PROCALCITONIN-GUIDED ANTIBIOTIC THERAPY FOR SUSPECTED AND CONFIRMED SEPSIS OF PATIENTS IN A SURGICAL-TRAUMA ICU

A prospective, two-period cross-over, interventional study

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Declaration

I, Rispah Chomba do hereby declare that this research report is the result of my investigation and research. It is being submitted for the Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any other degree or examination to any other university.

Rispah N. Chomba

12th day of December 2018 in Auckland Park, Johannesburg

Presentations

The findings from the study were presented orally at the 7th congress of the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) that was held in Cape Town from 9th to 12th November 2017. Study findings were also presented orally at the 46th Surgical Research Society meeting held in Mthatha on 22nd June 2018.

Abstract

Procalcitonin (PCT) is a biomarker used in sepsis to guide antibiotic duration of treatment. Clinical algorithms that utilise PCT have demonstrated value in reducing duration of antibiotic treatment in critically ill patients. There is lack of evidence regarding the utility of PCT-guided antibiotic algorithms in trauma patients and in patients from developing countries.

A prospective study was conducted in the surgical trauma intensive care unit (ICU) at Charlotte Maxeke Johannesburg academic hospital from April 2014 to July 2015 in a two period cross-over design. Patients with suspected or confirmed sepsis were recruited consecutively in two periods of almost equal length. In the first period, 40 patients were recruited as controls and antibiotics were discontinued as per standard of care. In the second period, 40 patients were recruited into the intervention group and antibiotics were discontinued if the PCT decreased by ≥ 80% from the peak PCT level, or to an absolute value of less than 0.5 µg/L. The antibiotic duration of treatment was the primary outcome. Patients were followed up for 28 days from the first sepsis event.

For the first sepsis event the intervention group had a mean antibiotic duration of 9.3 days while the control group had a mean duration of 10.9 days (p=0.10). The mean duration of treatment was 12.0 days for a second episode of sepsis in the control group and 9.6 days in the intervention group (p=0.09). Clinician compliance to the PCT algorithm was 62.5%. The intervention group had more antibiotic free days (7.8 days) compared to the control group (3.9 days) (p=0.004). The length of ICU stay and length of hospital stay for the two groups were similar. The in-hospital mortality was reduced in the intervention group (15%) compared to the control group (30%).

Our data supports the use of PCT-guided algorithms for antibiotic stewardship in surgical trauma patients. Clinician compliance would most likely increase the benefits observed in our study.

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Dr. R. Chomba

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NOMENCLATURE

AST	antibiotic susceptibility testing
BSI	blood stream infection
CEO	chief executive officer
CNS	central nervous system
CPAP	continuous positive airway pressure
CRP	C-reactive protein
ESBL	extended spectrum beta lactamase producer
GCS	Glasgow coma scale
HAI	hospital acquired infections
HIV	human immunodeficiency virus
ICU	intensive care unit
ISS	injury severity score
MDR	multidrug resistant
MRSA	methicillin resistant *Staphylococcus aureus*
PCT	procalcitonin
SIMV	synchronized intermittent mandatory ventilation
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
SSTI	skin and soft tissue infection
UTI	urinary tract infection

CHAPTER - 1. INTRODUCTION

1.1 General Introduction

The world is facing increasing rates of multidrug resistant bacteria in intensive care units (ICUs) mainly and hospitals in general. Over-use of antibiotics is a major factor driving antibiotic resistance. There is an urgent need to implement antibiotic stewardship in our ICUs to reduce antibiotic overuse.

The role of biomarkers, especially procalcitonin (PCT), as antibiotic stewardship tools has been investigated in several trials. Procalcitonin has been used in these trials as a tool for monitoring patients with sepsis and their clinical response to antibiotic treatment. Antibiotics are discontinued once the PCT drops to a predetermined level. This treatment approach was initially used in patients with lower respiratory tract infections. Recent studies however, have used PCT based algorithms in ICU patients to guide antibiotic duration in patients with various sources of sepsis.

