ORIGINAL ARTICLE

Point-of-Care Procalcitonin to Guide the Discontinuation of Antibiotic Treatment in the Intensive Care Unit: A Malaysian Randomised Controlled Trial

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ABSTRACT

Introduction: This work aims to establish the practicality of simple point-of-care (POC) measurements of procalcitonin (PCT) coupled with the standard PCT-guided antibiotic treatment discontinuation algorithm to guide the cessation of antibiotic treatment in intensive care unit (ICU). **Methods:** In this randomised-controlled trial, 80 adult patients with suspected bacterial infections were randomised to either the POC PCT-guided arm (n = 40) or the standard-of-care arm (n = 40). The decision to discontinue antibiotic treatment in the POC PCT-guided arm was based on the POC PCT-guided antibiotic-treatment discontinuation strategy, which states that discontinuation is urged once the PCT concentration has reduced by ≥ 80% or to < 0.5 ng/mL. In the standard-of-care arm, the antibiotic-treatment duration followed the local guidelines. **Results:** The median duration of antibiotic treatment was 6.5 [IQR = 5.0-7.0] days in the POC PCT-guided antibiotic-treatment arm versus 7.5 [IQR = 5.0-14.0] days in the standard-of-care arm (p = 0.010). The mean antibiotic-free days in the first 30 days after study inclusion was 20.7 (SD = 5.3) days in the POC PCT-guided antibiotic-treatment arm versus 16.4 (SD = 7.4) days in the standard-of-care arm (p = 0.004). The number of patients who took an antibiotic for more than 10 days was 2 (5%) in the POC PCT-guided antibiotic-treatment arm versus 13 (32.5%) in the standard-of-care arm (p = 0.002). **Conclusion:** Antibiotic use in patients with symptoms of bacterial infections in the ICU was substantially minimised with the installation of a POC PCT-guided antibiotic-treatment cessation.
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INTRODUCTION

In the management of intensive care unit (ICU) patients with suspected or confirmed bacterial infections, prompt and adequate antibiotic treatment is critical. Antibiotic treatment that lasts excessively long, on the other hand, is unfavourable due to side effects and the increase of antimicrobial resistance (AMR) (1). Despite their awareness of AMR, physicians in the ICU are usually reluctant to shorten the patients' antibiotic courses due to the understandable fear that this would be a premature decision on their part.

Procalcitonin (PCT) is increasingly being recognised as a relatively specific tool for bacterial-infection follow-up (2). The results of several randomised controlled trials (RCTs) and even meta-analyses have confirmed that the use of the PCT-guided antibiotic-treatment discontinuation algorithm can reduce the antibiotic use in the ICU without compromising patient safety (3-10). Nonetheless, all these studies utilised the central-laboratory method to measure PCT. Such measurement of PCT can be challenging, with a long turnaround time, which can depreciate the clinical benefit of the test. Furthermore, not all laboratories offer this test.

Point-of-care (POC) measurement of PCT may overcome some of the problems related to the current existing technologies. As such, POC testing has grown in popularity, where it is defined as any laboratory test conducted outside central laboratories. As of today, the use of POC testing in the field of sepsis remains limited to routine testing of lactate levels (11), a valuable but non-specific biomarker of sepsis (12). In line with the advancement in technologies, POC devices for PCT

have recently been industrialised into a fully automated, quantitative, rapid POC system, wherein the test can be run with a turnaround time of 20 min or less. The accuracy of POC PCT testing has also been shown to have a good correlation with the central-laboratory method (13). POC testing has the theoretical advantages of delivering more rapid medical choices, eliminating sample identification and transit issues, and requiring minimal specimen volumes, in addition to its quick turnaround time. Documentation on the quality and effectiveness of using POC PCT measurement as a strategy to guide antibiotic-treatment discontinuation in the ICU presumably remains scarce.

