/publication:	3.77
Ranking (SCImago):	D1:2 Q1:4
Number of publications related to the subject of the thesis:	2
Cumulative IF:	11.6
Av IF/publication:	5.8
Ranking (Sci Mago):	D1:1 Q1:1
Number of citations on Google Scholar:	115
Number of citations on MTMT (independent):	78
H-index:	4

The detailed bibliography of the student can be found on pages 61-63.

2.3. Future plans

I plan to involve more centres in our ongoing trial to achieve the sample size during the planned study period. After that, we would like to disseminate the study's results through national conferences and publish them in a highly cited journal in the field. After hopefully defending my thesis, I would like to serve as a supervisor at

Semmelweis University's Translational Medicine Centre, working with my colleagues to identify the best clinical questions and relevant answers for the benefit of critically ill patients, a truly vulnerable patient population.

3. SUMMARY OF THE THESIS

AB therapy is still quite challenging and an everyday struggle in intensive care units (ICUs), balancing between the early, adequate therapy for improving outcomes and the non-desired side effects of the antimicrobial agents, which are more prevalent in the case of unnecessary or excessively long therapies. At the core of this decision-making process are the medical history and the actual clinical picture, supported by imaging, microbiological, and blood results. Inflammatory biomarkers play an important role in diagnosis and response to therapy, making them a substantial piece of the puzzle. Indeed, the kinetics (i.e., trajectory) of a biomarker can reveal much more about the underlying pathophysiological process than a single measurement.

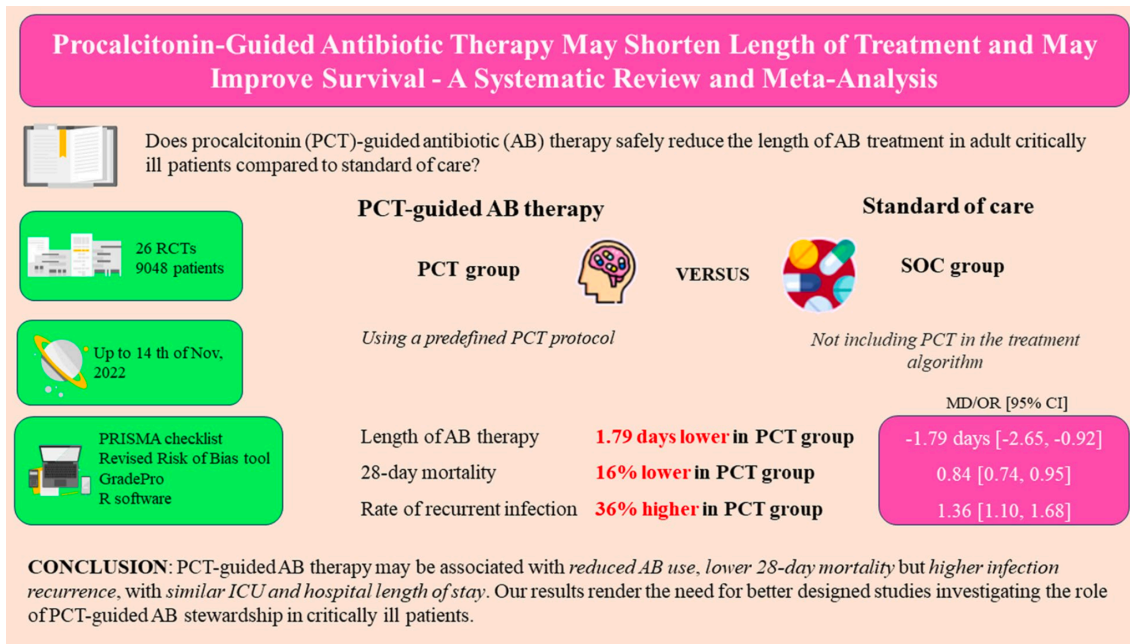
In this thesis, we investigate how the most studied inflammatory biomarker, PCT, can help the clinician to decide whether to start the treatment or not, and how long the antimicrobials should be given if the therapy is deemed necessary, hence optimising the therapy - maximising efficacy and minimising non-desired effects.

According to our results, PCT-guided therapy (i.e., stopping treatment when clinical improvement and a predefined decrease in PCT values are achieved) may be associated with significantly less AB use and improved survival in sepsis; this survival benefit is even more pronounced in the sepsis-3 cohort, according to the latest sepsis definition. Our RCT investigating the initiation of the therapy using PCT kinetics is ongoing, hopefully filling in the actual knowledge gap in the literature.

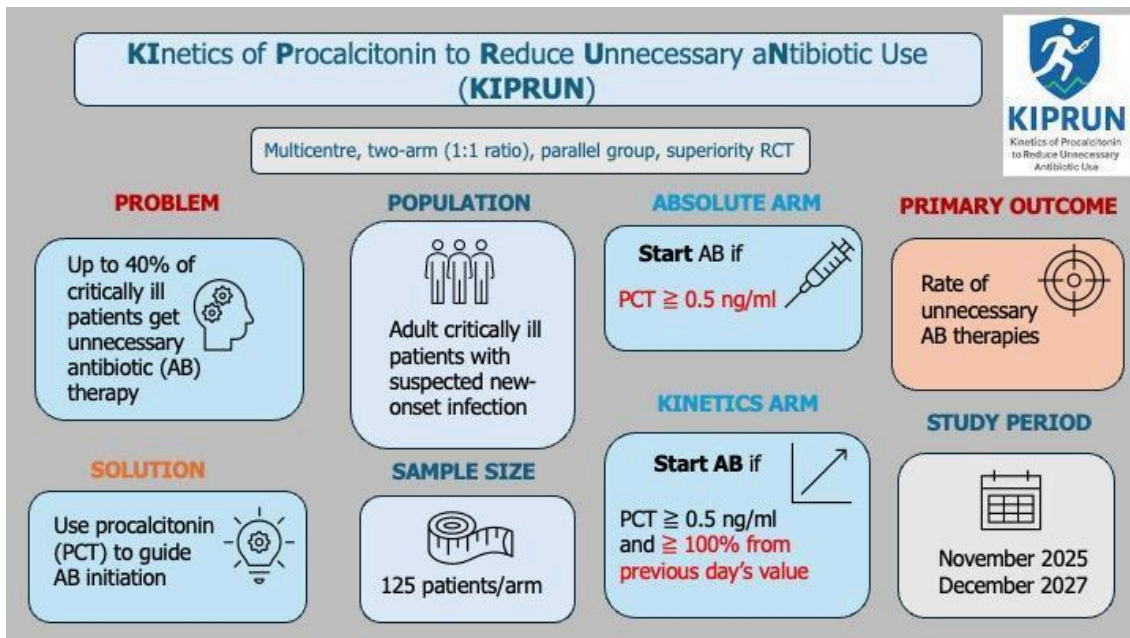
We conclude that monitoring the PCT trajectory in critically ill patients with sepsis can safely help to decide how long the actual AB therapy should be. For treatment initiation, we hope our ongoing trial will answer the same question: whether PCT kinetics can help determine when to start AB therapy.

4. GRAPHICAL ABSTRACT

Study I



Study II



5. INTRODUCTION

5.1. AB therapy in critically ill patients

AB therapy is still an everyday challenge in intensive care units. The number of inappropriate therapies varied in previous studies, ranging between 10-50%, and is associated with worse outcomes and is an independent determinant of higher 28-day all-cause mortality (1–3). As a consequence, antibiotic resistance is emerging, leading to approximately 700,000 deaths worldwide in 2014. It is predicted to be the number one cause of death worldwide by 2050, accounting for 10 million deaths per year (4).

Infection is common in critically ill patients: more than 50% of them are considered infected. Infection and related sepsis can more than double ICU mortality (5). However, more than 40% of critically ill patients with an initial diagnosis of sepsis were later confirmed not to have an infection at all (6).

To optimise the initiation and discontinuation of AB therapy, we can use the trajectories of blood-based inflammatory biomarkers, which serve as signals of the underlying pathophysiological process. Procalcitonin (PCT) is the most intensively studied biomarker (7) and can potentially discriminate bacterial from viral infections in critically ill patients (8,9). In contrast to C-reactive protein or white blood cells, PCT is released in response to endotoxin or other mediators that arise after bacterial infection (e.g., interleukin-6, tumor necrosis factor alpha), while PCT is downregulated by interferon-gamma, the most prevalent cytokine in viral infections (10). The PRORATA trial from 2010 (11) was the landmark trial using PCT kinetics to reduce AB exposure (i.e., PCT-guided AB therapy) proving efficacy and non-inferiority as compared to standard of care. It was followed by several RCTs using the same or slightly different PCT protocols in medical, surgical or mixed populations with different type of infections and sepsis. This method is most reliable in acute respiratory tract infections across a variety of clinical settings as a large individual patient data meta-analysis (MA) from 2017 concluded (12). In the same year, the U.S. Food and Drug Administration (FDA) expanded the use of one type of PCT assay for aiding AB starting and discontinuation in lower respiratory tract infections (LRTI), like community acquired pneumonia (CAP), acute bronchitis and acute exacerbation of chronic obstructive

pulmonary disease (AECOPD) (13). However, evidence is scarce and less convincing in other types of infection and sepsis.

5.1.1. To give or not to give ABs?

The actual, as well as the previous edition of the Surviving Sepsis Guideline, put continuous pressure on the treating clinician, recommending early AB administration (a strong recommendation with a very low level of evidence) in sepsis and septic shock, ideally within one hour of recognition (14). This ‘one-hour mantra’ led to the indiscriminate use of ABs with all the deleterious consequences - direct organ damage, disruption of the microbiome, emerging resistance, and mitochondrial dysfunction (15).

5.1.2. Let’s give ABs, but how long?

The duration of therapy also clearly affects patient outcomes. It can depend heavily on the infection type and the host's immune status (e.g., haematological patients have higher sepsis mortality). Too long therapies are associated with resistance and increasing healthcare cost (16,17), while too short therapies can lead to treatment failure and relapse (18). Balancing between these requires careful daily assessment of the patients themselves and the trajectory of inflammatory biomarkers.

5.2. Rethinking and updating sepsis guidelines

The aforementioned sepsis guideline (14) contains recommendations on the use of PCT: a conditional recommendation to use PCT and clinical evaluation to decide when to stop treatment (low-certainty evidence) and a recommendation against using PCT and clinical evaluation to decide when to start treatment (very low-certainty evidence). I hope these recommendations can be updated and refined based on the results of our studies.

6. OBJECTIVES

6.1. Study I. – Investigating the effects of procalcitonin-guided antibiotic therapy versus standard treatment in critically ill patients.

This study aimed to compare the effects of PCT-guided AB therapy (when a predefined PCT protocol is used to initiate and/or discontinue therapy) with the standard of care (without PCT) in critically ill patients.

6.2. Study II. – Using PCT kinetics to guide antibiotic initiation of critically ill patients with suspected new-onset infection.

This study aims to compare two PCT protocols for AB initiation in critically ill patients with new-onset infection upon admission or during ICU stay - using the absolute value or the kinetics of PCT.

7. METHODS

7.1. Study I.

7.1.1. Methodology and Protocol

We report our meta-analysis according to the 2020 PRISMA guidelines (19) and the Cochrane Collaboration's regulations (20). We registered the study protocol in advance on PROSPERO (registration number CRD42022374605). The only modification of the original protocol was adding “rate of secondary infection” as a new outcome and including two subgroups in the analysis (PCT protocol and patient population).

7.1.2. Eligibility Criteria

Randomized controlled trials (RCTs) were eligible for inclusion if they reported on adult critically ill patients with known or suspected infection treated with ABs according to either PCT-guided therapy or standard of care (without PCT use) evaluating the following outcomes: duration of AB therapy, mortality, rate of recurrent infection (clinically confirmed infection in the same location caused by the same pathogen as the primary one), rate of secondary infection (clinically confirmed infection caused by an organism different from the primary one), ICU, hospital LOS, and healthcare costs. RCTs conducted in the ICU were included in the quantitative analysis; others conducted outside the ICU were included in the qualitative analysis.

7.1.3. Information Sources and Search

Strategy

We searched the three main databases—CENTRAL, Embase, and Medline—on November 14, 2022, using the following search key in all databases: (sepsis OR septic OR infection) AND (PCT OR procalcitonin) AND (antibiotic* OR antimicrobial OR anti-microbial). We excluded conference papers.

7.1.4. Study Selection and Data Extraction

Study selection and data extraction were done in duplicate using a reference manager software and a predefined data extraction sheet, where the following data were extracted on top of the previously mentioned outcomes: digital object identifier, first author, publication year, countries, centers, study period, study population, sepsis definition,

age, gender, PCT protocol, protocol adherence, appropriateness of AB therapy, and exclusion criteria.

7.1.5. Subgroup analysis

We performed different subgroup analyses to reduce heterogeneity according to the used sepsis definitions (Sepsis-1 (21), 2 (22) and 3 (23), PCT protocol (liberal—stop AB if PCT reduced > 80% of the peak value or < 0.5 ng/mL; and conservative—stop AB if PCT reduced > 90% of peak value or < 0.1–0.25 ng/mL or < 1 ng/mL for 3 days) and patient population (medical, surgical and mixed). We categorised ventilator-associated pneumonia (VAP) as pulmonary sepsis.

7.1.6. Risk of Bias and Quality of Evidence

Assessment

Three authors independently assessed the risk of bias using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2) (24). GRADE Pro (25) was used to assess the quality of evidence, with disagreements resolved by a fourth author.

7.1.7. Data Synthesis and Analysis

For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were used to estimate effect sizes. Pooled OR based on raw data was calculated using the Mantel–Haenszel method (26,27). For continuous outcomes, the difference in means (MD) was used to estimate the effect size. To calculate the pooled difference, the sample size, the mean, and the corresponding standard deviation (SD) were extracted from each study. If the SD was not provided, but the standard error (SE) or confidence interval was available, we calculated the SD from it. We used inverse-variance weighting to calculate the pooled MD.

We used a Hartung-Knapp adjustment if it resulted in a more conservative estimate than the unadjusted estimate (28,29). We assessed heterogeneity using Higgins and Thompson I^2 statistics (30).

We performed all statistical analyses with *R* (R Core Team 2023, v4.2.3) (31), using the meta (Schwarzer 2023, v6.2.1) package (32) for basic meta-analysis calculations and plots, and dmetar (Cuijpers, Furukawa, and Ebert 2023, v0.0.9000) package (33) for additional influential analysis calculations and plots.

Small-study publication bias was assessed by visual inspection of funnel plots and Egger's test (modified Egger's test depends on the type of effect size measure) at the 10% significance level (34).

For subgroup analysis, we used a fixed-effects “plural” model (aka mixed-effects model). We assumed that subgroups had different τ^2 values because we anticipated differences in between-study heterogeneity across subgroups. However, for practical reasons, if any subgroup had a size of 5 or less, a common τ^2 assumption was used (35).

7.2. Study II.

7.2.1. Trial design

We followed the SPIRIT 2025 statement: updated guideline for protocols of randomised trials (36), when designing The KInetics of Procalcitonin to Reduce Unnecessary aNtibiotic use (KIPRUN) study. The SPIRIT flowchart is shown in Figure 1. This study is a randomised, controlled, two-arm (1:1 ratio), parallel-group superiority trial. We registered the trial on clinicaltrials.gov (NCT07211620), and the initial protocol release was on September 21, 2025.

The trial aims to assess whether a PCT-kinetics-guided AB initiation protocol results in fewer unnecessary AB treatments than an absolute PCT-guided protocol. We plan to enrol 250 adult critically ill patients in academic centres and public hospitals in Hungary. All adult (18 years old <) critically ill patients treated in an ICU are eligible for the study if the treating clinician suspects a new-onset bacterial infection on admission or during ICU stay. Participants are randomly assigned to the intervention (n=125, Kinetics Group, KG) or the control arm (n=125, Absolute Group, AG) in a 1:1 ratio stratified by study site.

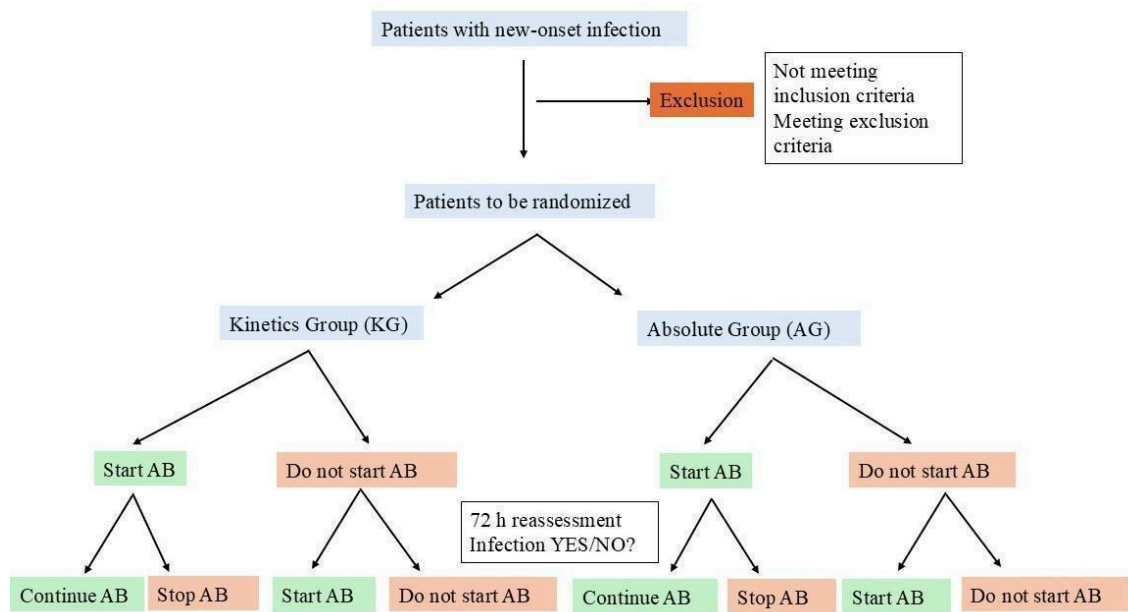


Figure 1: Flow chart of the study protocol; AB: antibiotic

7.2.2. Eligibility

Inclusion criteria:

- Adult (18 years <) non-surgical, surgical, or trauma patients.
- Suspected new-onset infection at admission or during ICU stay.
- The source of infection is known or strongly suspected, and source control has been implemented when necessary (e.g., removal of an infected device, such as a vascular access device or endoprosthesis).
- Two PCT values are available - one on the day of suspicion of infection and one 24±4 hours earlier.
- Microbiological sampling must be performed (according to all presumed sources, including two pairs of blood cultures (aerobic and anaerobic), lower respiratory tract sample (tracheal aspirate/bronchoalveolar lavage), urine, etc.).
- Written informed consent from the patient (or from a legal guardian if the patient is unable to provide consent).