1.2 Background to the problem

Studies on procalcitonin guided antibiotic therapy are mainly from Europe. There are few studies from developing countries on the use of PCT based algorithms for antibiotic stewardship. Most ICU studies contain relatively few numbers of surgical patients. It was useful to have a study that analyses the use of established PCT algorithms in surgical trauma patients in South Africa.

1.3 Research objective

The study was done to determine if a procalcitonin based clinical algorithm would decrease total antibiotic days compared to standard antibiotic treatment in an ICU setting. The study was done in surgical trauma patients with proven or suspected sepsis.

1.3.1 Primary outcomes:

1) Duration of antibiotic treatment for every sepsis episode until 28 days after study inclusion.
2) Clinical outcomes:
    a. Antibiotic free days alive at 28 days from study inclusion.
    b. 28 day hospital mortality (death from any cause).
    c. ICU length of stay.
    d. Recurrence or relapse of infection

1.3.2 Secondary outcomes:

1) Sources of sepsis as per positive microbiology cultures from clinical specimens with clinical correlation.

2) Bacterial species isolated from clinical specimens and susceptibility profiles.

3) Emergence of multidrug resistant bacteria in the two groups.

4) Profile of procalcitonin concentrations in septic trauma patients.

5) Compliance with procalcitonin study algorithm

6) Clinical outcomes of patients in whom study algorithm was over-ruled.

1.4 Significance of the study

The results of the study will be used to:

1) Encourage clinicians working in trauma ICUs in South Africa and the developing world to utilize procalcitonin based antibiotic algorithms in septic trauma patients for antibiotic stewardship.

2) Expand knowledge on potential value of PCT based antibiotic algorithms in reducing hospital morbidity and improving mortality outcomes.

1.5 Format of the study

The research report has five chapters:

Chapter 1, entitled Introduction elaborates on the problem under investigation.

Chapter 2, the Literature Review, critically analyses the findings of other researchers on the use of procalcitonin based algorithms to guide discontinuation of antibiotics in hospitalized and critically ill patients.

Chapter 3, the Research Methodology, discusses the research approach and the reasons for using it. It also discusses the study population, the data collection tool and defines terminologies used in the study.

Chapter 4, the Results, presents the findings obtained in the study in the form of descriptive and inferential statistics.

Chapter 5, the Discussion and Conclusion, interprets the results critically by relating study findings to the literature review, concludes the study and determines its significance.

1.6 Conclusion

Antibiotic overuse is a problem in many hospitals and antibiotic stewardship has a major role to play in the proper utilisation of antibiotics. Trauma patients with sepsis pose a unique challenge because underlying injuries may result in elevated biomarkers even after the infection is adequately treated. Information gathered from the current study will be used to guide clinicians on how to utilise procalcitonin measurements to determine the correct duration of antibiotic treatment. The following chapter is the literature review which presents the findings of other researchers on the topic of procalcitonin guided antibiotic treatment.

CHAPTER - 2. LITERATURE REVIEW

2.1 Introduction

Procalcitonin (PCT) is a peptide precursor of calcitonin, an important hormone in calcium homeostasis. Procalcitonin is found in C cells in the thyroid as well as in pulmonary endocrine cells, monocytes and hepatocytes (Becker et al. 2010; Zhangbin et al. 2010). In fact, all tissues in the body have been found to have the capacity to produce PCT (Becker et al. 2010).

PCT levels are usually low in normal conditions but increase in severe infections and inflammatory conditions e.g. pancreatitis, burns, multiple trauma and extensive surgery. However, the highest levels are found in septic patients (Becker et al. 2010). Systemic inflammation triggers calcitonin gene expression outside the thyroid. Procalcitonin is then released into the bloodstream in detectable quantities (Bréchot et al. 2015). Procalcitonin rises within a few hours of infection with bacteria. It rises quickly but reduces with appropriate antibiotic therapy. Levels are usually higher than 0.5 μg/L and persist at high levels for days to weeks as long as the disease persists (Becker et al. 2008). After the PCT reaches peak levels the amount in circulation reduces by half in one to 1.5 days (Meisner, 2014). Viral infections stimulate release of interferon-gamma (IFNγ) which is a down regulator of procalcitonin release (Bréchot et al. 2015).