Furthermore, most of the past ICU trials on PCT-guided antibiotic-treatment discontinuation was done with a Western population (3-7), thus suggesting the need for external validation of this strategy in low- and middle-income countries such as in Malaysia, in which the burdens imposed by sepsis and AMR are even higher (14). Due to various factors, it is unknown whether the results of the past ICU trials with a Western population are applicable and transferable to Malaysia's local ICU setting. As a result, a local study evaluating the efficacy and safety of adopting POC PCT to guide antibiotic treatment of ICU patients is essential.

The goal of this study is to determine how a combination of a simple PCT POC test with a well-established PCT-guided antibiotic-treatment termination protocol may reduce the total antibiotic use in patients with suspected bacterial infections who are admitted to Malaysian ICUs with suspected bacterial infections. It is hypothesised that the employment of PCT-guided approach could reduce the overall antibiotic use in Malaysia's ICUs without compromising patient safety, as previous studies demonstrated that the use of PCT-guided strategy resulted in a shorter duration of antibiotic treatment in units, where the antibiotic-treatment duration in Malaysia usually surpasses 10 days (3–6).

MATERIALS AND METHODS

Study design

From January to October 2017, an open-label RCT was done in the ICUs of two university-affiliated hospitals in Malaysia. The ethics committees of the respective university-affiliated hospitals approved this study, which fully acts in accordance with the Helsinki Declaration.

Study participants

Adult patients exhibiting suspected or confirmed bacterial infections on admission to or during their stay in the abovementioned hospitals' ICUs, and those who had received their first dose of a systemic antibiotic less than 24 hours prior to study inclusion, were screened for their participation eligibility in this RCT. Patients who had received antibiotics only for prophylaxis, with an infection for which prolonged antibiotic treatment is strongly recommended, with severe immuno-suppression, with an infection due to non-bacterial causes, and who were moribund or readmission cases were excluded from the study. For participation in this RCT, all trial participants or their next-of-kin provided written informed consent.

Randomisation, allocation concealment, and blinding

At a ratio of 1:1, study participants were assigned to either the POC PCT-guided group or the standard-of-care group. Randomisation and allocation concealment were performed by an independent research nurse who was not involved in the study. The randomisation scheme was produced via a computer-generated randomisation method. The randomisation particulars were provided to the investigators in sequentially numbered, opaque, and sealed envelopes according to the randomisation scheme. As per the open-label approach in this work, blinding to the allocation arm after randomisation was unachievable due to the inability to blind to PCT measurements in an acceptable manner.

Procedures

Alternate-day POC PCT measures were collected for trial participants who were randomly assigned to the POC PCT-guided group, and the data, including the baseline measurement, were made available to the attending clinicians within 24 hours of the antibiotic treatment onset. The PCT concentrations were measured until the systemic antibiotic treatment was discontinued, including in the subsequent ward. According to the previously published algorithm (Figure 1), treatment with the prescribed antibiotic should be stopped if the PCT concentration has decreased by 80% or more of its peak value, or if the concentration is within the 0.25–0.5 ng/mL range (relative discontinuation threshold), or when it has reached a value of less than 0.25 ng/mL (absolute discontinuation threshold) (4). PCT was not utilised to guide the start of antibiotic treatment in this study. Additionally, attending intensivists made the final call as to whether to continue or stop antibiotic treatment in patients who had achieved the discontinuance thresholds. The reasons for non-adherence (e.g., clinically persistent infection despite PCT clearance) were recorded.

Prior to the start of the trial, all investigators in the standard-of-care group received a reminder that included recommendations for the length of antibiotic therapy for the most prevalent infection types according to the national guideline for antimicrobial therapy in the adult ICU by Malaysian Society of Intensive (16). Nonetheless, the researchers were free to select the best antibiotic treatment length based on their own assessment of the infection's clinical development. The PCT concentrations in the standard-of-care group were not measured. There was no variation in the level of monitoring between the two groups except for the PCT measurements.