Exclusion criteria:

- Septic shock (hypotension requiring vasopressor therapy to maintain a mean blood pressure of 65 mmHg or higher and having a serum lactate level above 2 mmol/L after adequate fluid resuscitation) (37)
- Infections for which long-term AB treatment is strongly recommended (e.g.,

infective endocarditis, osteoarticular infections, chronic prostatitis, and tuberculosis)

- Infections associated with primary surgical intervention and adequate source control cannot be guaranteed (e.g., faecal peritonitis, pancreatic necrosectomy, infective necrotising fasciitis - i.e., Fournier's gangrene)
- Indisputable infections (e.g., hepatic abscess, empyema)
- Poor chance of survival (i.e., expected ICU stay less than 24 hours or initial Acute Physiology and Health Evaluation Score II (APACHE II) >30)
- Admissions after cardiopulmonary resuscitation
- Patients on ABs within 72 hours before inclusion
- Pregnant or breastfeeding patients. We will screen women of childbearing age with a urine pregnancy test before inclusion in the study.
- Severe immunosuppression other than steroid use
 - stem-cell transplant recipients
 - solid organ transplant patients
 - HIV infection with a CD4 count of less than 200 cells/mm³
 - neutropenia with a neutrophil count of less than 500 neutrophils/mm³

7.2.3. Study groups

Patients will be randomly assigned to either of the two study groups (KG and AG). A strong recommendation according to a predefined PCT protocol will guide AB initiation. In the KG, AB therapy is initiated if PCT ≥ 0.5 ng/mL and shows a $\geq 100\%$ increase from the previous day's value. In the AG, AB therapy is started if PCT ≥ 0.5 ng/mL.

The actual AB regimen depends on the source of infection, patient characteristics, and local AB resistance profiles. It is determined in accordance with national and international AB guidelines, as decided by the treating clinician and the responsible infectologist specialist. We will document protocol violations in detail.

7.2.4. Sample size

As the aim of this study is to reduce the number of unjustified AB treatments, the primary endpoint will be the proportion of unnecessary therapies. The proportion of such cases ranges from 20% (38) to 43% (6) in previous prospective observational

studies. On average, up to 30% of critically ill patients are incorrectly considered infected and receive unjustified AB therapy. To detect a clinically relevant difference based on expert consensus (from 30% to 15%) with 80% power and a significance level of 0.05, we have to enrol 250 patients (125/arm) into the trial.

7.2.5. Statistical analysis

For descriptive statistics, we will use means and standard deviations, or medians and IQR. For the primary outcome (rate of unnecessary AB therapy), and for dichotomous secondary endpoints, we will use Fisher's exact test; for continuous outcomes, we will use two-sample t-tests. All statistical analyses will be performed in R. Both intention-to-treat and per-protocol analyses will be performed.

7.2.6. Randomisation and data collection

Participants will be randomly assigned in a 1:1 ratio to the intervention and control groups, according to a computer-generated randomisation schedule stratified by site. Data collection and randomisation are managed through the online database RedCAP (39).

7.2.7. Outcomes

Primary outcome

The rate of unnecessary AB therapy. After 72 hours of treatment, an independent multidisciplinary committee (one intensivist, one microbiologist, and one infectologist) will determine whether the therapy was necessary based on all relevant patient results. If the members cannot reach consensus, the decision will be made by secret vote. Each participating centre will have its own committee.

Secondary outcomes

1. Organ-support free days (number of days alive without life support - mechanical ventilation, vasoactive therapy, renal replacement therapy)
2. LOS at the ICU
3. LOS at the hospital
4. Duration of mechanical ventilation in days
5. Duration of renal replacement therapy in days
6. Duration of catecholamine circulatory support in days

7. Mortality: ICU
8. Mortality: hospital
9. Mortality: at 28 days
10. Number of infections caused by multidrug-resistant organisms (i.e. bacteria resistant to one or more classes of antimicrobial agents (40))
11. Number of *Clostridioides difficile* infections

7.2.8. Interim analysis and trial termination

We will conduct an interim analysis after enrolling half of the planned number of patients (n=125). Re-estimation of the sample size will be allowed after the interim analysis to maintain statistical power. The steering committee (SC) can halt the trial due to safety or efficacy reasons.

7.2.9. Participating centres

Enrollment started on the 3rd of November 2025 in the Department of Intensive Therapy at Semmelweis University, in both units (Central ICU and Trauma ICU). Szent Margit Hospital joined the enrollment on the 15th of April 2026. Actually, three Hungarian centres (Gottsegen György National Cardiovascular Centre, Honvéd Hospital, and Bajcsy-Zsilinszky Hospital) are planning to join the study; the required modification to the ethical approval is in progress. Minimum requirements for joining: 1. PCT can be measured at any time, 2. The centre has additional personnel allocated for the trial (study nurses, research administrators, etc.), 3 The possibility of consultation with an infectious disease specialist.

7.2.10. Withdrawal from the study

Consent may be withdrawn orally or in writing at any time during or after participation by the patients or their representatives without providing a reason. This will not affect any further treatment of the patient.

7.2.11. Ethical approval and dissemination

The National Centre for Public Health and Pharmacy, through the Scientific and Research Ethics Committee of the Hungarian Medical Research Council accepted the protocol (BM/20019-1/2025) on September 9, 2025. The study is conducted in

accordance with the Declaration of Helsinki (41) and the International Conference on Harmonisation and Good Clinical Practice guidelines (42).

We will disseminate the trial results to the public, including study participants, through publication in peer-reviewed international medical journals and presentations at scientific meetings. Participant data will be securely stored online on the REDCap server of Semmelweis University in a de-identified format and will be accessible upon authorisation.

8. RESULTS

8.1. Study I: Investigating the effects of procalcitonin-guided antibiotic therapy versus standard treatment in critically ill patients -systematic review and meta-analysis of randomised controlled trials

8.1.1. Study Search and Selection

We identified 15,788 studies using the search key, of which 13,317 remained after duplicate removal for screening. The interrater agreement for title-abstract and full text selection was almost perfect (Cohen's kappa 0.94 for both). After selection, 26 RCTs conducted in ICUs comprising 9,048 patients were included in the meta-analysis (11,43–67), and 23 RCTs conducted outside the ICU were included in the systematic review (68–90). The PRISMA flowchart provides details on the selection process (Figure 2), while the basic characteristics of the included studies are presented in Table 1.

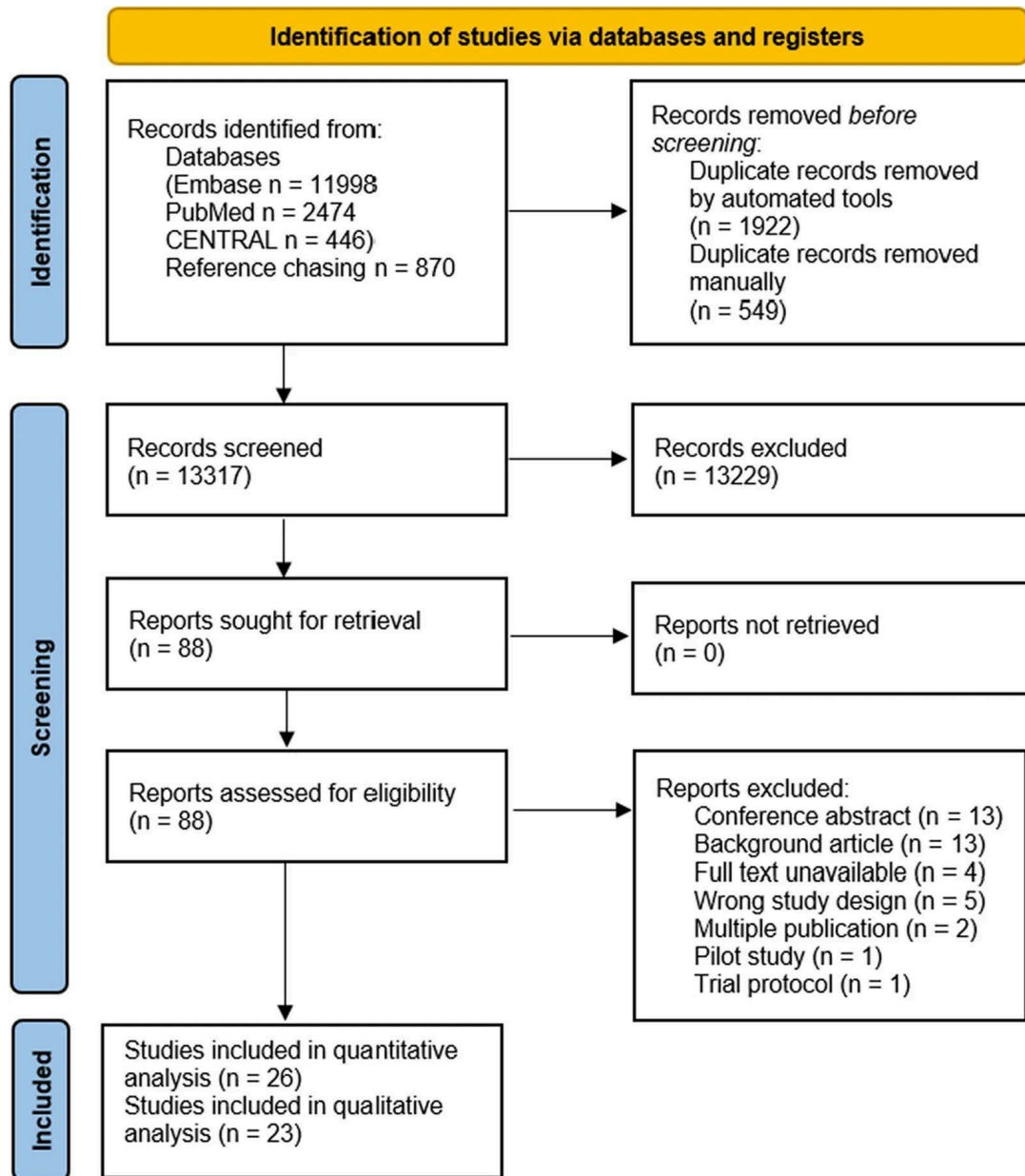


Figure 2: PRISMA 2020 flowchart representing the study selection process

Table 1: Characteristics of studies included

Study author, year	Country (centres)	Sample size (female% in PCT/control arm)	Clinical setting	Patient population	Age ^a in the PCT/control arm
Kyriazopoulou et al.,2021 (44)	Greece (7)	256 (59/54)	ICU ^b	medical patients with sepsis	80±10 / 78±13
Ali et al., 2021 (63)	Egypt (1)	60 (43/47)	ICU	patients with sepsis	57±1 / 56±2
Vishalashi et al., 2021 (45)	India (1)	90 (51/36)	ICU	medical/surgical (41/59%) patients with sepsis	42±17 / 47±16
Labro et al., 2021 (46)	France (5)	159 (35/47)	ICU	mechanically ventilated medical patients with coma	54±18 / 52±17
Lhopitallier et al., 2021 (68)	France (60)	469 (65/53)	primary care	medical patients with pneumonia	53±18 / 50±18
Mazlan et al., 2021 (47)	Malaysia (1)	85 (37/55)	ICU	medical patients with VAP	49±17 / 53±17
Jeon et al., 2019 (64)	South Korea (4)	52 (67/52)	ICU	medical patients with sepsis	69 (61-75) / 70 (63-77)
Montassier et al., 2019 (70)	France (12)	285 (44/38)	ED	medical patients with CAP	67 (46-83) / 67 (47-81)
O'Riordan et al., 2019 (69)	Ireland (1)	119 (39/58)	respiratory ward	medical patients with LRTI	69±14 / 68±15
Daubin et al., 2018 (48)	France (11)	302 (29/34)	ICU	medical patients with AECOPD	67 (61-76) / 67 (61-75)
Kip et al., 2018 ^c (65)	Netherlands (15)	1546 (39/40)	ICU	medical patients with sepsis	65 (54-75) / 65 (57-75)
van der Does et al., 2018 (72)	Netherlands (2)	551 (48/44)	ED	medical patients with fever	61 (43-70) / 62 (44-73)

Huang et al., 2018 (71)	USA (14)	1656 (57/57)	ED	medical patients with LRTI	53±18 / 53±19
Liu et al., 2017 (49)	China (1)	98 (45/41)	ICU	patients with sepsis	66±9 / 65±10
Xu et al., 2017 (43)	China (1)	156 (43/43)	ICU	patients with sepsis	67±9 / 65±9
Slieker et al., 2017 (74)	Switzerland (1)	162 (42/43)	surgical ward/ICU (88/12%)	surgical patients with peritonitis	56 [36-73] / 57 [36-71]
Mahmutaj et al., 2017 (73)	Kosovo (1)	100 (32/38)	surgical ward	surgical patients with an acute abdomen	39±20 / 47±19
Ulm et al., 2017 (75)	Germany (10)	227 (54/57)	neurology ward	medical patients after an ACM stroke	76±12 / 76± 11
Corti et al., 2016 (76)	Denmark (1)	120 (66/55)	ED	medical patients with AECOPD	72 (64-80) / 73 (61-78)
Bloos et al., 2016 (50)	Germany (33)	1089 (NA)	ICU	medical/surgical (43/57%) patients with sepsis	NA
de Jong et al., 2016 (51)	Netherlands (15)	1546 (39/40)	ICU	medical patients with sepsis	65 (54-75) / 65 (57-75)
Lima et al., 2016 (77)	Brazil (1)	61 (44/52)	hematology ward	medical patients with febrile neutropenia (FN)	36 (26-53.8) / 33 (26.50)
Branche et al., 2015(78)	USA (1)	150 (58/54)	general ward	medical patients with non-pneumonic LRTI	61 (51-72) / 64 (50-74)
Drozdov et al., 2015 (79)	Switzerland (1)	125 (70/81)	ED	medical patients with non-catheter-related UTI	71 (44-81) / 75 (51-80)
Verduri et al., 2015 (80)	Italy (18)	178 (13/14)	respiratory ward	medical patients with AECOPD	74 (69-78) / 73 (65-78)

Najafi et al., 2015 (66)	Iran (1)	60 (33/40)	ICU	medical/surgical (88/12%) patients with SIRS	40±18 / 41±21
Ogasawara et al., 2014 (81)	Japan (1)	96 (55/46)	respiratory ward	medical patients with aspiration pneumonia	85 (81-92) / 87 (85-89)
Shehabi et al., 2014 (52)	Australia (11)	394 (53/40)	ICU	medical surgical patients (88/12%) with suspected bacterial infection	63±15 / 66±16
Oliveira et al., 2013 (53)	Brazil (2)	94 (49/42)	ICU	medical/surgical patients (86/14%) with severe sepsis or septic shock	60±13 / 60±19
Annane et al., 2013 (54)	France (8)	58 (20/32)	ICU	medical/surgical patients (97/3%) with suspected sepsis	59 (40-67) / 54 (46-73)
Deliberato et al., 2013 (55)	Brazil (1)	81 (43/46)	ICU	patients with sepsis	68±21 / 62±19
Tang et al., 2013 (82)	China (1)	260 (50/54)	ED	medical patients with acute exacerbation of asthma	54±14 / 55±15
Layios et al., 2012 (62)	Belgium (1)	509 (48/39)	ICU	medical/surgical patients (60/40%) with suspected sepsis	66 (55-76) / 65 (53-75)
Qu et al., 2012 (56)	China (1)	71 (29/28)	ICU	medical patients with acute pancreatitis	43±11 / 44±11
Jensen et al., 2011 (57)	Denmark (9)	1200 (65/64)	ICU	medical/surgical patients (59/41%) with sepsis	67 (58-76) / 67 (58-75)
Long et al., 2011(83)	Japan (1)	162 (40/38)	ED	medical patients with CAP	44±16 / 47±19

Maravić-Stojković et al., 2011 (67)	Serbia (1)	205 (30/33)	ICU	patients after open-heart cardiac surgery	60±9 / 60±10
Burkhardt et al., 2010 (84)	Germany (15)	550 (60/59)	primary care	medical patients with respiratory tract infection	41±15 / 43±16
Bouadma et al., 2010 (11)	France (7)	621 (33/35)	ICU	medical/surgical patients (89/11%) with suspected bacterial infection	61±15.2 / 62±15
Stolz et al., 2009 (58)	Switzerland, USA (7)	101 (25/26)	ICU	medical/surgical (52.5/47.5%) patients with VAP	53 [21-88] / 59 [18-83]
Kristoffersen et al., 2009 (85)	Denmark (3)	210 (48/46)	general ward	medical patients with suspected LRTI	67±18 / 67±16
Hochreiter et al., 2009 (59)	Germany (1)	110 (49/ 46)	ICU	surgical patients with sepsis	67±14 / 67±16
Schuetz et al., 2009 (86)	Switzerland (6)	1359 (40/45)	ED	medical patients with LRTI	73 (59-82) / 72 (59-82)
Briel et al., 2008 (87)	Switzerland (53)	458 (58/62)	primary care	medical patients with respiratory tract infection	48±18 / 48±18
Schroeder et al., 2009 (60)	Germany (1)	27 (43/46)	ICU	surgical patients with severe sepsis	69±11 / 68±14
Nobre et al., 2008 (61)	Switzerland (1)	68 (32/32)	ICU	medical/surgical (75/25%) patients with sepsis	64±12 / 70±14
Stolz et al., 2007 (88)	Switzerland (1)	208 (51/59)	ED	medical patients with AECOPD	70 (65-77) / 70 (65-79)
Christ-Crain et al., 2006 (89)	Switzerland (1)	302 (38/38)	ED	medical patients with CAP	70±17 / 70±17
Christ-Crain et al., 2004 (90)	Switzerland (1)	243 (46/49)	ED	medical patients with LRTI	63±20 / 65±17

^a presented as mean±SD, median (IQR), median [range], ^b patients treated on wards under advanced supportive care because of a shortage of ICU beds, ^c cost-effectiveness analysis of de Jong et al., 2016; abbreviations: ACM: arteria cerebri media, AECOPD: acute exacerbation of chronic obstructive pulmonary disease, CAP: community-acquired pneumonia, ED: emergency department, ICU: intensive care unit, LRTI: lower respiratory tract infection, NA: not available, UTI: urinary tract infection, VAP: ventilator-associated pneumonia

8.1.2. Primary outcome: length of AB therapy

A meta-analysis including a total of 6669 patients from 21 RCTs (11,43–61,64) showed a reduced duration of AB therapy in the PCT-guided group compared to the SOC group (MD – 1.79 days, 95% CI: – 2.65, – 0.92, $p < 0.001$) (Fig. 3)

This shorter AB duration was noted in Sepsis-1 patients (MD – 2.58 days, 95% CI: – 3.87, – 1.29, $p = 0.004$) (Fig. 4A), in groups using a conservative or liberal PCT protocol (MD – 1.56 days, 95% CI: – 2.93, – 0.18, $p = 0.03$ vs. – 2.37 days, 95% CI: – 4.23, – 0.51, $p = 0.02$) (Fig. 4B) and in the 100% medical patient population (MD – 1.87 days, 95% CI: – 3.36, – 0.37, $p = 0.019$) (Fig. 4C). The Sepsis-3 cohort showed the biggest, however, non-significant difference (– 3.01 days, 95% CI – 7.72, 1.69).