The C-reactive protein (CRP) is a well known biomarker of infection. However, procalcitonin has better specificity than the CRP in sepsis (Koivula et al. 2011). After surgery the CRP may show a big increase while in severe sepsis the CRP may be only modestly raised (Meisner 2014). This reduces the value of the CRP in diagnosing sepsis in surgical and trauma patients. In contrast, the value of PCT measurements has been used to predict bacterial sepsis in diverse groups of patients such as neonates (Zhangbin et al 2010) and hematologic neutropenic patients (Koivula et al. 2011).

2.2 Procalcitonin concentrations in trauma patients

Raised PCT levels may occur in patients without sepsis but with other systemic inflammatory conditions e.g. pancreatitis, heat stroke, extensive surgery and mechanical trauma (Becker et al 2008). Billeter et al. (2009) found that after severe trauma the PCT reaches peak levels within 48 hours but the CRP and white cell count took much longer to peak and to clear. They also found that when trauma patients develop septic infections they fail to clear the initial high PCT levels. Wojtaszek et al. (2014) studied the PCT concentration changes in 45 patients with

multiple trauma. The highest PCT value was measured 24 hours after traumatic injury. Multiple trauma patients without central nervous system (CNS) injury had higher PCT values compared to trauma patients with CNS involvement.

In surgical patients procalcitonin has a specificity of 70-100% and a sensitivity of 37-100% as a marker of post-operative infection (Boysen et al. 2005). In patients with acute trauma, the PCT level may rise due to the systemic inflammatory response, hence a single reading may not be a valid marker of sepsis following trauma. Trauma patients require serial measurements of PCT concentrations to determine presence of infection.

Nie et al. (2011) used PCT as a sepsis marker in post-operative patients with spinal cord trauma due to motor vehicle accidents, falls, violence and other causes of injury. In non-infected patients the PCT had a range of 0.07-0.10 µg/L pre-operatively and 0.16-0.50 µg/L post-operatively. In infected patients the PCT range was 0.06-0.11 µg/L pre-operatively and 0.53-1.97 µg/L post operatively. This difference in the two groups was statistically significant. This study showed that PCT concentrations may be more reliable than other biomarkers like CRP and leukocytosis in diagnosing sepsis in trauma patients.

In another study, Haasper et al. (2010) analysed the kinetics of PCT in severely injured patients. PCT levels were elevated due to post-traumatic release but significantly higher levels were found from day 3 after trauma in patients with sepsis. PCT levels exceeded 5 µg/L in trauma patients with sepsis but the upper limit of 5.0 µg/L was never exceeded in patients without serious bacterial infection.

Linderberg et al. (2002) defined reference intervals of PCT due to surgical trauma in the first post-operative week following major surgery. The mean PCT value halved by the second post-operative day. On the first post-operative day the PCT had a range of 0.5-3.0 µg/L but dropped rapidly after the second post-operative day to a range of 0.1-1.0 µg/L by the seventh post-operative day. Heinz et al. (2000) studied a non-human primate model of trauma and found that the plasma PCT levels rose from undetectable to 2±1.8 pg/ml after trauma. Procalcitonin levels in the sepsis group were approximately three times higher than those seen in the shock group but levels were lower than those found in human septic patients. The release kinetics of PCT in sepsis was similar to those seen in humans with maximum PCT levels occurring at 6 to 24 hours in the non-human primates.

Meisner et al. (2005) evaluated the kinetics of PCT induction and the CRP in 90 adult polytrauma patients. They found that peak concentrations of PCT occurred on day 1 and 2 of

trauma and then declined rapidly afterwards. The CRP concentrations increased more slowly, peaked at about day 3 to 4 and remained elevated for a prolonged period. The rapid decline of PCT is therefore more useful than the CRP as it allows a more valid predictor of development of sepsis in the early period following trauma. Koutroulis et al. (2014) identified the possible utility of PCT as a septic marker in paediatric trauma patients who developed sepsis. Since the initial increase in the PCT drops 48 hours after trauma, any secondary increase is a significant predictor of sepsis. Meisner (2014) notes that a daily decline in PCT concentration of >30% indicates significant clinical improvement.