Procalcitonin measurement

PCT was measured using POC analysers (Finecare™ PCT Rapid Test along with Finecare™ FIA Meter [CIGA Healthcare Ltd., Ballymena, UK]), which were made available in each of the two participating ICUs. The system uses the fluorescence immunoassay technique and measures the PCT quantitatively. The turnaround time of the system is 15 min. The assay has a measuring range of 0.1–100 ng/mL. The manufacturer's claimed intra- and inter-assay coefficients of variation are less than 15%. A correlation study done in our local laboratory showed that the correlation between Finecare™ PCT and Elecys BRAHMS PCT is good, with a correlation coefficient of 0.9552. In all the study participants, PCT was measured in the whole blood obtained from the arterial line. All the measurements were performed by the researchers, who then relayed the PCT results to the attending intensivists.

Data collection

Each study participant's age, gender, admission category, baseline severity of illness as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score, presence of septic shock, baseline organ dysfunction as classified by the Sequential Organ Failure Assessment (SOFA) score, infection acquisition (community, hospital, or ICU acquired), presumed site of infection, microbiological culture results, and inflammation were all collected (mechanical ventilation, renal replacement therapy, inotropic or vasopressor support, corticosteroids).

Outcome measures and definitions

Antibiotic exposure was the central feature, which was evaluated as the length of the first antibiotic treatment session (defined as the number of 24 h periods between the start and end of antibiotic treatment). Mortality was not our primary outcome measure as the safety of PCT guidance has already been established in other studies (4–8). Meanwhile, within days 1–30 in the two arms for all randomised study participants, the secondary outcomes were number of antibiotic-free days, percentage of patients who had consumed antibiotic for more than 10 days, percentage of patients who had a recurrent infection (defined as the isolation of the initial causative bacterial strains from the second sample taken from the same site 48 h or more after the discontinuation of antibiotic treatment (combined with the clinical features of the infection), percentage of patients who had a repeated antibiotic course, percentage of patients from whose routine body fluid culture multi-drug-resistant (MDR) bacteria had been isolated (defined as one of the following: Acinetobacter baumannii, carbapenem-resistant Enterobacteriaceae, extended-spectrum β-lactam-producing Enterobacteriaceae, methicillin-resistant Staphylococcus aureus, Stenotrophomonas maltophilia, or ticarcillin-resistant Pseudomonas aeruginosa), lengths of ICU and hospital stays, and mortality from any cause 30 days subsequent to the study inclusion.

Statistical analysis

The data is presented as mean (standard deviation [SD]), median (interquartile range [IQR]), or count in this article (percentage). For continuous variables, comparison was made between the baseline characteristics and outcomes to the findings of the independent t-test or Mann–Whitney U test, and for nominal variables, to the results of the chi square test. The between-group absolute differences (95% confidence interval [CI]) for the primary and secondary outcomes were calculated. All of the tests were two-sided, and the statistical significance threshold was set at $p < 0.05$. SPSS v.20 was used for all of the analyses (IBM software).

Sample size calculation

The goal of the study is to determine if the POC PCT-guided technique outperformed the standard-of-care strategy in terms of antibiotic use duration. At least 36 patients in each group were required for assessment to confirm that employing POC PCT-guided strategy can shorten the course of antibiotic treatment by 4 (SD = 6) days (4). Using a two-tailed test with a 5% significance threshold, this would offer 80% power.

Ethical clearance

This study was approved by the International Islamic University Malaysia Research Ethics Committee (Code: IREC 696) and Universiti Sains Malaysia Human Research Ethics Committee (Code: USM/JEPeM/17030186).

RESULTS

Baseline demographic and clinical characteristics

A number of 345 patients were screened in the two participating ICUs between 9 January to 21 October 2017. A total of 80 patients (25.5%) were enrolled in the research (40 in the POC PCT-guided group and 40 in the standard-of-care group). The study participants in both arms had similar demographic and clinical characteristics at the start of the trial (Table I), although the proportion of those with pulmonary as the presumed site of infections was higher in the POC PCT-guided arm than in the standard-of-care arm, with the difference approaching statistical significance (32 [80%] vs. 24 [60%], p = 0.051]. Of note, median (IQR) of PCT for patients who were in the POC PCT-guided arm are shown in Table II. In both groups, there was no one who was lost to follow-up.