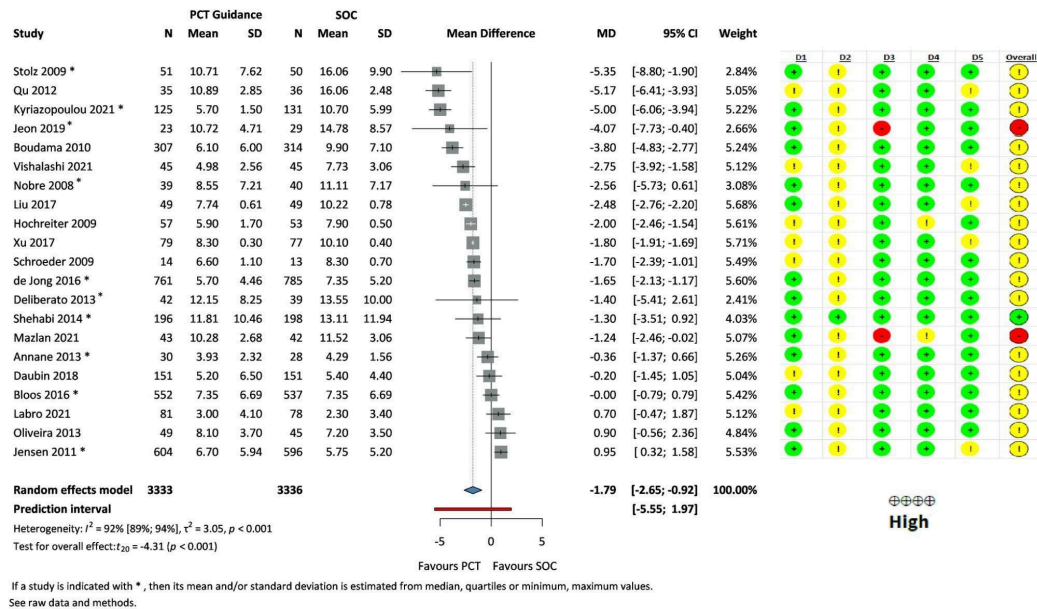


Figure 3: Forest plot representing the length of AB therapy in days in PCT guidance vs SOC. Outcome measure is MD with 95% CI. Results of the risk of bias assessment are depicted on the right by study, domain and overall. For the revised Cochrane risk-of-bias tool for randomised trials (RoB 2), the domains are: D1: Bias arising from the randomisation process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement

of the outcome, D5: Bias in the selection of the reported result. Under the RoB 2 assessment, the result of the GRADE assessment can be seen.

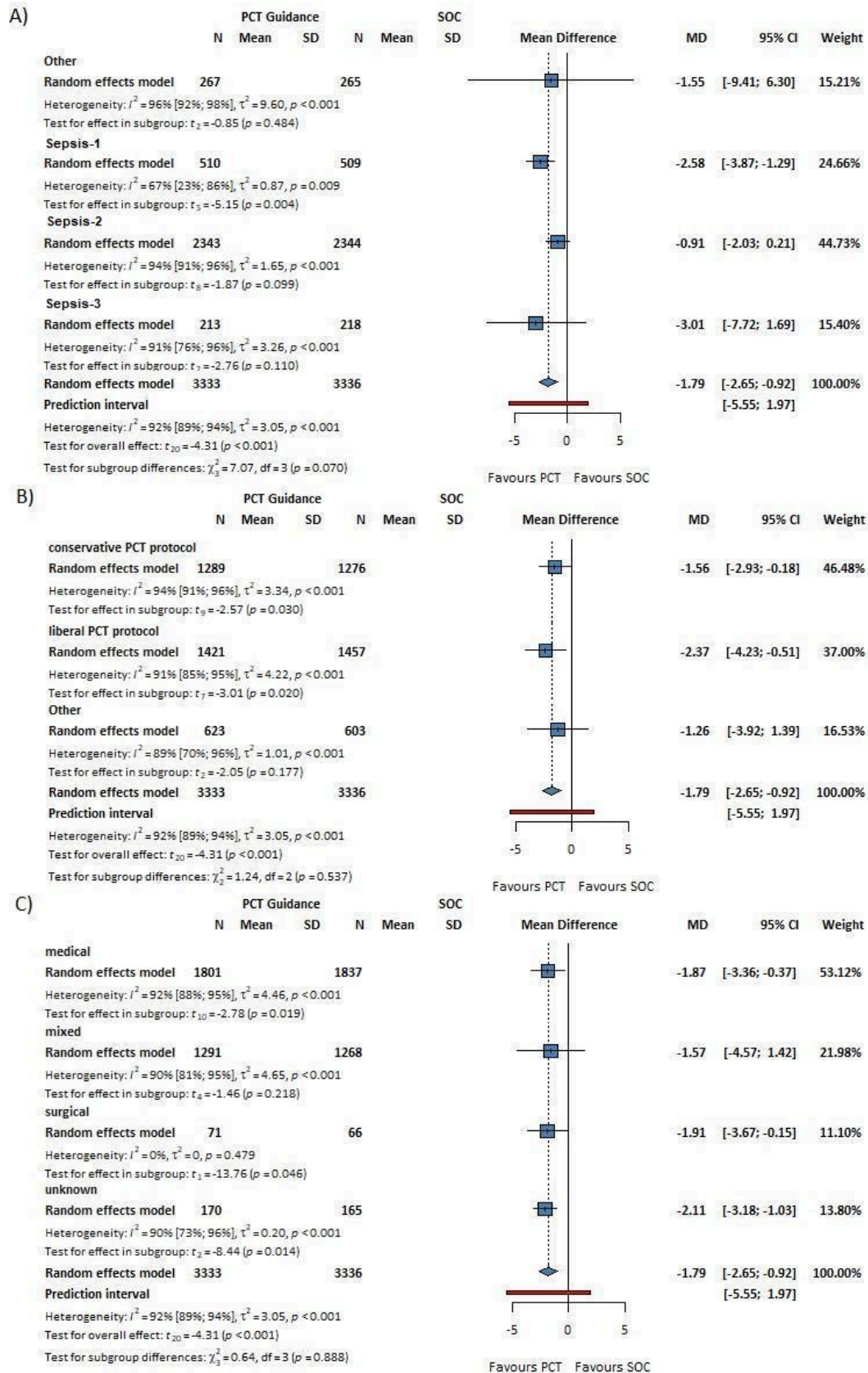


Figure 4: Forest plots representing the length of AB therapy in A sepsis subgroups, B PCT protocol subgroups, and C patient population subgroups

8.1.3. 28-day, ICU, and in-hospital mortality

There was a significantly reduced odds of 28-day mortality in the PCT group compared to SOC (OR 0.84, 95% CI: 0.74, 0.95, $p=0.008$) (Fig. 4), while in-hospital mortality was not significantly lower in the PCT group (OR 0.85, 95% CI: 0.66, 1.10). There was no difference in ICU mortality between the two groups (OR 1.00, 95% CI: 0.74, 1.36).

The 28-day survival benefit was observed in Sepsis-2 and Sepsis-3 patients (OR 0.86, 95% CI: 0.76, 0.97, $p=0.024$ and OR 0.46, 95% CI: 0.27, 0.79, $p=0.026$, respectively) (Fig. 6A), using liberal PCT protocol (OR 0.75, 95% CI: 0.59, 0.95, $p=0.024$) (Fig. 6B) and in exclusively medical patients (OR 0.76, 95% CI: 0.60, 0.97, $p=0.033$) (Fig. 6C).

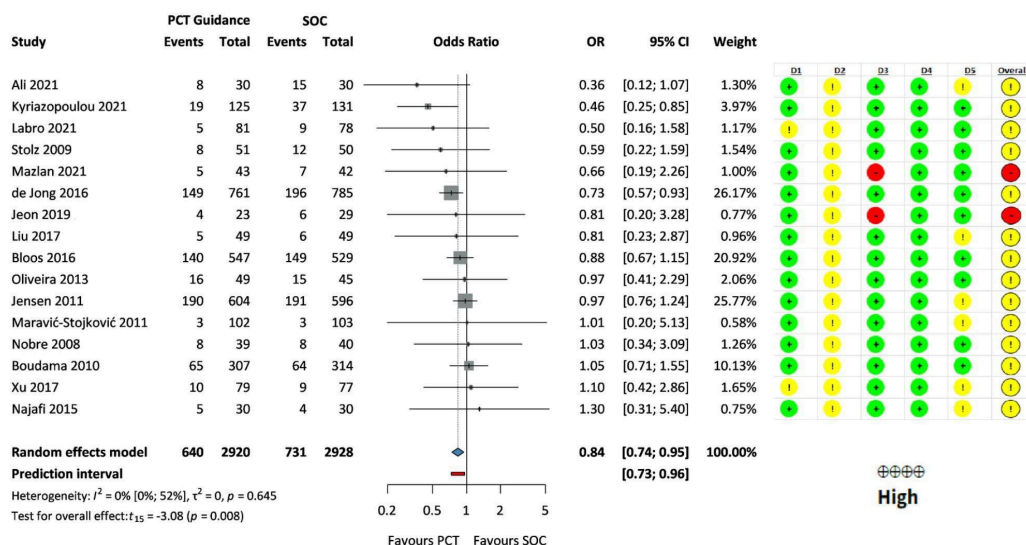


Figure 5: Forest plots representing the odds of 28-day mortality in the PCT vs the SOC group. Pooled results can be seen as OR with 95% CI. Results of the risk of bias assessment are depicted on the right by study, domain and overall. For the revised Cochrane risk-of-bias tool for randomised trials (RoB 2), the domains are: D1: Bias arising from the randomisation process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the

measurement of the outcome, D5: Bias in the selection of the reported result. Under the RoB 2 assessment, the result of the GRADE assessment can be seen.

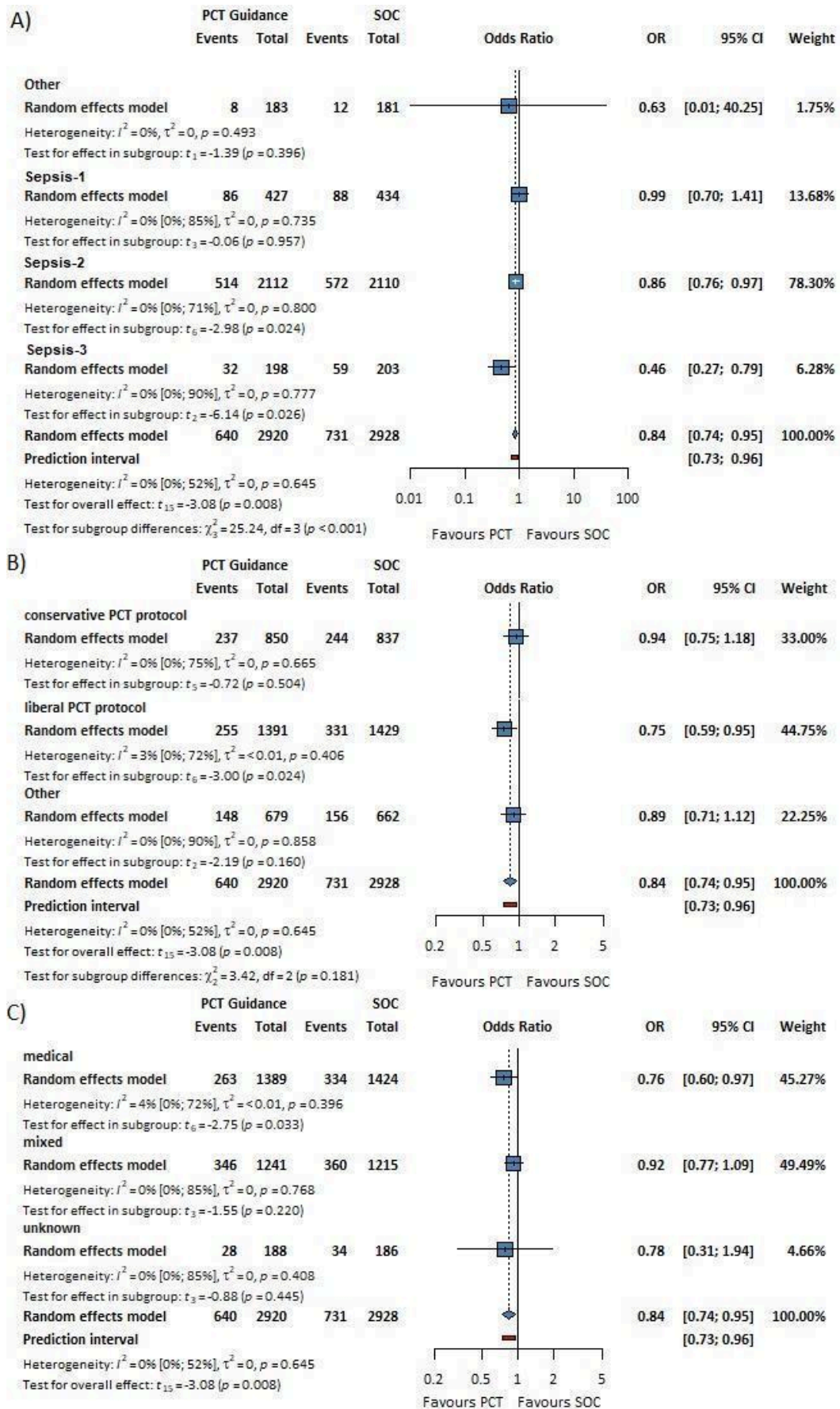


Figure 6: Forest plots representing the odds of 28-day mortality in **A** sepsis subgroups, **B** PCT protocol subgroups, and **C** patient population subgroups. Outcome measure is OR with 95% CI.

8.1.4. Recurrent and secondary infection

Infection recurrence was documented in 99 out of 2,070 patients in the PCT group and in 75 out of 2,080 patients in the SOC group, which means a significant difference (OR 1.36, 95% CI: 1.10, 1.68, $p = 0.008$) (Fig. 7).

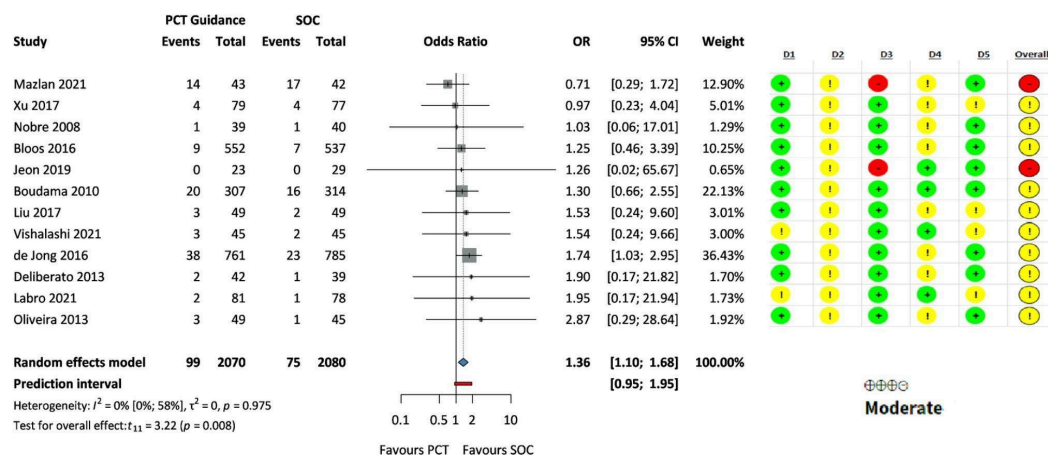


Figure 7: Forest plot representing the odds of recurrent infection in the PCT guidance and SOC group. Pooled results are depicted as OR with 95% CI. Results of the risk of bias assessment are depicted on the right by study, domain and overall. For the revised Cochrane risk-of-bias tool for randomised trials (RoB 2), the domains are: D1: Bias arising from the randomisation process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result. Under the RoB 2 assessment, the result of the GRADE assessment can be seen.

Regarding the rate of secondary infections, the difference was not significant (OR 0.81, 95% CI: 0.54, 1.21) (Fig. 8).

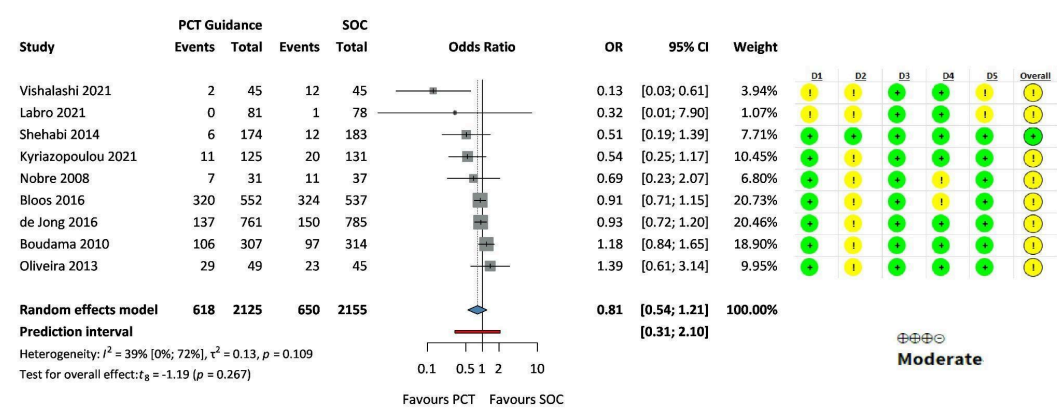


Figure 8: Forest plot representing the odds of secondary infections in the two study groups. Results are represented as OR with 95% CI. Results of the risk of bias assessment are depicted on the right by study, domain and overall. For the revised Cochrane risk-of-bias tool for randomised trials (RoB 2), the domains are: D1: Bias arising from the randomisation process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result. Under the RoB 2 assessment, the result of the GRADE assessment can be seen.

8.1.5. Length of stay and healthcare cost

Length of ICU stay and length of hospital stay were shorter in the PCT group compared to the SOC group; however, without statistical significance (MD - 0.67 days, 95% CI: -1.76, 0.41, and MD - 1.23 days, 95% CI: -3.13, 0.67, respectively) (Fig. 9 and Fig. 10). Only 5 studies (44,50,56,65,67) reported on healthcare costs in highly heterogeneous ways; using standardised mean differences, the results favoured PCT use.

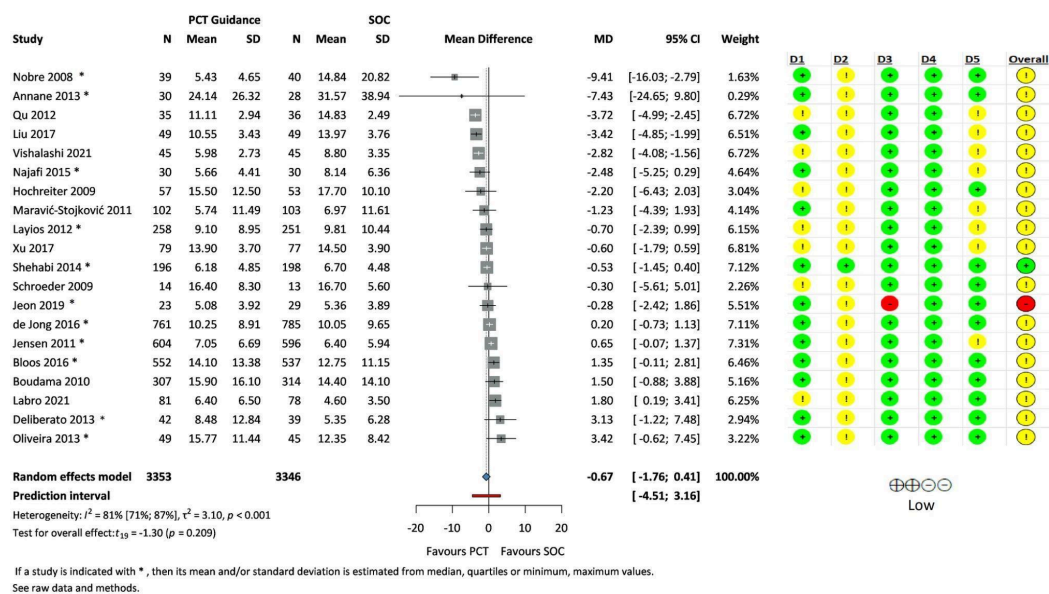


Figure 9: Forest plot representing the length of ICU stay in days, the outcome measure is MD with 95% CI. Results of the risk of bias assessment are depicted on the right by study, domain and overall. For the revised Cochrane risk-of-bias tool for randomised trials (RoB 2), the domains are: D1: Bias arising from the randomisation process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result. Under the RoB 2 assessment, the result of the GRADE assessment can be seen.