There is a paucity of PCT studies from developing countries. However, Rajkumari et al. (2013) conducted a prospective procalcitonin study in India in severely injured patients. They found that an initial high PCT (>2 ng/ml) correlated with development of infection and prolonged ICU stay.

These studies show that PCT is a reliable marker of sepsis in trauma patients in whom inflammatory processes may intrinsically cause a rise in other biomarkers. A PCT level greater than 0.5 µg/L seems to signify sepsis in trauma patients especially if the levels remain persistently high.

2.3 Procalcitonin concentrations in critically ill patients

There are only a handful of studies that have investigated the utility of PCT to diagnose sepsis in critical care. Balci et al. (2009) evaluated a cohort of 113 adult trauma patients and found that PCT levels were significantly increased in septic patients compared to patients without sepsis. They further found that the CRP could not be used to make this differentiation.

Reynolds et al. (2012) evaluated the changes in PCT in critically ill patients to see if PCT values are influenced by different patient and microbiologic factors. They found that median PCT values were similar between the surgical and medical patients except on days 6 to 8 where the surgical groups had sustained elevation in PCT but the medical groups had a progressive steady decline. There was no difference in baseline, peak or delta PCT values when comparing culture positive and culture negative infections. Patients in shock had higher PCT values between days 1 and 5 independent of whether there was an infection present. The PCT values of patients in shock had no significant difference between those with infection and those without.

This association is important in critically ill trauma patients as they are often in shock hence a high PCT cannot be assumed to be solely due to presence of infection. Patients with Gram

positive infections took longer to drop the PCT to 25% of peak value compared to Gram negative infections (5 days versus 2.5 days). This may be due to the association of Gram positive bacteria with prosthetic devices. (Reynolds et al. 2012).

Carr (2015) notes that procalcitonin levels tend to be higher in septic ICU patients compared to levels seen in patients with respiratory infections. The author attributes this difference to greater severity of infections in ICU patients. Sakran et al. (2012) conducted a retrospective study of 102 polytrauma patients. They found that PCT levels were higher (mean 6.6 ng/ml) in septic patients than in patients with systemic inflammatory response syndrome (SIRS) only. Rajkumari et al. (2013) found that septic trauma patients who were treated with appropriate antibiotics experienced a significant drop in PCT level between day one and day four of treatment.

2.4 Rationale for restriction of antibiotic policies in intensive care units (ICUs)

Intensive care units (ICUs) tend to become the source of antibiotic resistance in a hospital. This may be due to indiscriminate use of antibiotics for empirical therapy and widespread use of antibiotics to treat positive "routine" cultures that may be associated with contamination or colonization without infection.

It is therefore necessary to have a protocol on identification of patients who have had adequate antimicrobial therapy so that antibiotics can be discontinued appropriately and safely. Procalcitonin has generated a lot of interest not only in diagnosis of sepsis but also to determine antibiotic duration of treatment. This is a form of antibiotic stewardship and prevents overuse of antibiotics, reduces costs and potentially decreases the risk of bacteria developing resistance to antibiotics.

The most promising value of PCT has been as a biomarker of appropriateness of antibiotic therapy. Georgopoulou et al (2011) used PCT as a marker of response to therapy in a mixed group of patients from departments of internal medicine, surgery and mixed ICUs. A decrease in PCT level by 30% within 48 hours or levels lower than 0.25 µg /L indicated a favourable outcome. However, a decrease of less than 30% or an increase in PCT indicated inappropriate anti-microbial treatment. These findings applied to patients with all categories of sepsis. A potential caveat is that majority of the causative bacteria in this study were Gram negative bacteria.