Primary outcome

Table III illustrates the mean and absolute differences in the course of antibiotic treatment for the first episode of infection among study participants over the first 30 days after their study participation. The duration of antibiotic treatment in the POC PCT-guided group was considerably shorter than in the standard-of-care group (6.5 [IQR = 5.0-7.0] days vs. 7.5 [IQR = 5.0-14.0] days, p

Table I: Baseline clinical-demographic profiles

	All (n = 80)	POC PCT-guided arm (n = 40)	Standard-of-care arm (n = 40)	*P*-value
Age (years), mean (SD)	54 (16)	53 (18)	54 (15)	0.691
Gender, n (%)				
Male	44 (54.3)	25 (62.5)	18 (45.0)	0.396
Female	36 (45.7)	15 (37.5)	22 (55.0)	
Admission category, n(%)				
Medical	53 (65.4)	28 (70.0)	24 (60.0)	0.348
Surgical	28 (34.6)	12 (30.0)	16 (40.0)	
Charlson Comorbidity Index, mean (SD)	3.0 (2.1)	3.2 (2.1)	2.8 (2.1)	0.406
Severity of illness APACHE II, median (IQR)	12 (8-20)	11 (6-19)	13 (9-20)	0.371
Septic shock, n (%)	32 (40)	14 (35)	18 (45)	0.807
SOFA score, median (IQR)	4 (3-7.75)	4 (3-8)	4 (3-7)	0.822
Acquisition of infections, n (%)				
Community acquired	45 (56.25)	22 (55)	23 (57.5)	0.822
Hospital acquired	25 (31.25)	14 (35)	11 (27.5)	0.469
ICU acquired	10 (12.5)	4 (10)	6 (15)	0.499
Presumed infections site, n (%)				
Pulmonary	56 (70)	32 (80)	24 (60)	0.051
Skin and soft tissue	13 (16.25)	4 (10)	9 (22.5)	0.130
Catheter-related infections	2 (5)	1 (2.5)	1 (2.5)	1.000
Intra-abdominal infections	1 (2.5)	0 (0)	1 (2.5)	0.314
Bloodstream infections	3 (3.75)	1 (2.5)	2 (5.0)	0.556
Urinary tract infections	3 (3.75)	1 (2.5)	2 (5.0)	0.556
Unknown focus	2 (5)	1 (2.5)	1 (2.5)	1.000
Positive microbiological culture, n (%)	51 (63.8)	26 (65.0)	25 (62.5)	0.816
Infection and inflammation				
Temperature (°C), mean (SD)	37.3 (1.0)	37.2 (0.9)	37.4 (1.1)	0.439
Leukocytes (10^3 cells/μL), median (IQR)	15.8 (10.1-21.5)	16.4 (8.8-20.6)	13.9 (11.0-23.8)	0.907
Procalcitonin (ng/mL)	-	2.26 (0.51-15.35)	-	-
Treatment in first 24 h, n (%)				
Mechanical ventilation	45 (56.25)	24 (60)	21 (52.5)	0.301
Renal replacement therapy	21 (26.25)	9 (22.5)	12 (30)	0.862
Inotropic or vasopressor support	33 (41.25)	14 (35)	19 (47.5)	0.605
Corticosteroids	13 (16.25)	8 (80)	5 (12.5)	0.651

APACHE, Acute Physiological and Chronic Health Evaluation; CNS, central nervous system; ICU, intensive care unit; IQR, interquartile range; POC PCT, point-of care procalcitonin; SD, standard deviation; SOFA, Sequential Organ Failure Assessment

= 0.010). After adjusting for possible baseline imbalance in a linear regression analysis, POC PCT guidance remained as a significant independent variable for the duration of antibiotic treatment with p = 0.003 (Table IV).