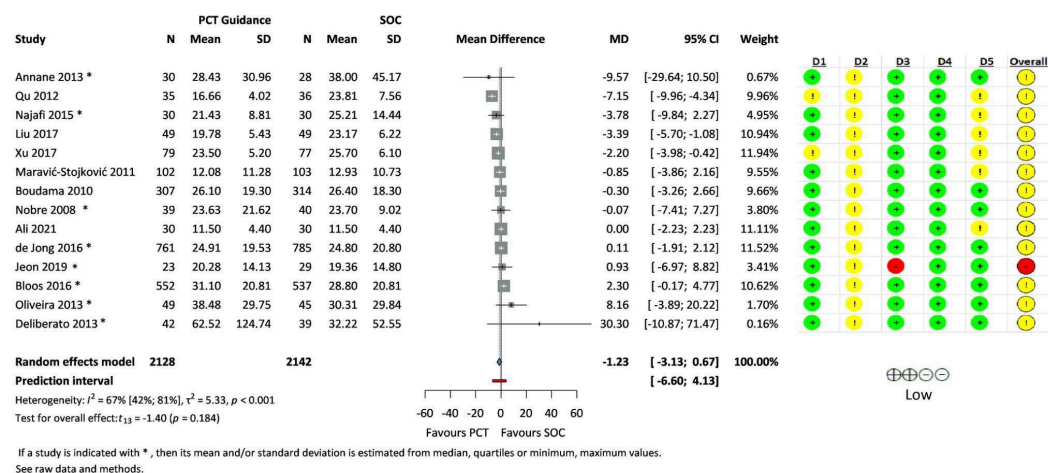


Figure 10: Forest plot representing the length of hospital stay in days. Results of the risk of bias assessment are depicted on the right by study, domain and overall. For the revised Cochrane risk-of-bias tool for randomised trials (RoB 2), the domains are: D1: Bias arising from the randomisation process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result. Under the RoB 2 assessment, the result of the GRADE assessment can be seen.

8.1.6. Qualitative assessment

23 RCTs (68–90) were included in the systematic review. 18 trials recruited patients with respiratory tract infections from the ED (58,70,71,76,78,82,83,86,89), from general wards (69,75,80,81,85), or from primary care (68,84,87). Other conditions were peritonitis in two studies (73,74), fever (72), febrile neutropenia (77) and urinary tract infection (UTI) (79) in one study each. In some cases, additional diagnostic modalities were used, such as viral PCR (78) or thoracic ultrasound (68,78). AB use was reduced in the PCT group or was similar across study groups, with no difference in adverse outcomes in patients with respiratory tract infection. One study from 2017 investigating patients with peritonitis reported a significant reduction in AB use in the intervention arm without an increased risk of infection recurrence (73), while another trial from the same year found no difference in AB treatment duration or adverse outcomes (74). Combining pyuria with PCT in UTI (79) safely reduced AB exposure by 30%. PCT did not affect AB use in febrile neutropenia (77).

8.1.7. Risk of Bias Assessment

Missing outcome data led to a high overall risk of bias in two trials (47,64). At the same time, deviations from the intended intervention or the scarcity of its reporting raised concerns in the ROB assessment in 23 studies (11,43–46,48–51,53–63,65–67). Only one trial had a low overall ROB (52).

8.1.8. Quality of Evidence

High certainty of evidence was found for the length of AB therapy and 28-day mortality; moderate for in-hospital mortality, ICU mortality, rate of recurrent infection, and rate of secondary infection; low for length of ICU stay and length of hospital stay; and very low for healthcare costs. The results of the ROB and GRADE assessment are depicted in the corresponding forest plots.

9. DISCUSSION

9.1. Summary of Findings, International Comparisons (including all studies)

Study I

Our meta-analysis, including 26 RCTs (11,43–67) with a total of 9,048 patients, compared the effects of PCT-guided AB therapy with standard of care without PCT measurement on length of AB therapy, mortality, rate of recurrent and secondary infections, length of hospital and ICU stay, and healthcare costs. To reduce heterogeneity and better understand the clinical translatability of the results, we conducted subgroup analyses based on different sepsis definitions, PCT protocols, and patient populations (medical, surgical, mixed).

The significantly reduced duration of AB therapy was a finding similar to previous meta-analyses (91–93). Moreover, an RCT from 2024 investigating biomarker-guided AB therapy with the largest sample size to date found the same significantly reduced treatment duration, albeit by only 1 day (94). What is more interesting, this is the only trial in which the treating clinician was blinded to the allocation group, thereby minimising performance bias.

Other factors, such as the predefined PCT protocol, also influence the duration of the AB treatment. A more strict (i.e., conservative) protocol may result in more days on ABs than a less strict one (i.e., liberal), as observed in our analysis. Moreover, protocol adherence in three of the studies using a liberal protocol (11,51,64) was very low (40-50%), so the difference could have been even larger with greater adherence.

According to our results, in mixed populations (containing at least 25% surgical patients in addition to medical patients), the length of AB therapy is slightly longer than in exclusively medical patient cohorts. All the included RCTs used the same protocol for AB cessation, regardless of whether the patient was medical or surgical, except for one that used different PCT cut-offs for patients during the 48-h postoperative period (54). PCT is an inflammatory biomarker that can increase in response to pathogen-associated molecular patterns (PAMPs) during infection. However, damage-associated molecular patterns (DAMPs) can also elevate PCT value after tissue injury (95). Therefore, PCT

values can be elevated after surgery without bacterial infection (96), and using absolute PCT values as criteria for stopping the therapy may inevitably lead to more AB use.

The other novelty of our meta-analysis was the subgroup analysis by different sepsis cohorts (sepsis-1, sepsis-2, and sepsis-3). Sepsis-3 (23) defined sepsis as a life-threatening organ dysfunction due to a dysregulated host response to an infection, which is the most pathophysiologically sound definition to date and results in a more homogeneous, more ill sepsis cohort than previous definitions using nonspecific systemic inflammatory response syndrome criteria (21,22). However, our results were somewhat contradictory, as only the sepsis-1 cohort showed a significantly reduced AB duration. The mean difference was largest in sepsis-3 patients, although it lacked statistical significance, a finding that the low sample size may partly explain. In the sepsis-2 cohort, 5 of 9 trials used very strict PCT protocols, leading to potential overtreatment and smaller differences compared to SOC.

Surprisingly, analysing mortality outcomes, we not only highlighted safety but also suggested a robust survival benefit. However, some trials showed reduced mortality (44,51), while others did not (11,53,57), which can be explained by several reasons. Interestingly, the survival benefit was observed in the sepsis-2, sepsis-3, and medical cohorts, as well as in trials using a liberal PCT protocol, all of which were associated with reduced AB duration. Although our results do not allow us to explain the relationship between AB duration and mortality, several previous studies emphasise the potential adverse effects of ABs, which are more pronounced with longer treatment. These can include direct organ injury and toxic effects (97), the emergence of AB resistance (16), mitochondrial dysfunction (98), and varying degrees of dysbiosis and the emergence of the pathobiome (99). Moreover, PCT can aid differential diagnosis, thereby improving mortality and reducing the likelihood of infection in cases with a negative PCT value.

The importance of infection recurrence, as another safety endpoint, cannot be underestimated; this is at stake when we stop AB treatment too early. The higher odds of infection recurrence in our analysis do not clearly contradict the latest network MA in the topic investigating biomarker-guided AB therapy (93), as they investigated the C-reactive protein-guided group separately, while we included them in the SOC group,

because no PCT guidance was used. Moreover, the event rate was very low (<5%), and the quality of evidence was rated as low or very low in the included studies.

Nevertheless, a higher rate of infection recurrence did not result in longer LOS, as was found in the latest MA including this outcome (92). Although cost-effectiveness was reported in a few studies with high heterogeneity, and has not been analysed before in an MA, our results suggest that PCT guidance may not be inferior to SOC in this regard.

Study II

This multi-centre RCT aims to investigate AB initiation using the PCT trajectory, which is the first to our knowledge to be tested in an RCT. The actual Surviving Sepsis Guideline (14) recommends against using PCT and clinical evaluation to decide when to start the treatment with very low certainty evidence. In reality, clinicians use PCT in these situations, but PCT kinetics can help differentiate bacterial infection from other causes of deterioration, based on previous prospective observational data (100,101). These studies underscore the importance of the topic and the unmet need to optimise AB initiation.

9.2. Strengths (including all studies)

Study I

The major strength of our MA is the inclusion of high-quality RCTs and a high number of patients. We are the first to analyse the efficacy and safety of the PCT-guided therapy in different sepsis cohorts, medical-surgical populations and using strict and less strict protocols, which all have important clinical consequences, namely that in the more homogenous and more ill sepsis-3 cohort using PCT for AB cessation may have even more benefit, than in other cohorts, surgical and medical patients may need different PCT protocols and conservative protocols have no benefit compared to liberal ones, therefore the “0.5 ng/ ml or 80% decrease from peak value” stopping rule can be used safely sparing more ABs. Finally, we strictly followed the Cochrane Collaboration guidelines, thereby ensuring the highest quality, transparency, and reproducibility of the results.

StudyII

The methodology is the major strength, as well as the planned interim analysis, due to efficacy and safety reasons. The KIPRUN trial is the first investigator-initiated trial in

our department at Semmelweis University. Participant enrollment began in November 2025; the study is ongoing in two centres, with three more centres set to join, with study completion anticipated by 2027.

9.3 Limitations (including all studies)

Study I

Our MA has several limitations. First, the control arm (SOC) was not “standardised” per definitionem; different AB guidelines across institutions could result in longer AB therapy durations in some regions, thereby overestimating the effect of PCT guidance. Second, the opportunity for an infectologist consultation has a strong effect on AB strategy, yet neither study mentioned this. Third, trials applied different PCT protocols: 16 of 26 used cessation rules, 3 used initiation rules, and 7 used both. Fourth, not all studies reported on all outcomes. Fifth, the source of infection varied widely across studies, and septic shock prevalence ranged from 7 to 87%, leading to substantial variability in severity. Sixth, only 15 studies reported protocol adherence, ranging from 44 to 97%, which can obviously have a huge effect on outcomes. Seventh, the lack of reporting on AB appropriateness in 21 of 26 studies means we do not know whether the patients got adequate treatment, which is a separate risk factor for mortality. Finally, almost all studies excluded patients with immunosuppression, limiting the generalizability of our results.

Study II

The major limitation of our RCT is the lack of blinding of the treating clinician, which is inherent to the study design. Moreover, suspecting a new-onset infection can be arbitrary; however, this is common practice. Different PCT assays used across separate centres can exhibit different performance, potentially leading to measurement bias.

10. CONCLUSIONS

PCT-guided AB therapy may be associated with reduced AB use, lower 28-day mortality, but higher infection recurrence, with similar ICU and hospital length of stay. The effects are more pronounced in regions where routine AB administration exceeds 7 days. The most beneficial PCT stopping rule is 0.5 ng/mL or a 80% decrease from the peak value. The role of PCT in optimising AB initiation warrants further investigation through well-designed RCTs.

11. IMPLICATIONS FOR PRACTICE

The results of this thesis highlight the importance of AB treatment optimisation using PCT and raise awareness against giving ABs “just in case” for critically ill patients. The initiation and duration of AB therapy should be individualised; patients should be reassessed daily; and clinicians should add PCT to the existing pieces of the “sepsis puzzle” to benefit patients. To the best of our knowledge, in a clinically improving septic patient, AB therapy may be stopped if PCT is below 0.5 ng/ml or decreased by more than 80% from its peak value. We should definitely forget one of the biggest dogmas in ICU: “give a week’s course of antibiotic treatment” (102). This concept is also supported by a recent 2024 review (103).

The results of our ongoing RCT will provide important data regarding the use of PCT kinetics when starting ABs.

12. IMPLICATIONS FOR RESEARCH

12.1 Methodology and Study Design

We suggest using “organ support free days” as the primary outcome (104) rather than mortality, which several factors can influence during a critically ill patient's ICU stay; therefore, it may be difficult to establish a cause-and-effect relationship with a particular intervention.

In future studies, rigorous cost-effectiveness analyses are indispensable to understand the financial burden of PCT use better and, hopefully, to facilitate its spread in low- and middle-income countries, where one of the biggest drawbacks of PCT is its price. At the same time, most of these countries use AB courses that are too long; therefore, the benefit to them would be much higher than in other regions, where shorter AB therapies are used.

12.2. New Areas

Our work encourages researchers to investigate further PCT-guided therapy in different patient populations (medical and surgical) and to examine the potential increased rate of infection recurrence. Immunocompromised (including haematological) patients should be included in future trials, as they were underrepresented in previous studies despite their higher overall sepsis mortality (105), which may have contributed to their omission.

13. IMPLICATIONS FOR POLICY MAKERS

The insights from this thesis raise awareness of the importance of AB stewardship and emphasise the need to measure biomarkers, especially PCT, to better tailor AB therapy for critically ill patients, thereby improving outcomes and decreasing healthcare costs by lowering AB costs and potentially shorter ICU stays. Rising numbers of AB resistance put constant pressure on clinicians and heads of departments due to the incredibly high costs of reserve ABs and the emerging problems with the allocation and isolation of patients infected or colonised by MDR pathogens, not to mention pandrug-resistant bacteria, that are resistant to all commercially available AB classes, leaving no option to treat them.

14. FUTURE PERSPECTIVES

Our future work will focus on escalating the KIPRUN trial. Our first investigator-initiated trial began recruitment in November 2025 at our department at Semmelweis University, and one additional public hospital in Budapest is participating in the trial (Szent Margit Hospital). Three other centres from Budapest are about to join the study; their ethical approval is in progress, and one more potential centre from Poland has contacted us, raising the possibility of an international collaboration. This cooperation is not just important for faster recruitment, but also represents a great opportunity to work and conduct research together with other ICUs, which will lay the groundwork for more fruitful future studies.

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16. BIBLIOGRAPHY

16.1 Publications Related to the Thesis

Papp, Márton; Kiss, Nikolett; Baka, Máté; Trásy, Domonkos; Zubek, László; Fehérvári, Péter; Harnos, Andrea; Turan, Caner; Hegyi, Péter; Molnár, Zsolt

Procalcitonin-guided antibiotic therapy may shorten length of treatment and may improve survival-a systematic review and meta-analysis

CRITICAL CARE 27 : 1 Paper: 394 , 15 p. (2023)

Citing papers: 60 | Independent citation: 59 | Self citation: 1 | Unknown citation: 0 |
Number of citations in WoS: 54 | Number of citations in Scopus: 55 | WoS/Scopus assigned: 58 | Number of citations with DOI: 60

Journal subject: Scopus - Critical Care and Intensive Care Medicine Rank: D1 IF: 9.3

Papp, Márton; Turan, Caner; Kiss, Nikolett; Zubek, László; Karim, Dilan Márk; Hegyi, Péter; Molnár, Zsolt

KInetics of Procalcitonin to Reduce Unnecessary aNtibiotic use (KIPRUN) : protocol for a multicentre, randomised, superiority trial to compare the efficacy and safety of procalcitonin kinetics-guided and absolute procalcitonin value-guided antibiotic initiation in critically ill patients.

BMJ OPEN 16 : 5 Paper: e115344 , 9 p. (2026)

Journal subject: Scopus – Medicine (miscellaneous) Rank: Q1 IF: 2.3

16.2 Publications not Related to the Thesis

Papp, Marton; Ince, Can; Bakker, Jan; Molnar, Zsolt

Endothelial Protection and Improved Micro- and Macrocirculation with Hemoadsorption in Critically Ill Patients

JOURNAL OF CLINICAL MEDICINE 13 : 23 Paper: 7044 , 9 p. (2024)

Citing papers: 7 | Independent citation: 6 | Self citation: 1 | Unknown citation: 0 |
Number of citations in WoS: 7 | Number of citations in Scopus: 5 | WoS/Scopus
assigned: 7 | Number of citations with DOI: 7

Journal subject: Scopus - Medicine (miscellaneous) Rank: Q1 IF: 2.9

Karim, Dilan Mark; **Papp, Márton**; Fehérvári, Péter; Turan, Caner; Hegyi, Péter;
Molnar, Zsolt; Madách, Krisztina

No difference in microbial diversity between bronchoalveolar lavage and tracheal sampling : a systematic review and meta-analysis

BMJ OPEN RESPIRATORY RESEARCH 12 : 1 Paper: e003456 , 7 p. (2025)

Citing papers: 3 | Independent citation: 3 | Self citation: 0 | Unknown citation: 0 |
Number of citations in WoS: 3 | Number of citations in Scopus: 2 | WoS/Scopus
assigned: 3 | Number of citations with DOI: 3

Journal subject: Scopus - Pulmonary and Respiratory Medicine Rank: Q1 IF: 3.4

Kiss, Nikolett; **Papp, Márton**; Turan, Caner; Kói, Tamás; Madách, Krisztina; Hegyi,
Péter; Zubek, László; Molnár, Zsolt

Combination of urinary biomarkers can predict cardiac surgery-associated acute kidney injury : a systematic review and meta-analysis

ANNALS OF INTENSIVE CARE 15 : 1 Paper: 45 , 17 p. (2025)

Citing papers: 10 | Independent citation: 10 | Self citation: 0 | Unknown citation: 0 |
Number of citations in WoS: 9 | Number of citations in Scopus: 8 | WoS/Scopus
assigned: 10 | Number of citations with DOI: 10

Journal subject: Scopus - Critical Care and Intensive Care Medicine Rank: D1 IF: 5.5

Szőke, Eszter; Szántó, Ildikó; Turan, Caner; Szabó, Bence; **Papp, Márton**; Horváth,
Gábor; Zubek, László; Hegyi, Péter; Molnár, Zsol; Lovas, András

Evaluation of the diagnostic value of the Modified Evan's Blue Dye Test for assessing
aspiration in tracheostomized critically ill patients: A systematic review and
meta-analysis

PLOS ONE 21 : 5 Paper: e0349092 , 13 p. (2026)

Journal subject: Scopus - Multidisciplinary Rank: Q1 IF: 2.6

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RESEARCH Open Access

Procalcitonin-guided antibiotic therapy may shorten length of treatment and may improve survival—a systematic review and meta-analysis

Abstract

Background Appropriate antibiotic (AB) therapy remains a challenge in the intensive care unit (ICU). Procalcitonin (PCT)-guided AB stewardship could help optimize AB treatment and decrease AB-related adverse effects, but firm evidence is still lacking. Our aim was to compare the effects of PCT-guided AB therapy with standard of care (SOC) in critically ill patients.

Methods We searched databases CENTRAL, Embase and Medline. We included randomized controlled trials (RCTs) comparing PCT-guided AB therapy (PCT group) with SOC reporting on length of AB therapy, mortality, recurrent and secondary infection, ICU length of stay (LOS), hospital LOS or healthcare costs. Due to recent changes in sepsis definitions, subgroup analyses were performed in studies applying the Sepsis-3 definition. In the statistical analysis, a random-effects model was used to pool effect sizes.

Results We included 26 RCTs ($n = 9048$ patients) in the quantitative analysis. In comparison with SOC, length of AB therapy was significantly shorter in the PCT group (MD -1.79 days, 95% CI: $-2.65, -0.92$) and was associated with a significantly lower 28-day mortality (OR 0.84 , 95% CI: $0.74, 0.95$). In Sepsis-3 patients, mortality benefit was more pronounced (OR 0.46 95% CI: $0.27, 0.79$). Odds of recurrent infection were significantly higher in the PCT group (OR 1.36 , 95% CI: $1.10, 1.68$), but there was no significant difference in the odds of secondary infection (OR 0.81 , 95% CI: $0.54, 1.21$), ICU and hospital length of stay (MD -0.67 days 95% CI: $-1.76, 0.41$ and MD -1.23 days, 95% CI: $-3.13, 0.67$, respectively).