2.5 Procalcitonin as a tool for antibiotic stewardship

The earliest studies that used PCT based antibiotic algorithms focused on patients with lower respiratory tract infections. Recent studies however, have evaluated diverse groups of patients including those in critical care. However, PCT is a laboratory marker and should not be used alone but as an adjunct to clinical evaluation.

Procalcitonin has been used in the outpatient setting to guide decisions on whether or not to start antibiotic treatment in patients with upper respiratory tract infections as well as pneumonia. In one study, antibiotics were not administered if PCT levels were less than 0.25 µg/ L. This resulted in reduced usage of antibiotics without adverse outcomes in the procalcitonin group compared to the control group (Fazili et al 2012).

Liu et al. (2016) performed a meta-analysis of 86 studies comprising 10,438 subjects that evaluated different sepsis markers in SIRS patients. Procalcitonin showed moderate accuracy in differentiating sepsis from SIRS. A cell surface marker, CD64 was highly accurate in differentiating between SIRS and sepsis. However, it is costly and requires flow cytometry which limits its applicability.

Studies conducted in ICU patients have avoided using PCT in decisions on whether to start or withhold antibiotics in critically ill patients. Instead, PCT has been used to make decisions to stop antibiotics based on declining PCT values. Early studies on procalcitonin guided antibiotic treatment were mostly in primary care patients with pneumonia. Christ-Crain et al. (2004) randomized 243 patients admitted with suspected pneumonia to receive PCT-guided antibiotic initiation or to get antibiotics as per standard of care. The proportion of patients who received antibiotics in the PCT group was 47% less than in controls. Briel et al. (2008) also used PCT to guide initiation of antibiotics and duration of treatment in pneumonia. In the PCT group, antibiotics were only encouraged if the PCT concentrations were more than 0.25 µg /L and discouraged if lower than this level. Patients were reassessed after 3 days and if the PCT level was 0.25 µg/ L or lower it was recommended to stop antibiotics. For patients in the control group physicians chose the antibiotic and duration of treatment preferably with the use of recommended guidelines. For patients on PCT guided therapy 25% received antibiotics compared to 97% of patients in the control group. The mean duration of antibiotic therapy was 7.1 days in the control group compared to the PCT arm which had a mean duration of 6.2 days. Adherence to the PCT algorithm was 85%. At 28 days, 30% of patients on PCT guided therapy reported ongoing/relapsing respiratory tract infection which was the same as reported in the control group (30%). Adverse events were similar in both groups and PCT guided

treatment was non inferior to standard treatment in restricting patients' activities as a result of the infection.

Albrich et al (2012) performed an observational post-study survey in Europe and the U.S. to look at use of the PCT algorithms in real life in adults with infections of the lower respiratory tract in an outpatient setting (ProREAL). The duration of antibiotic therapy was 6.2 days as compared to historical controls from a randomized control trial they had done earlier which was 7.9 days. Early cessation of antibiotics when PCT concentration fell below 0.25 µg/L or showed >80% reduction from peak had no association with increased risk of 30-day complications. The study affirms the safety of PCT-guided treatment in real-life situations.

Schuetz et al (2012) did a meta-analysis of 14 studies involving 4211 patients with acute infections of the respiratory tract. Mortality was comparable in both the PCT group (5.7%) and the control group (6.3%). The risk for treatment failure in the PCT group was significantly lower than in controls. Duration of therapy was reduced in heterogeneous patient populations including the emergency department (–3.70 days) the ICU (-3.17 days) and those with CAP (-3.34 days). In patients with VAP the adjusted difference in days was -2.23 ($p = 0.01$).

In an earlier study, Schuetz et al (2011) proposed an algorithm for use of PCT in low risk /low acuity, moderate risk/moderate acuity and high risk/high acuity settings based on their systematic review of 14 clinical trials. In the low risk and moderate risk setting they strongly discourage antibiotics at PCT concentrations of less than 0.1 µg/L but encourage antibiotics at concentrations greater than 0.25 µg/L. At levels of >0.5 µg/L antibiotics are strongly recommended.