Secondary outcomes

The antibiotic-free days were substantially longer in the POC PCT-guided group than in the standard-of-care group over the 30-day period after time of onset (20.7 [SD = 5.3] days vs. 16.4 [SD = 7.4] days; between-group absolute difference, 4.35 [95% CI: 1.45, 7.25]; p = 0.004). In the POC PCT-guided group, the number of patients who took an antibiotic for more than 10 days was also lower than in the standard-of-care group (2 [5%] vs. 13 [32.5%]; between-group absolute difference, 27.5% [95% CI: 8.67, 44.74]; p = 0.002). Other secondary outcome measures, such as 30-day mortality, revealed no significant differences between the two groups (Table II). Fourteen patients in the POC PCT-guided group and 9 patients in the standard-of-care group died within 30 days after study inclusion due to multi-organ failure (4 vs. 3 patients), non-infectious complications (5 vs. 4 patients), or an underlying disease (5 vs. 2 patients).

Adherence to the study protocol

An antibiotic-treatment discontinuation criterion was met by 43 of the 46 study participants in the POC PCT-guided group (93.5%). Adherence to the discontinuation recommendation within 24 h after reaching the discontinuation threshold was advised for 18 study participants in the group (41.8%), and within 48 h for 22 study participants in the group (51.2%). Three patients (7%) were not advised to stop taking antibiotics even if they had met an antibiotic-treatment discontinuation criterion because the physicians felt that these patients had persistent infection and were clinically unstable despite PCT clearance.

The ICU physicians advised 15 (37.5%) of the 40 study participants in the POC PCT-guided group to stop taking antibiotics because their PCT concentration had been reduced by 80% or more compared to its peak value, 18 (45%) were advised to quit taking antibiotics because their PCT concentration was lower than 0.5 ng/mL, and 7 (17.5%) concurrently met the antibiotic-treatment discontinuation recommendation.

DISCUSSION

Given that the burdens imposed by sepsis and AMR have become an ever-increasing problem worldwide (15), tools to reduce antibiotic exposure are crucially needed. The pro-hormone of calcitonin, PCT, is thought to be a useful diagnostic for detecting bacterial sepsis (17). It also reflects the systemic response to bacterial infection, as well as the severity of the infection (18).

Table II: Procalcitonin levels (in ng/mL) on different study days

	Day 1 (n = 40)	Day 3 (n = 40)	Day 5 (n = 35)	Day 7 (n = 20)	Day 9 (n = 6)	Day 11 (n = 3)
Procalcitonin (ng/ml), median (IQR)	1.86 (0.50-17.07)	1.41 (0.75-1.41)	0.93 (0.48-5.63)	0.90 (0.37-3.52)	5.05 (0.82-0.85)	3.75

Table III: Primary and secondary outcome measures (n = 80)

	POC PCT-guided group (*n* = 40)	Standard-of-care group (*n* = 40)	Between-group absolute difference (95% CI)	*P*-value
Primary outcome				
Duration of first episode of antibiotic treatment (days), median (IQR)	6.5 (5.0-7.0)	7.5 (5.0-14.0)	-	0.010
Secondary outcomes				
Antibiotic free days in first 30 days, n (%)	20.7 (5.3)	16.4 (7.4)	4.35 (1.45, 7.25)	0.004
Antibiotic use for 10 days or more, n (%)	2 (5.0)	13 (32.5)	27.5 (8.67, 44.74)	0.002
Recurrent infections, n (%)	5 (12.5)	5 (12.5)	2.13 (-15.22, 19.25)	1.000
Repeated course of antibiotic, n (%)	8 (19.5)	15 (37.5)	17.99 (-3.38, 37.52)	0.073
Multi-drug resistant bacteria, n (%)	7 (17.1)	10 (25.0)	7.93 (-11.58, 26.92)	0.381
Length of stay on the ICU (days), mean (SD)	7.7 (4.9)	10.6 (11.0)	2.87 (-6.68, 0.95)	0.137
Length of stay in the hospital (days), mean (SD)	17.2 (12.4)	23.5 (20.8)	6.33 (-13.95, 1.29)	0.102
30-day mortality, n (%)	14 (35.0)	9 (22.5)	6.25 (-5.72, 18.14)	0.217

ICU, intensive care unit.