Conclusions PCT-guided AB therapy may be associated with reduced AB use, lower 28-day mortality but higher infection recurrence, with similar ICU and hospital length of stay. Our results render the need for better designed studies investigating the role of PCT-guided AB stewardship in critically ill patients.

Keywords Intensive care, Procalcitonin, Antibiotic therapy, Sepsis

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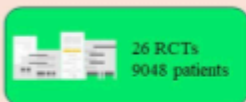


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Procalcitonin-Guided Antibiotic Therapy May Shorten Length of Treatment and May Improve Survival - A Systematic Review and Meta-Analysis



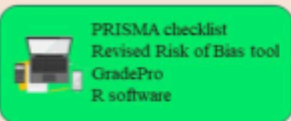
Does procalcitonin (PCT)-guided antibiotic (AB) therapy safely reduce the length of AB treatment in adult critically ill patients compared to standard of care?



26 RCTs
9045 patients



Up to 14 th of Nov,
2022



PRISMA checklist
Revised Risk of Bias tool
GradePro
R software

PCT-guided AB therapy

PCT group



Using a predefined PCT protocol

Standard of care

SOC group



Not including PCT in the treatment
algorithm

		MD/OR [95% CI]
Length of AB therapy	1.79 days lower in PCT group	-1.79 days [-2.65, -0.92]
28-day mortality	16% lower in PCT group	0.84 [0.74, 0.95]
Rate of recurrent infection	36% higher in PCT group	1.36 [1.10, 1.68]

CONCLUSION: PCT-guided AB therapy may be associated with *reduced AB use, lower 28-day mortality but higher infection recurrence, with similar ICU and hospital length of stay*. Our results render the need for better designed studies investigating the role of PCT-guided AB stewardship in critically ill patients.

Introduction

Inappropriate use of antibiotics (ABs) has serious adverse effects. As a result, antibiotic resistance is emerging, causing approximately 700,000 deaths worldwide in 2014 and is predicted to be the leading cause of death world-wide by 2050—accounting for 10 million deaths per year [1]. Critically ill patients in ICU are at high risk of becoming infected with multidrug-resistant organisms (MDRO) due to their acquired immune deficiency, resulting in unacceptably high morbidity and mortality [2].

In general, more than 50% of critically ill patients are considered as infected. Infection and related sepsis can more than double ICU mortality [3]. However, less than 60% of critically ill patients with an initial diagnosis of sepsis are confirmed to be infected [4]. Despite the known challenges in the differential diagnosis of infection and sepsis, there is an urgent constraint to administer ABs shortly after the onset of sepsis and septic shock [5]. This strategy may inevitably result in unnecessary AB therapy, thus increasing the chance of harm and costs associated with AB treatment.

Procalcitonin (PCT) is one of the most studied inflammatory biomarkers [6] and can distinguish bacterial infections from viral infections in critically ill patients [7, 8]. There is growing evidence that PCT-guided AB therapy can safely reduce antimicrobial consumption—by reducing the number of unnecessary or excessively long therapies. The results of a large, individual patient data meta-analysis in 2017 support the use of PCT in the management of AB stewardship in acute respiratory infections in a variety of clinical settings [9]. However, the evidence is less convincing in other types of infection and sepsis.

The PRORATA study was the first big, multicenter RCT to demonstrate the efficacy and non-inferiority of AB management guided by a predefined PCT protocol in septic critically ill patients [10]. Subsequent trials conducted in ICUs used an approach identical with or similar to PRORATA, but PCT levels for starting and stopping thresholds varied, patient populations were also heterogeneous with medical, surgical, or mixed populations treated for different types of infections, and therefore the overall interpretation and implementation of PCT-guided AB therapy in ICU setting remains challenging. Moreover, with the implementation of the new Sepsis-3 definition [11], study inclusion criteria for sepsis and septic shock have also changed in the most recent clinical trials as compared to the definitions previously used for decades [12, 13]. An update

comprehensive analysis of PCT stewardship in ICU set-ting, including Sepsis-3 patients, was lacking.

Therefore, we aimed to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) that investigated the effects of PCT-guided AB therapy compared to standard of care (SOC) in critically ill patients.

Methods

We report our systematic review and meta-analysis based on the recommendations of the PRISMA 2020 guideline [14] (see Additional file 1: Table S1), while we followed the Cochrane Handbook [15]. The protocol of the study was registered on PROSPERO (registration number CRD42022374605), and we adhered to it except for one additional outcome measure (rate of secondary infection) and two subgroup analyses (PCT protocol and patient population).

Eligibility criteria

Applying the PICO (Population, Intervention, Comparator, Outcome) framework, we included RCTs that were conducted in P: adult patients with known or suspected infection treated with antibiotics; I: PCT-guided AB therapy; C: SOC (without PCT use); and they provided data on either of the following, O: length of AB therapy, mortality, rate of recurrent infection (clinically confirmed infection in the same location caused by the same pathogen as the primary one), rate of secondary infection (clinically confirmed infection caused by an organism different from the primary one), length of ICU stay, length of hospital stay and healthcare costs. RCTs conducted in the ICU were included in the quantitative, those conducted in other clinical settings, were included in the qualitative analysis.

Information sources and search strategy

Our systematic search was conducted in three main data-bases—CENTRAL, Embase and Medline—on November 14, 2022. We used the following search key in all data-bases: (sepsis OR septic OR infection) AND (PCT OR procalcitonin) AND (antibiotic* OR antimicrobial OR anti-microbial). Conference papers were excluded.

Selection process and data extraction

Selection was performed by two independent review authors (M.P. and N.K.) using a reference management software

(EndNote 20, Clarivate Analytics). After auto-matic and manual duplicate removal, reviewers screened titles and abstracts, then full texts against predefined eligibility criteria. Data were collected independently by two authors (M.P. and M.B.) on a standardized data extraction sheet. We used Google translate for an article in Chinese [16]. The following data were extracted in addition to the previously mentioned outcomes: digital object identifier, first author, publication year, countries, centers, study period, study population, sepsis definition, age, gender, PCT protocol, protocol adherence, appropriateness of AB therapy, and exclusion criteria.

Subgroup analysis

We planned to perform subgroup analyses to reduce heterogeneity according to the applied sepsis definitions (Sepsis-1 [13], 2 [12] and 3 [11]), PCT protocol (liberal—stop AB if PCT reduced > 80% of the peak value or < 0.5 ng/mL; and conservative—stop AB if PCT reduced > 90% of peak value or < 0.1–0.25 ng/mL or < 1 ng/mL for 3 days) and patient population (medical, surgical and mixed). We considered ventilator-associated pneumonia (VAP) as pulmonary sepsis.

Risk of bias assessment and evidence level

Three authors (M.P., M.B. and D.T.) performed the risk of bias assessment independently using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [17] and GRADE Pro [18] to assess the quality of evidence, with disagreements resolved by another author (C.T.).

Synthesis methods

At least three studies had to be included to perform a meta-analysis. As we assumed considerable between-study heterogeneity in all cases, a random-effects model was used to pool effect sizes.

For dichotomous outcomes, odds ratio (OR) with 95% confidence interval (CI) was used to measure the effect size. Pooled OR based on raw data was calculated using the Mantel-Haenszel method [19, 20]. For continuous outcomes, the difference between means (MD) was used to measure the effect size. To calculate the pooled difference, the sample size, the mean and the corresponding standard deviation (SD) were extracted from each study. If the SD was not provided, but the standard error (SE) or confidence interval was available, we calculated the SD from it. The inverse variance weighting method was used to calculate the pooled MD.

We used a Hartung-Knapp adjustment if it resulted in a more conservative estimate than without adjustment [21, 22]. Results were considered statistically significant if the CI did not include the value zero. We summarized the findings for the meta-analysis in forest plots. Where appropriate, we reported the prediction intervals (i.e., the expected range of effects of future studies) of results. Heterogeneity was assessed using Higgins and Thompson I^2 statistics [23]. All statistical analyses were performed with *R* (R Core Team 2023, v4.2.3) [24], using the *meta* (Schwarzer 2023, v6.2.1) [25] package for basic meta-analysis calculations and plots, and *dmeter* (Cuijpers, Furukawa, and Ebert 2023, v0.0.9000) [26] package for additional influential analysis calculations and plots.

When necessary and possible, model fitting parameters, and potential outlier publications were explored using different influence measures and plots (e.g., leave-one-out analysis for changes in fitted values, Bujat diagnostics values and plots) as recommended by Harrer et al. (2021) [27]. Small study publication bias was assessed by visual inspection of funnel plots and Egger's test (modified Egger's test depends on the type of effect size measures) with 10% significance level [28]. For subgroup analysis, we used a fixed-effects "plu-ral" model (aka. mixed-effects model). We assumed that subgroups had different τ^2 values as we anticipated differences in the between-study heterogeneity in the subgroups, although for practical reasons, if any of the subgroup size was five or less, a common τ^2 assumption was used [29].

Results

Search and selection

Our systematic search resulted in 15,788 eligible articles. After the selection process, 26 articles were included in the meta-analysis [10, 16, 30–53] and 23 articles in the systematic review. The latter included those patients who were treated outside the ICU [54–76]. Figure 1 shows the PRISMA 2020 Flow diagram of the search.

Basic characteristics of included studies

Baseline characteristics of the included studies are detailed in Table 1. Other relevant information is summarized in Additional file 1: Table S2.

We included mainly open-label, parallel group trials. One study had a factorial design [39]. Twenty studies recruited patients with suspected or confirmed infection/sepsis [10, 16, 30–32, 35, 37–48, 51–53], two studies included patients with ventilator-associated pneumonia (VAP) [34, 50]. We also included studies on acute exacerbation of COPD [36], aspiration pneumonia [33], pancreatitis [47] and one study on postoperative (cardiac surgery) patients [49]. PCT protocol was used to stop ABs [16, 30, 31, 34, 35, 37–40, 42, 43, 45, 50–53], to start ABs [41, 46, 49] or both [10, 32, 33, 36, 44, 47, 48]. Two studies [32, 43] used a predefined C-reactive protein (CRP) protocol in the control arm, all others used current AB guidelines.

Primary outcome: length of antibiotic therapy

A meta-analysis of 21 RCTs [10, 16, 30, 31, 33–36, 38–40, 42–45, 47, 48, 50–53] with a total of 6669 patients revealed that the duration of AB therapy was reduced in the PCT-guided group compared to the SOC group (MD – 1.79 days, 95% CI: – 2.65, – 0.92, $p < 0.001$) (see Additional file 1: Figure S1).

This significantly reduced AB length was observed in Sepsis-1 patients (MD – 2.58 days, 95% CI: – 3.87, – 1.29, $p = 0.004$) (Fig. 2A), whether a conservative or liberal PCT protocol was used (MD – 1.56 days, 95% CI: – 2.93, – 0.18, $p = 0.03$ vs. – 2.37 days, 95% CI: – 4.23, – 0.51, $p = 0.02$) (Fig. 2B) and in the 100% medical patient population (MD – 1.87 days, 95% CI: – 3.36, – 0.37, $p = 0.019$) (Fig. 2C). In the Sepsis-3 cohort, the difference was non-significant (– 3.01 days, 95% CI – 7.72, 1.69).

28-day, ICU and in-hospital mortality

The odds of 28-day mortality and in-hospital mortality was reduced in PCT guidance compared to SOC, the former being statistically significant (OR 0.84, 95% CI: 0.74, 0.95, $p = 0.008$ (Additional file 1: Figure S2) and OR 0.85, 95% CI: 0.66, 1.10 (Additional file 1: Figure S3), respectively). There was no difference in ICU mortality between the two groups (OR 1.00, 95% CI: 0.74, 1.36) (Additional file 1: Figure S4).

This significantly reduced 28-day mortality was observed in Sepsis-2 and Sepsis-3 patients (OR 0.86, 95% CI: 0.76, 0.97, $p = 0.024$ and OR 0.46, 95% CI: 0.27, 0.79, $p = 0.026$, respectively) (Fig. 3A), applying liberal PCT protocol (OR 0.75, 95% CI: 0.59, 0.95, $p = 0.024$) (Fig. 3B) and in medical patients (OR 0.76, 95% CI: 0.60, 0.97, $p = 0.033$) (Fig. 3C).

Recurrent and secondary infection

Infection recurrence was observed in 99 out of 2,070 patients in the PCT group and in 75 out of 2,080 patients in the SOC group, indicating a significant difference (OR 1.36, 95% CI: 1.10, 1.68, $p = 0.008$) (Fig. 4). There was no significant difference in the rate of secondary infections (OR 0.81, 95% CI: 0.54, 1.21) (Fig. 5).

Length of ICU stay, length of hospital stay and healthcare costs

Length of ICU stay and length of hospital stay were non-significantly reduced in the PCT group compared to the SOC group (MD – 0.67 days 95% CI: – 1.76, 0.41 and MD – 1.23 days, 95% CI: – 3.13, 0.67, respectively) (Additional file 1: Figures S5 and S6). Due to the highly heterogeneous reporting of healthcare costs, we used

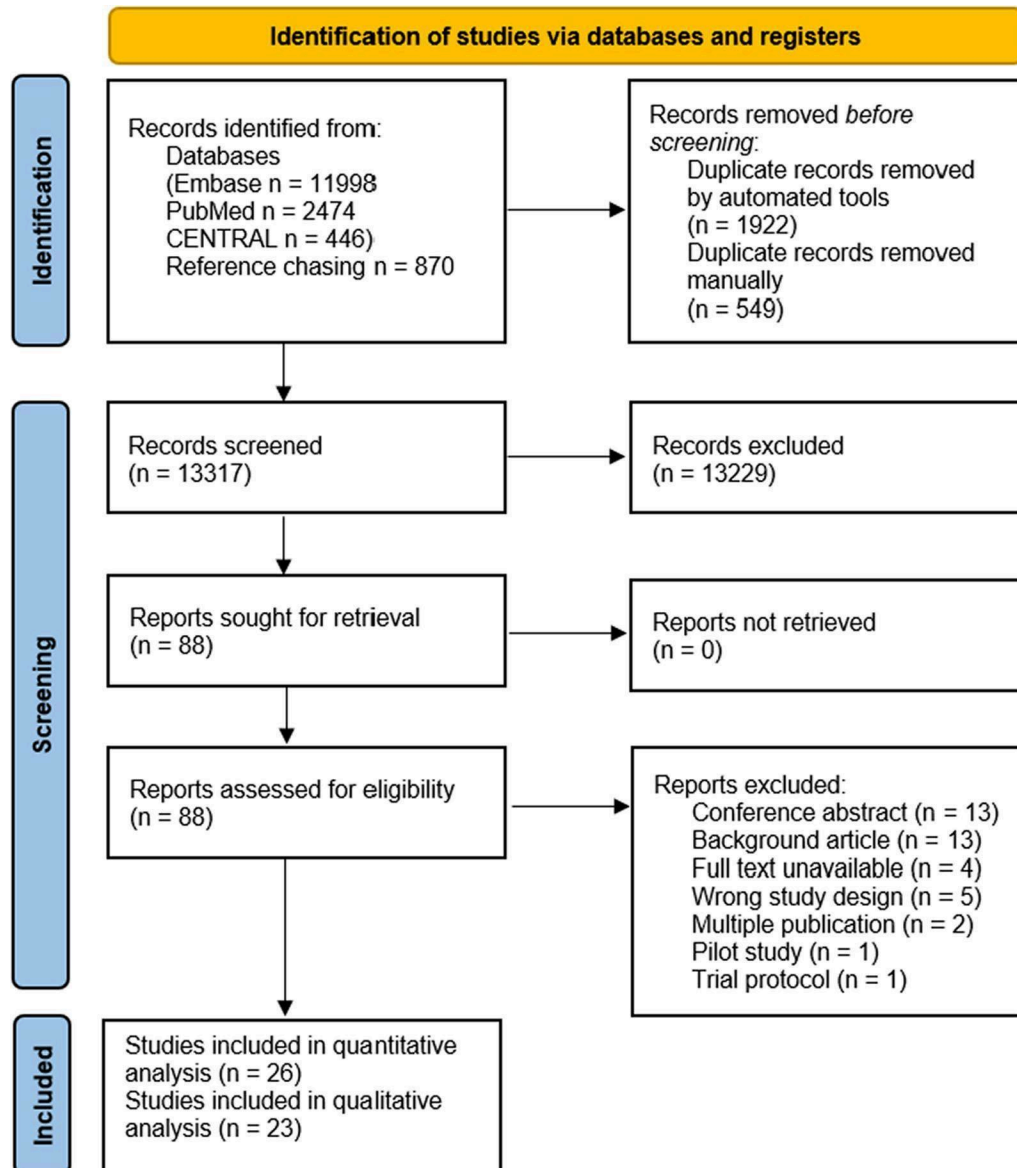


Fig. 1 PRISMA 2020 flowchart representing the study selection process non-comprehensive method in the analysis, with results favoring PCT use (Additional file 1: Figure S7).

Risk of bias and GRADE assessment

Two trials had high overall ROB due to missing outcome data [34, 35], whereas 23 trials had some concerns about ROB assessment due to deviations from intended intervention (PCT protocol violations) or the lack of reporting it [10, 16, 30–33, 36–41, 43–53]. Only one trial had over-all low ROB [42]. For assessing publication bias, funnel plots can be found in the supplementary material (Additional file 1: Figure S8 (a–f)).

Certainty of evidence proved to be high for length of AB therapy and 28-day mortality. Moderate results were observed for in-hospital mortality, ICU mortality, rate of recurrent infection and rate of secondary infection, while GRADE was low for length of ICU stay and length of hospital stay and very low for healthcare costs. ROB and GRADE results are shown in the respective forest plots.