Pvoa and Sallah (2012) note that in most of the clinical trials, the control group is treated according to the existing standard of care. They emphasize the need to differentiate terms like best care, standard of care and usual care. They emphasize that any minimum duration of treatment for patients in the control group should be clearly stated. Clinicians may be uncomfortable withholding antibiotics in critically ill patients based on a PCT value. Recommendations need to be set out for the antibiotic duration in the control group e.g. according to the site of infection and pathology.

Bréchot et al. (2015) note that the PCT has poor diagnostic accuracy in the ICU for detection of bacterial infections. They attribute the poor performance of PCT for diagnosis in the critically ill to a high baseline PCT that may be already present in ICU patients. Schuetz et al

(2011) suggest that in the ICU procalcitonin measurement should not delay initiation of antibiotics. The preferred strategy would be periodic measurement of procalcitonin concentrations after starting empiric antibiotic treatment. If the PCT level drops to <0.5 µg/L or by at least 80-90% from baseline with clinical improvement, antibiotics can be stopped. They suggest that in the surgical ICU a drop in the absolute procalcitonin measurement to <1.0 µg/L can guide discontinuation of antibiotics.

In the ICU setting PCT has therefore been used not as a diagnostic marker of sepsis but usually as part of an algorithm to discontinue antibiotics. One of the earliest studies that used PCT in decision making to stop antibiotics in the ICU was by Nobre et al. (2008). They carried out a randomized controlled trial in septic ICU patients. Antibiotic exposure for the first sepsis episode was 3.5 days shorter in the PCT arm compared to controls. There was clinical cure in 90.3% of patients in the PCT arm versus 83.8% in the controls. Patients in the PCT arm had reduced median length of stay in ICU (3 days) compared to the control group (5 days). Mortality at 28 days was similar for both groups (16.2%) as well as in-hospital mortality (19.4% in PCT group; 18.9% in the control group). The procalcitonin group therefore had reduced exposure to antibiotics and shorter ICU stay without increased mortality.

The PRORATA trial conducted by Bouadma et al. (2010) is a landmark study done in ICU patients that utilised a procalcitonin algorithm for antibiotic treatment. It was a multicenter study that was done in France and enrolled 630 patients in medical and surgical ICUs. Clinicians were asked to stop antibiotic treatment if the PCT level was <0.5 µg/L or showed a reduction of greater than 80% from peak levels. If the PCT concentration decreased by less than 80% and the level was ≥0.5 µg/L, continuation of antibiotic therapy was encouraged. If there was an increase from the peak level and the concentration was ≥0.5 µg/L a change of antibiotics was strongly encouraged. There was a 23% relative reduction in days of antibiotic exposure in the PCT group compared with controls. The 60 day probability of survival for the two groups as estimated by the Kaplan-Meier curve showed no difference.

Hochreiter et al. (2009) published another landmark study that used PCT to guide antibiotic duration of treatment in a surgical ICU. Antibiotics were discontinued in the PCT group when patients improved and the PCT level decreased to below 1 µg/L or decreased to 25-35% of baseline concentration. The PCT group had reduced duration of antibiotic treatment (5.9 days)

compared to the control group (7.9 days) without an increase in mortality. The PCT arm also had reduced length of ICU stay.

Kopterides et al. (2010) conducted a meta-analysis of 7 clinical trials where PCT algorithms were used to guide antibiotic duration in the ICU. They found that antibiotic duration was reduced for the first episode of sepsis in the PCT group, compared to the control group, by approximately two days without increased rates of relapse or mortality. In another meta-analysis of 15 clinical trials (Lam et al. 2018) there was a significant reduction in antibiotic duration under procalcitonin guidance. Jensen et al. (2011) used PCT in a strategy that escalated antibiotics whenever an "alert procalcitonin" occurred. The PCT group had prolonged antibiotic treatment, increased ICU stay and worse organ dysfunction compared to the control group. Such a PCT strategy designed solely to escalate antibiotic therapy may be detrimental and is therefore not encouraged.