Table IV: Point-of-care procalcitonin guidance adjusted for possible baseline imbalance

	Beta coefficients	t	*P*-value
Constant		12.679	<0.001
POC-PCT guidance	-0.338	-3.120	0.003
Pulmonary site of infection	-0.118	-1.084	0.282

Several previously conducted RCTs have shown a reduction in antibiotic use when the POC PCT-guided antibiotic-treatment discontinuation algorithm was employed (3-7). However, these studies were mainly conducted in Western ICUs. Furthermore, all the studies utilised the standard laboratory method of measuring PCT that requires specific expertise, whose application in daily clinical practice is therefore challenging.

Following that, researchers analysed on whether simple POC PCT measurements combined with the algorithm could guide ICU clinicians in monitoring their patients' antibiotic response and, as a result, reduce overall antibiotic use. The results indicate that through the use of the POC PCT-guided method, the initial episode of antibiotic treatment can be reduced from 9 to 6 days. Moreover, the use of the POC PCT-guided strategy prolonged the study participants' antibiotic-free days from 16 to 20 days and lowered the percentage of study participants who took an antibiotic for more than 10 days from 32.5 to 5% in the first 30 days after study inclusion. This reduction in the overall antibiotic use with the use of the POC PCT-guided strategy did not appear to compromise patient safety.

As a result, the findings of RCT in this work validated the findings of previous research and demonstrate the efficacy of POC PCT-guided antibiotic treatment management. Furthermore, POC PCT measurements appear to be at least as efficient as standard assays and can thus be used in everyday practise, particularly in centres where the test is not available at the central laboratory. This study included critically ill patients with sepsis and septic shock, the majority of whom (55%) had pneumonia. According to a recent review, it is this group of patients that showed strong evidence of the effectiveness of POC PCT-guided antibiotic-treatment stewardship (19). This study is regarded to be the first to describe the effectiveness of POC PCT measurements combined with the POC PCT-guided algorithm in minimising antibiotic exposure in critically ill patients with bacterial sepsis. However, POC PCT has been used in the past, although in a different setting: in patients admitted with acute exacerbations of chronic obstructive pulmonary disease (20).

There were three drawbacks to this study, where its biggest limitation was the small sample size (80 patients). Post-hoc power analysis revealed that the power for the mean difference in the antibiotic-treatment duration was only 77.5%. Despite this, the sample size was sufficient to identify a difference in antibiotic use. Also, as this was an open-label study, it is clearly reasonable to suspect bias although we have attempted to minimize this by ensuring that the data collectors and outcome assessor were blinded to treatment allocation. Another major limitation of this study, as with other trials of POC PCT-guided antibiotic treatments, was whether the control group received the best care (21). According to the World Medical Association's Helsinki Declaration, 'the benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best current proven intervention' (22 p.3), but as is widely known, defining the best current proven intervention is difficult. The main argument against utilising ordinary care as a comparative for POC PCT-guided intervention has been the lack of homogeneity in existing practise.

Moreover, while mastering POC PCT measurement is simple, it can be difficult at times in a busy daily routine. As a result, it's unclear whether a high POC PCT-guided antibiotic-treatment termination algorithm adherence rate can be achieved in a real-world context or even in larger-scale multicentre trials in the future.

POC PCT measurements and the use of the POC PCT-guided algorithm, on the other hand, increased clinician awareness of the dangers of prolonged antibiotic treatment and prompted them to take a stand on antibiotic prescription and treatment discontinuation, resulting in lower antibiotic use than in the control arm. However, a proper analysis of the cost effectiveness of this strategy is needed, although the calculation of its cost is challenging to conduct because the financial implications of possibly reduced AMR are hard to quantify.

CONCLUSION

This study revealed that an antibiotic-treatment approach algorithm based on PCT POC measurements in critically ill patients may decrease the total antibiotic consumption while posing no risk to the patients. Given the findings of this study, it is recommended that patients with bacterial infections in the ICU have better access to PCT measurements using the POC device, and that the POC PCT-guided antibiotic-treatment cessation protocol be employed. Furthermore, because of the direct obtainability of the test, POC PCT measurement may be a viable choice in contexts where doctors' attention to and interest in antibiotic-treatment stewardship is suboptimal.

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