Discussion

In our meta-analysis, we analyzed 26 RCTs [10, 16, 30–53] with a total of 9,048 patients, comparing the effects of PCT-guided AB therapy with standard of care on length

Table 1 Characteristics of studies included

Study author	Country (centers)	Sample size (female% in PCT/ control arm)	Clinical setting	Patient population	Age ^a in PCT/control arm
Kyriazopoulou et al., [30]	Greece (7)	256 (59/54)	ICU ^b	Medical patients with sepsis	80 ± 10 / 78 ± 13
Ali et al., [32]	Egypt (1)	60 (43/47)	ICU	Patients with sepsis	57 ± 1 / 56 ± 2
Vishalashi et al., [31]	India (1)	90 (51/36)	ICU	Medical/surgical (41/59%) patients with sepsis	42 ± 17 / 47 ± 16
Labro et al., [33]	France (5)	159 (35/47)	ICU	Mechanically venti-lated medical patients with coma	54 ± 18 / 52 ± 17
Lhopitallier et al., [54]	France (60)	469 (65/53)	primary care	Medical patients with pneumonia	53 ± 18 / 50 ± 18
Mazlan et al., [34]	Malaysia (1)	85 (37/55)	ICU	Medical patients with VAP	49 ± 17 / 53 ± 17
Jeon et al., [35]	South-Korea (4)	52 (67/52)	ICU	Medical patients with sepsis	69 (61–75) / 70 (63–77)
Montassier et al., [56]	France (12)	285 (44/38)	ED	Medical patients with CAP	67 (46–83) / 67 (47–81)
O’Riordan et al., [55]	Ireland (1)	119 (39/58)	respiratory ward	Medical patients with LRTI	69 ± 14 / 68 ± 15
Daubin et al., [36]	France (11)	302 (29/34)	ICU	Medical patients with AECOPD	67 (61–76) / 67 (61–75)
Kip et al., ^c [37]	Netherlands (15)	1546 (39/40)	ICU	Medical patients with sepsis	65 (54–75) / 65 (57–75)
van der Does et al., [58]	Netherlands (2)	551 (48/44)	ED	Medical patients with fever	61 (43–70) / 62 (44–73)
Huang et al., [57]	USA (14)	1656 (57/57)	ED	Medical patients with LRTI	53 ± 18 / 53 ± 19
Liu et al., [38]	China (1)	98 (45/41)	ICU	Patients with sepsis	66 ± 9 / 65 ± 10
Xu et al., [16]	China (1)	156 (43/43)	ICU	Patients with sepsis	67 ± 9 / 65 ± 9
Slieker et al., [60]	Switzerland (1)	162 (42/43)	Surgical ward /ICU (88/12%)	Surgical patients with peritonitis	56 [36–73] / 57 [36–71]
Mahmutaj et al., [59]	Kosovo (1)	100 (32/38)	surgical ward	Surgical patients with acute abdomen	39 ± 20 / 47 ± 19
Ulm et al., [61]	Germany (10)	227 (54/57)	neurology ward	Medical patients after ACM stroke	76 ± 12 / 76 ± 11
Corti et al., [62]	Denmark (1)	120 (66/55)	ED	Medical patients with AECOPD	72 (64–80) / 73 (61–78)
Bloos et al., [39]	Germany (33)	1089 (NA)	ICU	Medical/surgical (43/57%) patients with sepsis	NA
Lima et al.,(77)	Brazil (1)	61 (44/52)	haematologic ward	medical patients with febrile neutropenia (FN)	36 (26–53.8) / 33 (26.50)
Branche et al., (78)	USA (1)	150 (58/54)	general ward	medical patients with non-pneumonic LRTI	61 (51–72) / 64 (50–74)
Drozдов et al., (79)	Switzerland (1)	125 (70/81)	ED	medical patients with non-catheter-related UTI	71 (44–81) / 75 (51–80)
Verduri et al., (80)	Italy (18)	178 (13/14)	respiratory ward	medical patients with AECOPD	74 (69–78) / 73 (65–78)
Najafi et al., (66)	Iran (1)	60 (33/40)	ICU	medical/surgical (88/12%) patients with SIRS	40±18 / 41±21
Annane et al., (54)	France (8)	58 (20/32)	ICU	medical/surgical patients (97/3%) with suspected sepsis	59 (40–67) / 54 (46–73)
Deliberato et al., (55)	Brazil (1)	81 (43/46)	ICU	patients with sepsis	68±21 / 62±19
Tang et al., (82)	China (1)	260 (50/54)	ED	medical patients with acute exacerbation of asthma	54±14 / 55±15
Layios et al., (62)	Belgium (1)	509 (48/39)	ICU	medical/surgical patients (60/40%) with suspected	66 (55–76) / 65 (53–75)

				sepsis	
Qu et al., (56)	China (1)	71 (29/28)	ICU	medical patients with acute pancreatitis	43±11 / 44±11
Jensen et al., (57)	Denmark (9)	1200 (65/64)	ICU	medical/surgical patients (59/41%) with sepsis	67 (58-76) / 67 (58-75)
Long et al., (83)	Japan (1)	162 (40/38)	ED	medical patients with CAP	44±16 / 47±19
Maravić-Stojković et al., (67)	Serbia (1)	205 (30/33)	ICU	patients after open heart cardiac surgery	60±9 / 60±10
Burkhardt et al., (84)	Germany (15)	550 (60/59)	primary care	medical patients with respiratory tract infection	41±15 / 43±16
Bouadma et al., (11)	France (7)	621 (33/35)	ICU	medical/surgical patients (89/11%) with suspected bacterial infection	61±15.2 / 62±15
Stolz et al., (58)	Switzerland, USA (7)	101 (25/26)	ICU	medical/surgical (52.5/47.5%) patients with VAP	53 [21-88] / 59 [18-83]
Kristoffersen et al., (85)	Denmark (3)	210 (48/46)	general ward	medical patients with suspected LRTI	67±18 / 67±16
Hochreiter et al., (59)	Germany (1)	110 (49/ 46)	ICU	surgical patients with sepsis	67±14 / 67±16
Schuetz et al., (86)	Switzerland (6)	1359 (40/45)	ED	medical patients with LRTI	73 (59-82) / 72 (59-82)
Briel et al., (87)	Switzerland (53)	458 (58/62)	primary care	medical patients with respiratory tract infection	48±18 / 48±18
Schroeder et al., (60)	Germany (1)	27 (43/46)	ICU	surgical patients with severe sepsis	69±11 / 68±14
Nobre et al., (61)	Switzerland (1)	68 (32/32)	ICU	medical/surgical (75/25%) patients with sepsis	64±12 / 70±14
Stolz et al., (88)	Switzerland (1)	208 (51/59)	ED	medical patients with AECOPD	70 (65-77) / 70 (65-79)
Christ-Crain et al., (89)	Switzerland (1)	302 (38/38)	ED	medical patients with CAP	70±17 / 70±17
Christ-Crain et al., (90)	Switzerland (1)	243 (46/49)	ED	medical patients with LRTI	63±20 / 65±17

^a presented as mean ± SD, median (IQR), median [range], ^b patients treated on wards under advanced supportive care because shortage of ICU beds, ^c cost-effectiveness analysis of de Jong et al., 2016; abbreviations: AECOPD—acute exacerbation of chronic obstructive pulmonary disease, CAP—community acquired pneumonia, ED—emergency department, ICU—intensive care unit, LRTI—lower respiratory tract infection, NA—not available, UTI—urinary tract infection, VAP—ventilator-associated pneumonia

of AB therapy, mortality, rate of recurrent and secondary infections, length of hospital and ICU stay and healthcare costs.

Length of AB therapy

Our study confirms the findings of previous meta-analyses [77, 78] that PCT-guided AB therapy, including AB cessation rules can significantly reduce the length of AB therapy in ICU patients. An interesting finding in our study was that the three different sepsis definitions had an impact on the results, with significantly shorter AB therapy in the PCT group in the Sepsis-1 cohort and non-significant results in Sepsis-2 and 3 cohorts. Although the mean difference was by far the largest in Sepsis-3 patients [30, 31, 34], the results lacked statistical significance. The relatively low sample size of Sepsis-3 patients compared to other sepsis cohorts could be an explanation for the lack of significant results. On the other hand, five out of nine trials in the Sepsis-2 cohort used conservative PCT protocols, two of them [43, 48] demonstrated even longer AB duration in the PCT group, which may also have contributed to the observed smaller effect on AB length in this patient population.

We further classified the trials into two subgroups (liberal and conservative) depending on the stopping rule in the PCT group except for three trials [39, 51, 52] that used a very unique protocol and studies using only start-ing rules that did not report this outcome [41, 46, 49]. Our analysis overtly suggests that a liberal PCT protocol may result in shorter AB duration compared with a conservative one. Furthermore, protocol adherence was very low (40–50%) in three trials of the group using the liberal protocol [10, 35, 40], so the

difference could have been larger with fewer protocol violations.

Our results show that in mixed populations (the proportion of surgical patients is at least 25%), the length of AB therapy is slightly longer than in medical patients. Apart from one study with different PCT cut-offs for patients during the 48-h postoperative period [44], the trials included used the same protocol regardless of the population. PCT values can be elevated after surgery even in the absence of infection [79], and the use of abso-lute PCT stopping thresholds in these cases might result in AB overuse. Data on populations including only surgi-cal patients were insufficient for meta-analysis, but pool-ing data from two surgical cohorts [51, 52] results in an even more pronounced reduction in the length of AB therapy. This may be explained by the high absolute stop-ping threshold (1 ng/mL) used in the study protocols.

28-day, in-hospital and ICU mortality

Our results suggest that 28-day and in-hospital mortality is lower in the PCT group than in the SOC group. However, results are conflicting, as some trials showed survival benefit [30, 40], and some others did not [10, 43, 48]. This contradiction may be partially resolved by our results, namely that mortality benefit is only observed in Sepsis-2 and Sepsis-3 patients, medical patients and tri-als using liberal PCT protocol, all of which are associated with shorter AB duration. Unfortunately, our results do not allow us to explain the relationship between AB therapy duration and mortality. Nevertheless, several studies have shown the potential harmful effects of ABs. These include direct toxic

effects and organ injury [80], development of AB resistance and potentially higher chances of secondary infections, mostly caused by MDRO [1], mitochondrial dysfunction associated with ABs [81] and injury and collapse of the microbiome [82]. Moreover, an initial low PCT value can help the differential diagnosis, thereby optimizing patient care and reducing mortality.

Recurrent and secondary infections

Theoretically, too short course of ABs could risk infection recurrence, while overuse of ABs is a risk for secondary infections. Our data show significantly higher recurrence of infection in the PCT group, which contradicts the latest meta-analysis [77]; however, they included mostly non-ICU patients with respiratory tract infections. We share the view of the open-label SAPS trial group [40] that bias cannot be excluded, as clinicians might think

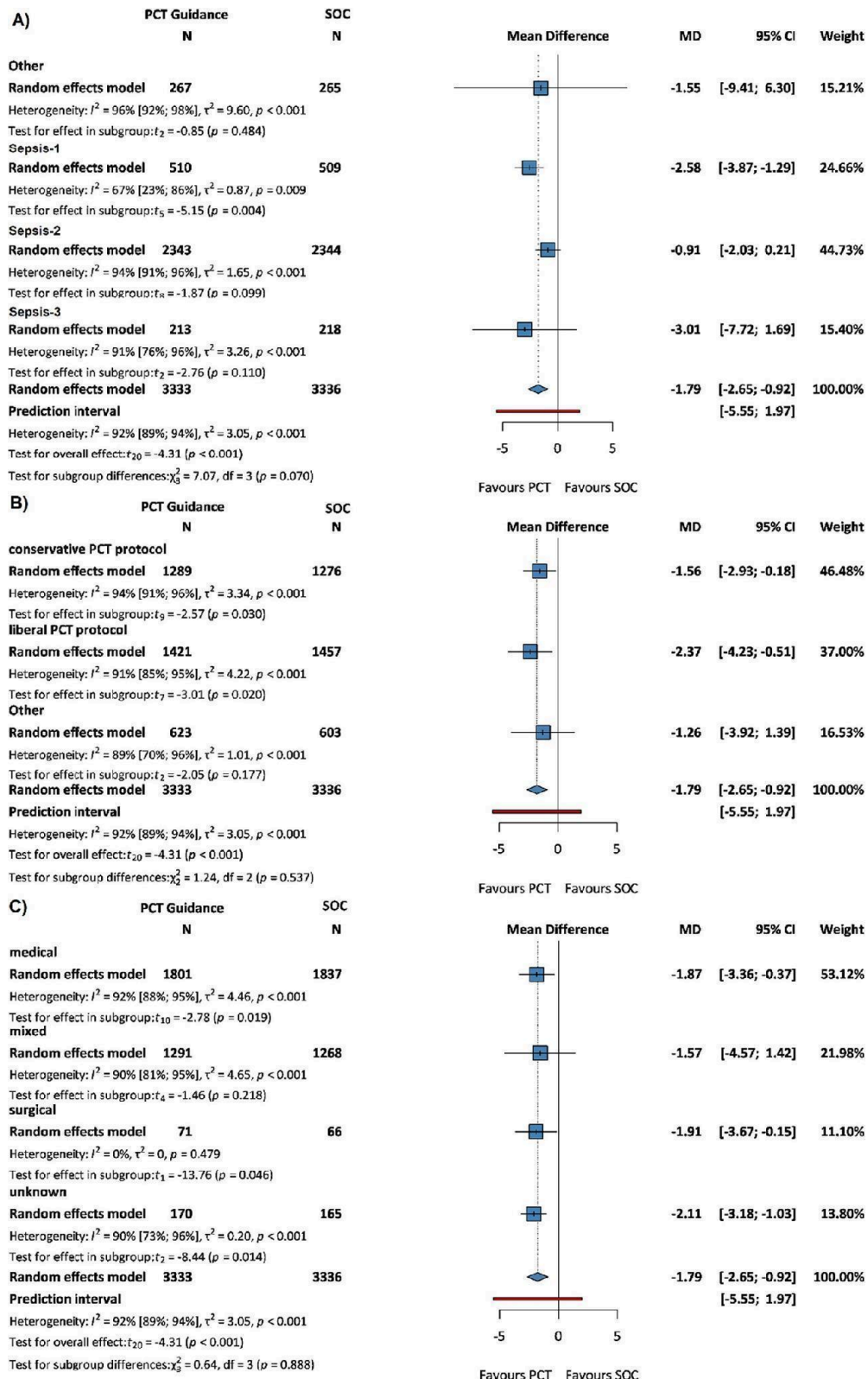


Fig. 2 Forest plots representing the mean difference in length of AB therapy in A sepsis subgroups, B PCT protocol subgroups, and C patient population subgroups

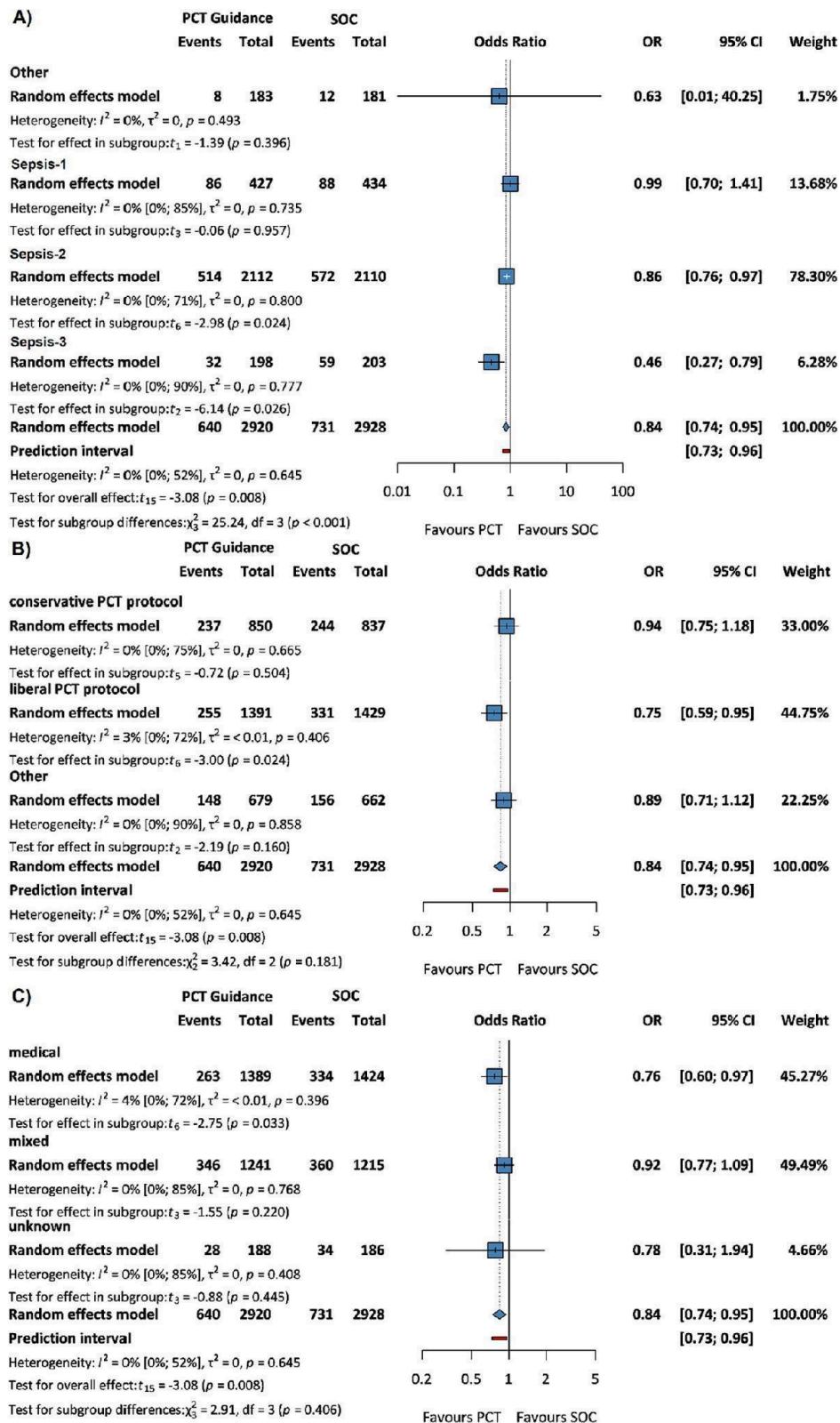


Fig. 3 Forest plots representing the odds of 28-day mortality in A sepsis subgroups, B PCT protocol subgroups, and C patient population subgroup

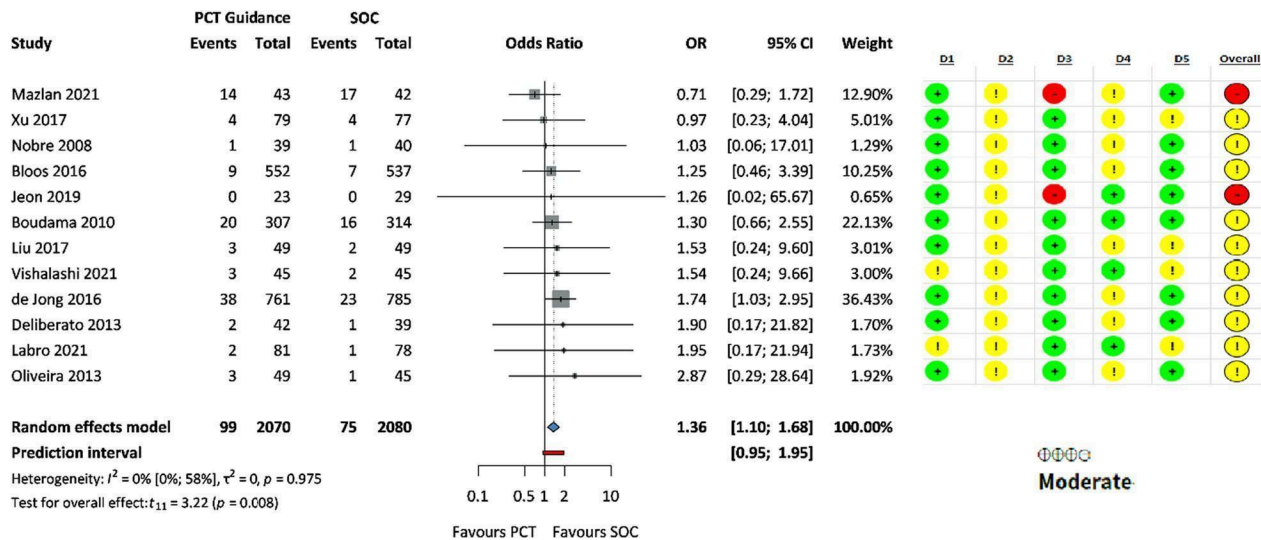


Fig. 4 Forest plot representing the odds of recurrent infection

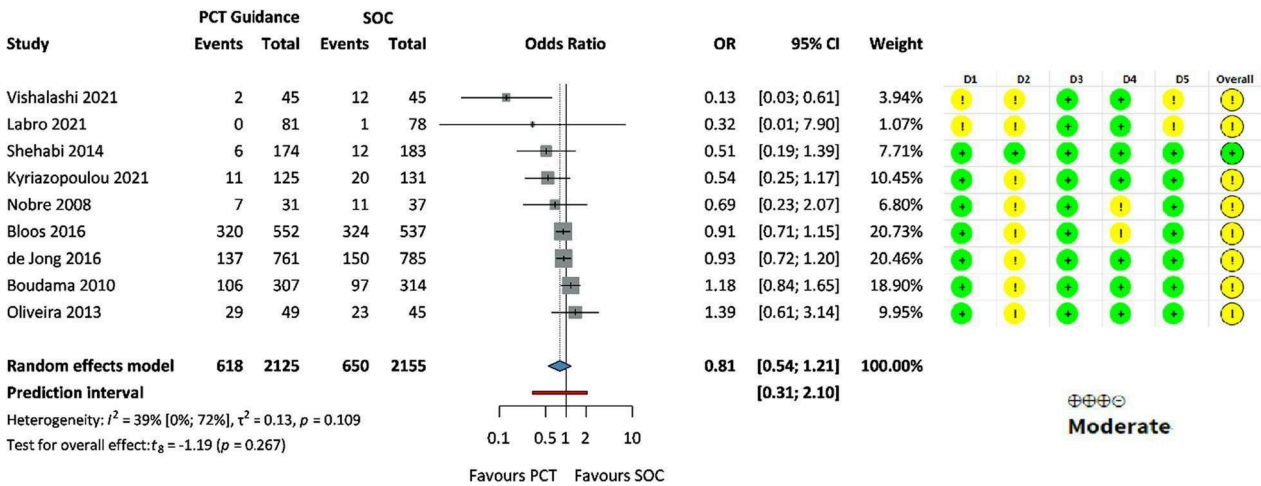


Fig. 5 Forest plot representing the odds of secondary infection

of a reinfection sooner in the PCT group. The results on secondary infections are conflicting; hence, PCT guidance had uncertain effects on this outcome.