Broyles (2017) performed a single centre retrospective study to evaluate the impact of a PCT algorithm to antibiotic stewardship practices. In the four years after implementation of a PCT algorithm there was a significant reduction in median days of therapy compared to the pre-PCT algorithm period (9 days vs. 17 days; $p<.0001$). There are few studies that have performed economic evaluations of PCT-based antibiotic algorithms. Heyland et al. (2011) evaluated such a strategy and found that PCT-guided treatment resulted in mean cost savings of 470 Canadian dollars for each antibiotic course.

Different trials use different cut-off values to discontinue antibiotic treatment in septic ICU patients. Carr (2015) argues that it is more important to follow PCT trends in the individual patient rather than using absolute values to either initiate or discontinue antibiotic treatment. Procalcitonin based antibiotic algorithms therefore offer clinical benefits and also cut down on treatment costs. The studies above show clear benefits in reducing antibiotic duration of therapy without an increase in infection relapse rates or mortality. There is no published data from Africa regarding the utilization of PCT based algorithms to guide antibiotic duration of treatment. Most published studies have focused on use of PCT in outpatients and in medical ICU patients. There is need for more data on use of PCT in surgical trauma settings both in the developed world and in resource limited settings like Africa. The current study aims to bridge this gap and evaluate the utility of PCT-based antibiotic treatment in a surgical trauma ICU in South Africa.

2.6 Conclusion

Procalcitonin is a biomarker that was used in early studies for diagnosis of sepsis. Its main use in ICU patients however, is in monitoring response to antibiotic treatment and determining when antibiotics may be safely discontinued. This role is especially important in septic multiple trauma patients in whom other biomarkers may be persistently elevated. The following chapter presents the research methodology used to collect and present data.

CHAPTER - 3. RESEARCH METHODOLOGY

3.1 Introduction

This chapter discusses the research design and the study population. The data collection tool is discussed as well as limitations of the study methodology. Finally the ethical considerations are elaborated upon.

3.2 Rationale for the methodology

A crossover design was chosen because patients in both study groups would be cared for by the same clinicians. The PCT result was non-blinded and available to clinicians. This might have introduced treatment bias by influencing clinicians to follow a PCT algorithm in both groups if all patients were recruited concurrently. A crossover design eliminated potential bias because control group patients were recruited first followed by the intervention group with no overlap in treatment periods.

3.3 Research design

The study was a prospective, two-period crossover case-controlled, interventional study conducted in the trauma ICU at Charlotte Maxeke Johannesburg hospital. Patients were recruited from April 2014 to July 2015.

3.3.1 Sample size

The ICU used for the study is a 9 bed trauma ICU. The following factors were considered in calculating the sample size.

- An α level (p value) of 0.05
- Power $(1-\beta)$ of 0.80
- Standard deviation (σ) of 3 days
- A difference of 2 days between the mean in one group and the mean in the other group $(\mu_1 - \mu_2)$ of 2 days would be significant.
- The z values were obtained from statistics tables.

The formula used for calculation of sample size (n) = $2\left[\frac{(z\alpha - z_{\beta})\sigma}{\mu_1 - \mu_2}\right]^2$

= **36 patients** per group.

= **40 patients** per group to cover for any patient that is lost to follow-up.

3.3.2 Control period:

The initial phase was a period of gathering baseline data on antibiotic prescribing habits in the ICU. Forty patients with suspected or confirmed sepsis were recruited consecutively into the control group between April 2014 and January 2015. All the data described in section 3.5 was collected during this period. Procalcitonin was not routinely measured in patients with confirmed or suspected sepsis and there was no algorithm in place to guide duration of antibiotic treatment. Antibiotics were given according to the existing standard of care and to cover the expected spectrum of micro-organisms. Antibiotics were changed to cover the spectrum of organisms cultured from the site of sepsis. Decisions regarding discontinuation of antibiotic treatment were left at the attending doctor's discretion.