Length of ICU stay, length of hospital stay, healthcare costs

Higher infection recurrence rate did not result in excessive ICU and in-hospital stay in the PCT group, which is consistent with the previous meta-analysis in septic ICU patients [78]. Despite the high heterogeneity in cost-effectiveness reports, our results suggest that PCT guidance at least does not appear to be inferior to SOC, but further research is needed to draw firm conclusions about this outcome.

PCT-guided AB therapy outside the ICU

We included 23 RCTs [54–76] in our review. Eighteen studies recruited patients with respiratory tract infections treated in ED [56, 57, 62, 64, 68, 69, 72, 74–76], general ward [55, 61, 66, 67, 71] or primary care [54, 70, 73]. Two trials included patients with peritonitis [59, 60] and one study each included patients with fever [58], febrile neutropenia [63] and urinary tract infection (UTI) [65]. Some studies used additional diagnostics: thoracic ultrasound [54] or viral PCR [64]. In studies on respiratory tract infection, AB use was either reduced in the PCT group or similar between study arms with no difference in adverse outcomes. In patients with peritonitis, Mahmutaj et al. reported a significant reduction in AB use in the PCT arm without an elevated risk of infection recurrence [59]. Sliker

et al. in a similar trial reported no adverse outcomes associated with non-significantly reduced AB treatment duration [60]. An approach based on PCT and pyuria in UTI patients [65] reduced AB exposure by 30% without adverse effects, whereas in febrile neutropenia, [63] PCT had no effect on AB use.

Strengths and limitations

To the best of our knowledge, this meta-analysis contains the largest number of studies to date, all of which are RCTs. We are also the first to perform subgroup analyses based on sepsis definitions, patient populations, and PCT protocols: our results provide some support that recruiting patients into studies according to the Sepsis-3 definition may have an impact on outcomes; that surgical and medical patients may require separate treatment protocols; and conservative guidance is not superior to a liberal strategy. Finally, we rigorously followed all Cochrane Collaboration guidelines, thereby ensuring maximum quality, transparency, and reproducibility of the results.

Our meta-analysis has certain limitations. First, in the control arm, SOC was not “standardized” as different AB guidelines were applied in different institutions that could potentially result in longer duration of AB therapy in some regions, thus overestimating the effect of PCT guidance. Second, “PCT guidance” does not mean a standard approach, as studies applied different PCT protocols: 16 out of 26 included studies used PCT protocol to stop ABs, 3 used PCT protocol to start ABs, while 7 used PCT guidance for both starting and stop-ping AB therapy. Furthermore, not all studies reported

on all outcomes. The source of infection varied between the studies and the number of patients with septic shock ranged between 7 and 87%, indicating a huge variability in severity of patient populations on the one hand and, on the other hand, a possible impact on outcomes cannot be excluded according to the 15 studies reporting PCT protocol adherence, which ranged between 44 and 97%. Furthermore, AB appropriateness could have an important effect on outcome. However, we do not know whether patients received appropriate or inappropriate ABs in the same or similar proportion in the PCT-guided and control groups as this outcome was only reported in 5 studies in which the groups were well balanced in this regard [10, 30, 35, 45, 50], but we still cannot draw conclusions on this topic. Finally, almost all studies excluded immunocompromised patients in their medical history; therefore, the generalizability of our results is limited.

Implications for practice and research

The rapid application of scientific results is of utmost importance [83, 84]. Our results suggest that PCT-guided AB management could reduce the length of AB therapy in ICU patients, especially in countries and institutes where routine AB administration exceeds 7 days.

The current sepsis guideline [5] recommends against the use of PCT and clinical evaluation to decide when to start AB therapy in septic patients. However, we believe that further research is needed in this field, especially to evaluate PCT kinetics (i.e., changes in 12–24 h) compared to protocols based on a fixed value (i.e., 0.5 ng/mL as cut off) [79, 85]. Furthermore, the increased rate of recurrent infections, the difference between medical and surgical patients and finally testing whether a liberal or a conservative regime is more beneficial should also deserve further investigations. We also suggest that in future trials, “organ support free days” should be used as the primary outcome [86] rather than mortality, which is affected by a number of confounding factors during the full course of a critical illness; therefore it may not necessarily reflect the efficacy of a particular intervention. Finally, we need data on immunocompromised patients who may also benefit from this approach.

Conclusion

PCT-guided AB therapy may be associated with reduced AB use, lower 28-day mortality but higher infection recurrence, with similar ICU and hospital length of stay. Our results render the need for better designed studies investigating the role of PCT-guided AB stewardship in critically ill patients.

Abbreviations

AB	Antibiotic
ABs	Antibiotics
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
CAP	Community acquired pneumonia
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
ED	Emergency department
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICU	Intensive care unit
LOS	Length of stay
LRTI	Lower respiratory tract infection
MD	Mean difference
MDRO	Multidrug-resistant organism
OR	Odds ratio
PCR	Polymerase chain reaction
PCT	Procalcitonin
RCT	Randomized controlled trial
RCTs	Randomized controlled trials
ROB	Risk of bias
SD	Standard deviation
SE	Standard error
SOC	Standard of care
SOFA	Sequential organ failure assessment or Sepsis-related organ failure assessment
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-023-04677-2>.

Additional file1: Table S1 Prisma Checklist 2020. Table S2 Other characteristics of included studies. Figure S1 Length of AB therapy. Figure S2 28-day mortality. Figure S3 In-hospital mortality. Figure S4 ICU mortality. Figure S5 Length of ICU stay. Figure S6 Length of hospital stay. Figure S7 Healthcare costs. Figure S8 (a-f) Funnel plots.

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Not applicable.

Author contributions

MP contributed to conceptualization, investigation, writing—original draft; MB contributed to investigation, writing—review and editing; NK contributed to investigation, writing—review and editing; DT contributed to conceptualization, supervision, investigation, writing—review and editing; LZ contributed to conceptualization, supervision, writing—review and editing; FP contributed to conceptualization, statistical analysis review and editing; HA

contributed to statistical methodology, writing—review and editing; CT contributed to methodology, supervision, writing—review and editing; PH contributed to supervision, project administration, funding acquisition, writing—review and editing; ZM contributed to conceptualization, project administration, supervision, writing—original draft.

All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

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Availability of data and materials

The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

Declarations

Ethics approval and consent to participate

No ethics approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct or interpretation of our study.

Competing interests

The authors declare no competing interests.

Consent for publication

Not applicable.

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KInetics of Procalcitonin to Reduce Unnecessary aNtibiotic use (KIPRUN): protocol for a multicentre, randomised, superiority trial to compare the efficacy and safety of procalcitonin kinetics-guided and absolute procalcitonin value-guided antibiotic initiation in critically ill patients

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ABSTRACT

Introduction Appropriate antibiotic (AB) therapy remains a challenge in intensive care units (ICUs). Guidelines recommend against using procalcitonin (PCT) to guide the initiation of AB therapy, although with low certainty and a very low level of evidence. Recent studies suggest that changes in PCT levels may be more accurate than a single measurement; however, this has never been tested in a randomised trial.

Methods and analysis In this multicentre,

randomised controlled trial (RCT), we aim to compare the efficacy and safety of two different PCT protocols for initiating AB therapy. Hemodynamically stable, critically ill adult patients with suspected new-onset infection at admission or during ICU stay will be randomised in a 1:1 ratio. In the treatment arm (Kinetics Group, KG), initiation of AB treatment is strongly recommended if PCT ≥ 0.5 ng/mL and increases by more than 100% compared with the previous day. In the control arm (Absolute Group, AG), the initiation of AB treatment is strongly recommended if PCT ≥ 0.5 ng/mL. The primary outcome will be the rate of unnecessary AB therapy: 72 hours after recruitment, an independent intensivist, microbiologist and infectologist will determine whether the therapy was necessary, using all relevant clinical, microbiological and radiographic results. If no consensus is reached, a decision will be made by secret vote. We plan to enrol 250 participants in the study, with 80% statistical power and a 5% alpha level.

Ethics and dissemination Ethics approval was obtained from the National Centre for Public Health and Pharmacy (BM/20019/2025). We plan to present our results at relevant national and international conferences and meetings and to submit them for publication in a peer-reviewed journal. Moreover, we plan to disseminate the results to important stakeholders in the Hungarian healthcare system.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Prospective, randomised, controlled, multicentre study.
- Planned interim analysis due to safety, efficacy reasons and sample-size reestimation.
- Healthcare providers cannot be blinded to the intervention due to the nature of the trial.
- Suspicion of a new-onset infection can be arbitrary, although this is common practice.
- Centres can use different types of procalcitonin (PCT) assays with different performance.

Trial registration number This is the first version of the trial protocol, prepared in accordance with the SPIRIT 2025 guideline (version 1.0, dated 30 September 2025). The trial has been registered on ClinicalTrials.gov ([NCT07211620](https://clinicaltrials.gov/ct2/show/study/NCT07211620)).

BACKGROUND

Appropriate antibiotic (AB) therapy remains a significant challenge in intensive care units (ICUs). More than 50% of critically ill patients are considered potentially infected, and infection alone can double mortality¹; however, infection is later confirmed in less than 60% of patients admitted with

an initial diagnosis of sepsis.² Previous studies have shown that at least one in five patients in ICUs receives unnecessary ABs,^{2–3} leading to the well-known adverse effects of ABs without any benefit. The emergence of AB resistance has been associated with 700 000 avoidable deaths in 2014, and the WHO estimates that it will contribute to 10 million deaths by 2050.⁴ Procalcitonin (PCT) is one of the most frequently studied inflammatory biomarkers. Several randomised controlled trials (RCTs) and meta-analyses have concluded that PCT-guided AB treatment can reduce the duration of AB therapy without adverse effects; moreover, it may be associated with a lower 28-day mortality rate, a finding also confirmed by our 2023 study.⁵ Accordingly, the current sepsis guideline from 2021 recommends a combined evaluation of the clinical picture and PCT when discontinuing AB therapy.⁶ However, it contains a weak recommendation against using PCT to initiate treatment, supported by a ‘very low’ level of evidence. The latter proposition is based on three studies,^{7–9} two of which included a significant number of surgical patients (approximately 40%),^{7–8} in whom the applied PCT cut-off (0.5–1 ng/mL) was presumably too low, supported by several previous studies.^{10–11} Therefore, the overuse of ABs was, to some extent, the inevitable consequence of the study design.

Despite the lack of strong recommendations in the guidelines, there is an urgent need to optimise the initiation of ABs at the bedside. Expert panel opinions based on literature reviews recommend a fixed PCT value, which generally reflects the clinical practice of most practitioners.¹² However, the fundamental problem with guiding AB initiation based on a fixed value of PCT (ie, an intervention threshold of 0.5 or 1.0 ng/mL) is that, on the one hand, PCT reflects the response of the individual host, which causes great variability between patients, and, on the other hand, PCT levels may also rise after non-infectious insults, such as trauma, sterile inflammation as well.¹³ Therefore, using an absolute value as a starting criterion may lead to overtreatment. However, PCT kinetics, ie, an 80–90% decrease in peak values, have been shown to reduce the duration of AB therapy by a median of 2 days, with a significant mortality benefit,¹⁴ and have prognostic value, as shown in the MOSES study.¹⁵ Theoretically, early kinetics, that is, the increase in PCT over a given period, may also indicate a new-onset infection in an ICU patient, although this requires daily PCT measurement in every patient, which can theoretically entail a significant financial burden and, in some cases, additional blood sampling. However, robust economic data from the USA indicate that PCT protocols for acute respiratory infections are associated with substantial savings, mainly through reductions in unnecessary AB use.¹⁶ This concept has been supported by two observational studies, which suggest that a roughly twofold increase in PCT from the preceding day to the day of a new suspected infection yields a mean area under the curve of 0.85 for predicting infection.^{17–18} However, this concept has never been tested in an RCT.

AIM OF THE STUDY

The study aims to compare the efficacy and safety of an absolute PCT value-guided AB initiation protocol (AG) with

a protocol based on the kinetics of PCT (defined as

the ratio of the value on the current day and that of the previous day, KG) in hemodynamically stable, critically ill patients with suspected new-onset infection. We hypothesise that we can safely reduce the number of unjustified AB therapies in the KG, thereby minimising the adverse effects of ABs and reducing the emergence of AB resistance, which is a separate risk factor for mortality in nosocomial infections compared with infections caused by non-antimicrobial-resistant strains.^{1–19}

METHODS AND ANALYSIS

Study design

The KINetics of Procalcitonin to Reduce Unnecessary antibiotic use (KIPRUN) study is designed per the SPIRIT 2025 statement: updated guideline for protocols of randomised trials.²⁰ The KIPRUN study will be a prospective, randomised, controlled, two-arm (1:1 ratio), parallel-group superiority trial.

Study setting

The KIPRUN study is a national, multicentre study conducted in public hospitals and academic centres in Hungary. The study will take place in adult ICUs. The list of study sites is available on clinicaltrials.gov (NCT07211620).

Randomisation

Participants will be randomly assigned in a 1:1 ratio to one of the intervention groups, according to a computer-generated randomisation schedule stratified by site. We will use the simple randomisation module of REDCap for this purpose.²¹ Personnel responsible for enrolling patients and assigning participants to interventions will not have access to the random allocation sequence.

Blinding

Trial participants and their relatives will be blinded after assignment to interventions, as will the outcome assessors (members of the multidisciplinary team who will assess the primary outcome) and the data analysts. Patients will know whether they are receiving ABs, but the rationale for this will remain hidden. Unblinding of participants during the study period is not permitted. The treating physician will be aware of the assignment group, as the physician in charge must decide whether to start AB treatment based on the allocation group. However, other healthcare personnel (eg, nurses, physiotherapists) will also be blinded.

Duration

After randomisation (t_0), the study will begin for both groups. Laboratory measurements will be performed daily. Within 72 hours after randomisation, a multidisciplinary team reassesses the initial decision based on the available clinical and laboratory data and informs the treating physician of the decision. Based on this, the ongoing therapy should be continued, discontinued or changed.

Patients will be followed for at least 28 days, or until hospital discharge or death (whichever occurs first). The study is scheduled to start on 1 December 2025, with an anticipated duration of 2 years

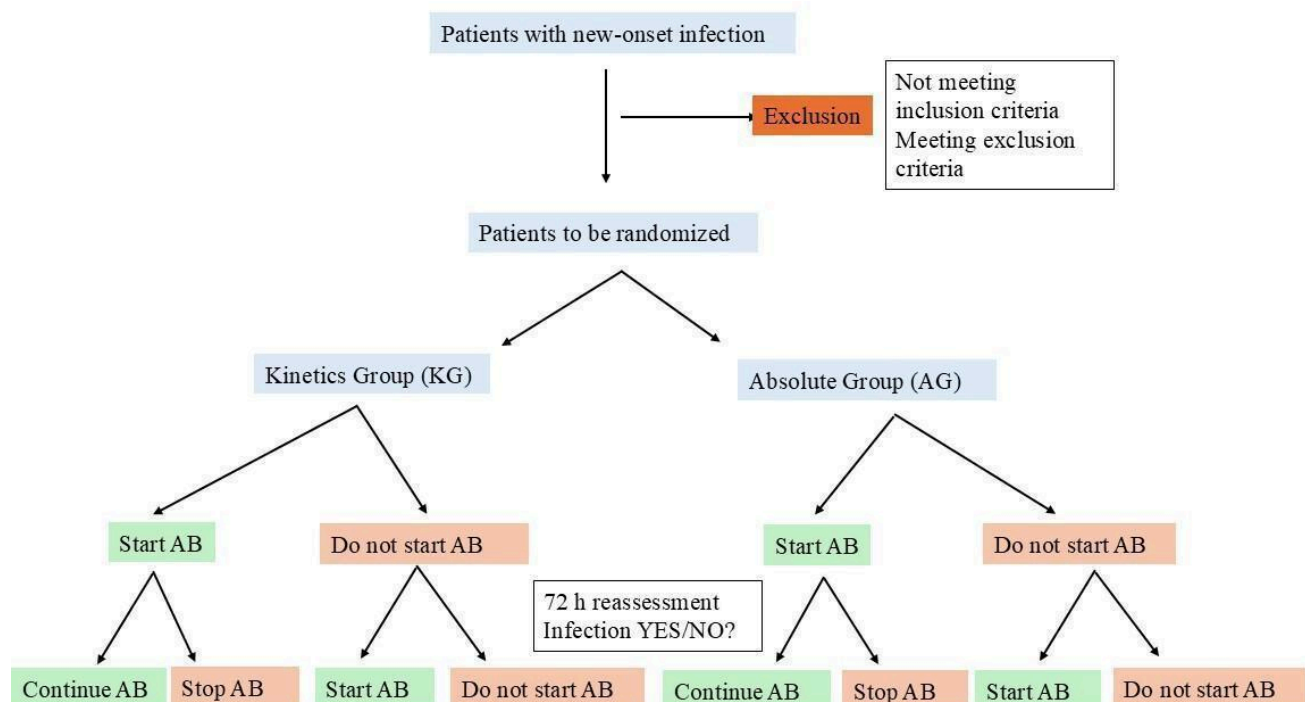


Figure 1 Flow chart of the interventions. The figure presents the two arms of the study (KG and AG) and the reassessment after 72 hours of therapy. AB, antibiotic.

Study groups

Patients eligible for the study will be randomly assigned to one of the two study groups (KG and AG). A predefined PCT protocol will guide the initiation of ABs in both groups. In the KG, starting ABs is strongly recommended if PCT ≥ 0.5 ng/mL and shows a PCT elevation of $\geq 100\%$ compared with the previous day's value. In the AG, starting ABs is strongly recommended if PCT ≥ 0.5 ng/mL (figure 1).

The treating physician, in collaboration with the ward's infectious disease specialist, will select the AB regimen based on national and international guidelines, patient characteristics and local AB resistance profiles, and may modify the initial AB therapy if deemed necessary.

AB therapy is initiated according to protocol in both groups, but the treating physician may overrule it. In such cases, the reasons for overruling must be documented in detail. In previous trials, septic shock was the primary reason for protocol non-adherence, with protocol overruling rates reaching up to 50%. As our study population will be haemodynamically stable, we anticipate a high rate of protocol adherence, estimated at 80–90%.^{22 23}

PATIENT ENROLMENT

Eligibility criteria

All adult (≥ 18 years) critically ill patients treated in the ICU who are suspected by the treating physician to have a bacterial infection at admission or during ICU stay are eligible for inclusion in the study. If the patient meets all inclusion criteria and none of the exclusion criteria, recruitment can proceed after obtaining adequate written informed consent. For patients unable to provide informed consent, the next of kin or an eligible legal guardian will be

contacted to provide written, informed consent on their behalf. Screening will be conducted by all attending physicians and study nurses during regular ward rounds.

Inclusion criteria

- ▶ Adult (≥ 18 years) non-surgical, surgical, or trauma patients.
- ▶ Suspected new-onset infection at admission or during ICU stay.
- ▶ The source of infection is known or strongly suspected, and source control has been implemented when necessary (eg, removal of an infected device, such as a vascular access device or endoprosthesis).
- ▶ Two PCT values are available: one on the day of suspicion of infection and the other 24 ± 4 hours earlier.
- ▶ Microbiological sampling must be performed (according to all presumed sources, including two pairs of blood cultures (aerobic and anaerobic), lower respiratory tract sample (tracheal aspirate/broncho-alveolar lavage), urine, etc).
- ▶ Written informed consent from the patient (or from a legal guardian if the patient is unable to provide consent).

Exclusion criteria

- ▶ Septic shock (hypotension requiring vasopressor therapy to maintain a mean blood pressure of 65 mmHg or higher and having a serum lactate level above 2 mmol/L after adequate fluid resuscitation).²⁴
- ▶ Infections for which long-term AB treatment is strongly recommended (eg, infective endocarditis, osteoarticular infections, chronic prostatitis and tuberculosis).
- ▶ Infections associated with primary surgical intervention and adequate source control cannot be guaranteed (eg, faecal peritonitis, pancreatic necro-sectomy, infective necrotizing fasciitis—ie, Fournier's gangrene).
- ▶ Indisputable infections (eg, hepatic abscess, empyema).

- ▶ Poor chance of survival (ie, expected ICU stay less than 24 hours or initial Acute Physiology and Health Evaluation Score II >30).
- ▶ Admissions after cardiopulmonary resuscitation.
- ▶ Severe immunosuppression other than steroid use.
 - Stem-cell transplant recipients.
 - Solid organ transplant patients.
 - HIV infection with a CD4 count of less than 200 cells/mm³.
 - Neutropenia with a neutrophil count of less than 500 neutrophils/mm³.
- ▶ Patients on ABs within 72 hours before inclusion.
- ▶ Pregnant or breastfeeding patients. Women of child-bearing age will be screened with a urine pregnancy test before inclusion in the study.

PCT measurement

Daily PCT measurement has been routinely performed in participating ICUs for several years (eg, blood samples are typically collected between 05:00 and 06:00). No additional blood will be taken for the investigation, and no additional discomfort will be caused to participants. The turnaround time for PCT measurements is approximately 90 min, which aligns with morning rounds in participating centres, allowing the treating physician to make an informed decision about initiating new antimicrobial therapy.

The Elecsys BRAHMS PCT electrochemiluminescence immunoassay will be used to measure PCT levels in trial participants in our department. In healthy individuals, normal values are below 0.046 ng/mL (95th percentile). At Szent Margit Hospital, the Access PCT chemiluminescent immunoassay (Beckman Coulter, California, USA) is used with the UniCel DxI800 analyser (Beckman Coulter). The limit of detection of this test is 0.01 ng/mL. In a study comparing these two methods, the latter reported higher overall PCT levels than the former, with high agreement between the two ($\kappa=0.941$). Biases varied across different PCT concentration intervals, being less in the lower range (<0.5 ng/mL).²⁵

PCT values may be affected by insults other than bacterial infections, such as ischaemia-reperfusion injury, immunosuppression, burns, polytrauma and chronic kidney disease. These factors were addressed in the exclusion criteria.

In the AG, AB initiation is based on the actual measured PCT value. In the KG, changes in PCT relative to the previous day's value (ie, kinetics, the ratio of the actual value to the previous day's value) will guide the initiation of AB treatment.

Outcomes

Primary outcome

The primary endpoint of the KIPRUN study will be the rate of unnecessary AB therapy. AB treatment is considered unnecessary (ie, unjustified) if there is no bacterial infection (no infection at all or another causative pathogen, eg, a virus, is present). After 72 hours of treatment, a multi-disciplinary adjudication committee (comprising one intensivist, one microbiologist and one infectologist not involved in the patient's care) will determine whether the therapy was necessary. The committee will review all relevant clinical, microbiological and radiographic data, uploaded online in an anonymised format. If a consensus cannot be reached, the

decision will be made by secret vote. Each participating centre will have its own committee. A detailed description of the committee's decision-making process is provided in the online supplemental material.

Treatment may be discontinued before the 72-hour reassessment, following prior consultation with the inter-disciplinary team, if the available diagnostic data and the clinical picture make the presence of infection highly unlikely.

Secondary outcomes

1. Organ-support free days (number of days alive with-out life support—mechanical ventilation, vasoactive therapy, renal replacement therapy).
 2. Length of stay at the ICU.
 3. Length of stay at the hospital.
 4. Duration of mechanical ventilation in days.
 5. Duration of renal replacement therapy in days.
 6. Duration of catecholamine circulatory support in days.
 7. Mortality: ICU.
 8. Mortality: hospital.
 9. Mortality: at 28 days.
 10. Number of infections caused by multidrug-resistant organisms (ie, bacteria resistant to one or more classes of antimicrobial agents²⁶).
 11. Number of *Clostridioides difficile* infections.
- Exploratory outcome: cost-effectiveness.

Follow-up

A follow-up assessment will be conducted 28 days after randomisation, then weekly thereafter, to evaluate in-hospital outcomes, using our medical system and the Hungarian National eHealth Infrastructure (EESZT) as needed to collect relevant information. For any additional missing data, we will contact the patient or their next of kin by email or phone.

Participant timeline

The schedule of enrolment, intervention and assessment can be found in the online supplemental material.

STATISTICAL ANALYSIS

Sample size calculation

As the aim of this study is to reduce the number of unjustified AB treatments, the primary endpoint will be the proportion of unjustified AB treatments among all cases. According to previous prospective observational data, infection was ruled out or deemed less likely in 43% of patients initially diagnosed with sepsis, based on post-hoc assessment.² Montravers *et al* found that nearly 20% of AB treatments in suspected ICU infections are unnecessary.³ On average, up to 30% of critically ill patients are incorrectly considered infected and receive unjustified AB therapy. Based on expert consensus, we consider a 50% reduction in unnecessary treatments to be a clinically relevant difference (from approximately 30%–15%), which serves as the basis for our sample size calculation.

A total of 250 patients with possible infection need to be included in the planned study, based on the following assumptions:

- ▶ Two arms (arm A: absolute PCT, arm B: kinetics of PCT).
- ▶ Binary outcome variable (ie, rates between groups).
- ▶ Aim: to demonstrate a statistically significant difference

between the two arms.

- ▶ Arm A: event rate hypothesised at 30%.
- ▶ Arm B: event rate hypothesised at 15%.
- ▶ Power: 80%.
- ▶ Type I error rate: 5% (two-sided, equal to 2.5% one-sided).
- ▶ Analyses: one interim analysis at 50% of cases (flexible) and one final analysis.
- ▶ Alpha spending function: Hwang-Shih-DeCani, $\gamma = -2$.
- ▶ Randomisation: 1:1.

Analysis plan and statistics

For descriptive statistics, we will use means and SD, or medians and IQR. For the primary outcome (rate of unnecessary AB therapy), we will use Fisher's exact test. For secondary endpoints, we will use Fisher's exact test (for dichotomous outcomes) and two-sample t-tests (for continuous outcomes). All statistical analyses will be performed using R (V.4.5.2).

Interim analysis

We plan to conduct an interim analysis after enrolling half of the planned number of patients ($n=125$). As the prevalence of unjustified AB therapy in critically ill patients varied across previous studies, we used an average estimate of 30% for the sample size calculation. Re-estimation of the sample size will be allowed after the interim analysis to maintain statistical power. As we will have to conduct an unblinded sample size re-estimation, the p-value will be adjusted accordingly.

Study populations

We plan to perform the analysis on two study populations. The per-protocol set includes all participants who completed the study fully in accordance with the protocol, whereas the intention-to-treat set includes all enrolled participants, excluding those who withdrew consent.

Patient and public involvement

Patients or the public were not and will not be involved in the design and analysis of any aspect of our research.

Recruitment

Patients will be recruited in the ICU on admission or during ICU stay, if the treating physician suspects a new-onset infection.

On admission, the physician on duty may suspect an infection that has not been treated previously. If the patient meets all inclusion criteria and none of the exclusion criteria, the treating physician may enrol the patient after obtaining informed consent and collecting the relevant microbiological samples.

For patients already being treated in the ICU, members of the treating team can suspect an evolving infection (ie, nosocomial infection) during morning rounds after examining the patient. Clinical signs may include fever, new-onset purulent sputum, changes in sputum characteristics, and worsening oxygenation in mechanically ventilated patients with ventilator-associated pneumonia (VAP), suprapubic pain and cloudy urine in patients with catheter-associated urinary tract infection (UTI). Laboratory

and radiological diagnostics can help confirm suspected infection, such as a new infiltrate on chest X-ray or consolidation on a lung ultrasound (VAP), bacteriuria, and leukocyturia (UTI). For a comprehensive approach to assessing hospital-acquired infections, we refer to the guidelines of the European Centre for Disease Prevention and Control.²⁷

ETHICS AND DISSEMINATION

Ethical and legal considerations

The study will be conducted in accordance with the Declaration of Helsinki, ensuring full compliance with the protocol, Good Clinical Practice, and the local laws and regulations of Hungary. The current version of the protocol has been approved by the National Center for Public Health and Pharmacy (BM/20019-1/2025).

Data collection, management, and analysis

Data collection methods

Data will be collected in electronic case report forms (eCRFs) on a secure web platform for building and managing online databases and surveys.²¹ Different types of data (eg, medical history, physical examination, laboratory parameters, imaging) will be input. In Form A, we will collect data from enrolment, and Form B will contain parameters collected daily during hospitalisation. Form C will contain data after the patient's discharge from the ICU. All case report forms (CRFs) are available in the Supplementary Material. These CRFs were imported into the REDCap online database.

Primary outcome data (ie, the rate of unnecessary AB therapy) will be assessed after 72 hours of treatment by a multidisciplinary adjudication committee, with all relevant microbiological data in hand. After the committee decision, the result will be input into the online database.

Organ support-free days, length of ICU stay, number of multidrug-resistant organism-caused infections and number of *C. difficile* infections will be assessed using the eCRFs after the patient's discharge from the ICU or the patient's death.

We will follow-up patients after ICU discharge to assess secondary outcomes, including 28-day mortality (if the ICU stay is less than 28 days), length of hospital stay and in-hospital mortality. These will also be input into the eCRFs.

Data management

Data will be handled using eCRFs. The detailed process of data flow and handling will be discussed in the data management plan. The Clinical Data Management (CDM) team will continuously review and validate data input to ensure both accuracy and completeness. Members of the CDM are Márk Karim Dilan, Márton Papp and Máté Baka. Any missing, inconsistent or implausible recordings in the eCRFs will be referred back to the investigator using a data query form.

Data monitoring

The Data Management Committee will comprise statisticians and clinicians from the field who are independent from the funders. The members of the statistical subgroup will be Gergő Agócs and Andrea Harnos, while the members of the clinical data subgroup will be Zsolt Molnár, Caner Turan and Márton Papp. We plan one interim analysis on the primary

endpoint when 50% of the patients have been randomised and discharged from the hospital. The steering committee (SC) members will have access to the interim analysis results, and a consensus among them is required to terminate the trial.

Publication policy

Every centre that recruited more than 50 patients has the right to add two authors to the authorship list. All the physicians who enrolled at least five patients will be listed as members of the KIPRUN Study Group. We plan to publish the trial results in a highly cited peer-reviewed journal in the field. De-identified data collected throughout the trial and the results of interim analyses may be used at the discretion of the SC for the purposes of education. We also plan to present the trial results at national and international scientific and clinical meet-ings, including medical conferences.

Trial organisation, committees and boards

KIPRUN was designed in collaboration with the Centre for Translational Medicine at Semmelweis University in Budapest and is coordinated by the Department of Intensive Therapy of the same university.

Steering committee

The SC will be led by ZM (intensive care specialist). Other members will be MP (intensive care specialist,

PhD candidate), NK (intensive care specialist, PhD candidate), DMK (intensive care specialist, PhD candidate), LZ (intensive care specialist) and CT (medical doctor, methodology supervisor). SC will discuss all key issues, including dropouts and new participating centres.

Participating centres

The study will start in two centres in Budapest, Hungary (Semmelweis University, Department of Intensive Therapy and Szent Margit Hospital, Department of Intensive Therapy). After initiation, the study is open to other centres joining. These centres will be referred to and assessed by the SC. The SC will decide whether the centre can join. Minimum requirements for joining:

(1) PCT can be measured at any time at the discretion of the treating physician(s), (2) the centre has additional human resources dedicated for the trial besides the regular patient-care giving team (study nurses, research administrators, etc), (3) regular rounds with an infectologist and the possibility of consultation (in-person or tele-consultation) and (4) one member of the participating centre should join the meeting held before joining to discuss all the relevant information regarding the study. The potential centre should email the corresponding author a letter of intent if they want to participate.

Withdrawal from study

Patients or their representatives may withdraw consent orally or in writing at any time without providing a reason. This will not affect any further treatment of the patient. In a case of consent withdrawal, the treating physician consults with the trial personnel (the study nurse or the trial investigators), whose responsibility is to withdraw the patient from the trial and to stop collecting further data.

Protocol amendments

Important protocol modifications will be communicated

directly to the centres' chief investigators, who will then notify the investigators at their respective centres. The regional ethics committee will be reached through the ethics coordinator with all the relevant modifications. The investigators will indicate every modification on clinicaltrials.gov, and during publication, the protocol amendments will be documented in the article.

DISCUSSION

To the best of our knowledge, this is the first multicentre RCT to assess PCT-guided AB initiation in critically ill patients using PCT kinetics.

Strengths and limitations

Initiation of AB therapy is crucial in our critically ill patients, but besides acknowledging the importance of timely antimicrobial therapy, the 'each hour delay' mantra led to indiscriminate AB usage with all the unwanted consequences of unjustified AB therapy—emerging AB resistance, organ injury, mitochondrial dysfunction and disruption of the microbiome.²⁸ Our study raises awareness against treating every patient 'just in case' as having an infection. With the routine use of the best inflammatory biomarker so far (more importantly, its kinetics), we can personalise treatment, which is the path we must undoubtedly move forward on.²⁹

We will only recruit haemodynamically stable patients, prioritising their safety and well-being, as data exist on the detrimental effects of delayed AB administration. However, the 7% increased hourly risk of death was only observed in patients with suspected sepsis on vasopressors.³⁰ On the other hand, even in the case of hospital-acquired infections, too rapid initiation of ABs in the absence of shock can be associated with worse outcomes, including higher mortality in critically ill patients.³¹ Therefore, we should wisely balance between initiating early broad-spectrum ABs and waiting a few (3–5) hours while assessing our patients for other potential causes of deterioration. Without a doubt, we should opt for the latter in a patient without shock, as the latest guidelines from the Surviving Sepsis Campaign and the Infectious Diseases Society of America recommend.^{6 32}

We plan to monitor the appropriateness (ie, concordance) of the therapy (if the pathogen is susceptible to the given AB regimen). Previous RCTs assessing PCT-guided AB therapy hardly reported this outcome; in our meta-analysis of such studies, only 5 of 26 trials monitored this,⁵ which could be balanced via randomisation; however, it could be the source of serious confounding in cohort studies, because inadequacy of the therapy is a major contributor to mortality. Other confounding factors may include the dose of the ABs (adjusted for body weight and renal function), which we will document rigorously, and the adequacy of source control, a separate inclusion criterion in our study. Inadequate early source control can significantly reduce the survival of our critically ill patients despite appropriate initial AB treatment.³³

In assessing the primary outcome, an independent, multidisciplinary team will determine whether the initial decision on AB treatment was appropriate, and they won't be involved in the patient's therapy to minimise bias.

One limitation is that we cannot blind the treating physician, as their decision to start therapy depends on the absolute value or the kinetics of PCT. Nevertheless, other

healthcare professionals (nurses, physiotherapists) will be blinded. The varying performance of the used PCT assays across centres is also a limitation.³⁴

The rate of unjustified AB therapies varies between studies; therefore, we used an average number (ie, 30%) for the sample size calculation. We agreed on a 50% decrease as a clinically meaningful difference between the two groups.

In summary, after numerous RCTs investigating when to stop AB treatment using PCT kinetics, it is time to answer the question: 'Can we use PCT kinetics for starting AB therapy in ICU patients?' Evaluating dynamic changes rather than treating a single number may help personalise and, hence, optimise antimicrobial therapy for critically ill patients with a suspected new-onset infection.

Trial sponsor

No sponsor was involved in the study design. Sponsors will have no access to the randomisation code and the database generated during the trial.

Trial organisation

Professor Zsolt Molnár, from Semmelweis University, and Professor Péter Hegyi, from Centre for Translational Medicine, serve as guarantors of the trial. The Department of Intensive Therapy at Semmelweis University will serve as the lead site.

The other centre will be Szent Margit Hospital in Budapest (chief investigator: Lóránt Csiki). The study is open to other centres joining during the study period.

The SC will be led by Professor Zsolt Molnár (head of department); its members will include Nikolett Kiss, Caner Turan, László Zubek, Márton Papp and Dilan Márk Karim.

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Patient consent and confidentiality

All patients and/or their legally authorised representatives will be informed verbally and in writing about the goals and procedures of the trial. If a patient is unconscious, sedated, intubated or otherwise unable to provide informed consent, consent will be sought from a legally authorised representative, next of kin or legal guardian. The representative will receive the same written and verbal information as would be provided to the patient. Their decision will be documented in writing.

Patients or their representatives may withdraw consent at any time, without penalty or effect on standard medical care. All patient data transferred between centres for analysis and publication will be depersonalised. Data and linking codes will be stored separately, and investigators will minimise the number of personnel who can access these.

Data availability statement

Trial results will be disseminated to the public, including study participants, through publication in peer-reviewed international medical journals, presentations at scientific meetings and outreach programmes such as informational sessions. De-identified participant data will be securely stored on the REDCap server at Semmelweis University and will be accessible on authorisation.

Individual trial participant data sharing statement

ZM will receive invitations/requests to share the data of individual participants, and will consider whether the request: (1) explicitly serves public benefit, (2) complies with local ethical and data security regulations of the requesting and providing institutions, (3) specifies the existing or planned legal and technical infrastructure for data transfer and (4) provides a publicly available protocol for planned statistical analyses.

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Contributors All authors contributed critical conceptual input and approved the final version of the article. MP contributed to conceptualisation, project administration, writing - original draft preparation; CT contributed to conceptualisation, methodology, project administration, writing - review and editing; NK contributed to conceptualisation, writing - review and editing; LZ contributed to conceptualisation, writing - review and editing; DMK contributed to conceptualisation, writing - review and editing; PH contributed to conceptualisation, supervision, writing - review and editing; ZM is the guarantor, contributed to conceptualisation, supervision, writing - review and editing.

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Competing interests ZM receives occasional honoraria for lectures and consultations from Thermo Fisher Scientific. All other authors have no competing interest to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

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