3.3.3 Intervention period:

In the intervention period, 40 patients with confirmed or suspected sepsis were recruited consecutively into the intervention group between February 2015 and July 2015. The PCT level was measured at study recruitment and then on alternate days. Antibiotics were given empirically according to the site-specific ICU algorithm and always covering at least the spectrum of previously prescribed antimicrobials as well as expected organisms. Antibiotics were escalated or de-escalated according to proven culture results. If the PCT decreased to an absolute value of less than 0.5 µg /L or by ≥80% from the peak PCT concentration, clinicians were encouraged to stop antibiotics. Antibiotics were not stopped if there were ongoing signs of sepsis (e.g. temperature ≥ 38.3ºC) with an obvious source of sepsis. The PCT complemented but did not replace clinical decision making and clinicians were able to deviate from the PCT algorithm if the need arose. Although clinicians were encouraged to stop antibiotics according to this PCT algorithm the decision to stop was at the discretion of the attending clinician.

3.3.4 Definitions of terminologies used in the study

Sepsis was defined according to previously accepted sepsis 2 criteria. It was defined clinically when systemic inflammatory response syndrome (SIRS) criteria such as tachycardia, tachypnoea and fever occurred in combination with a possible source of sepsis.

Sepsis was suspected if there was clinical suspicion of sepsis as defined above but negative microbiology cultures. Sepsis was confirmed if a clinically obvious source of infection was present or if microbiology cultures obtained from suspected sites of infection were positive.

Antibiotic dose duration was calculated by dividing number of total doses by number of daily doses. This gave more accuracy especially in cases of missed doses. To calculate antibiotic usage in cases of combination treatment, antibiotic dose duration was calculated from the antibiotic given the longest. If the antibiotic regimen was changed without interruption the antibiotic usage was calculated as a continuum for both antibiotics.

The intervention was done for every episode of sepsis with follow-up for a total of 28 days from the date of study inclusion or until discharge from hospital.

A relapse was defined as culture of at least one of the initial causative bacteria (same phenotype with $\leq$3 differences in the antimicrobial susceptibility profile and same species) and same organ occurring more than 48 hours after discontinuation of appropriate antibiotics and with accompanying clinical evidence of infection.

A hospital acquired infection (HAI) was defined as an infection acquired more than 48 hours after hospital admission and was not present prior to admission. A community acquired infection was defined as an infection that existed at admission and becomes apparent less than 48 hours after hospital admission.

Bacteria were defined as multi drug resistant (MDR) if they were not susceptible to at least one antibiotic in three or more antibiotic classes (Magiorakos et al. 2012). These bacteria included methicillin resistant *Staphylococcus aureus* (MRSA), extended spectrum β-lactamase (ESBL) producing *Enterobacteriaceae*, MDR *Acinetobacter baumannii* and MDR *Pseudomonas aeruginosa*.

Antibiotics were considered appropriate if including at least one drug to which the isolate was susceptible and appropriate for the site of infection

3.4 Study Population

Adult patients in the trauma ICU suspected clinically to have sepsis and who were either not on antibiotics or had been on antibiotic therapy for less than 48 hours were requested to give written consent to participate. First degree relatives were approached for patients who could not consent. Patients were recruited consecutively until the sample size was achieved.

3.4.1 Inclusion criteria:

Patients above the age of 18 years admitted to the trauma ICU with suspected or confirmed bacterial sepsis with written consent and who survived more than 48 hours after study inclusion.

3.4.2 Exclusion criteria:

This included patients in whom consent could not be obtained and those who had severe co-morbidities e.g. congestive cardiac failure, cirrhosis, insulin dependent diabetes, chronic renal failure requiring dialysis, pregnancy and advanced HIV infection with CD4 <100 cells/μL. Patients requiring prolonged antibiotic therapy e.g. *Clostridium difficile, Listeria monocytogenes,* tuberculosis, fungal sepsis, osteomyelitis, lung abscess and sepsis involving a prosthetic device that could not be removed were also excluded. Patients who had received more than 48 hours of antibiotics before enrolment and those with poor chance of survival (ISS score ≥45, injury critical or untreatable at screening) were also excluded.

3.5 Research instrument

3.5.1 Format of the data collection sheet

The following data was collected:

1) Each patient had the following baseline demographic data recorded at study inclusion (age, gender and hospital number).
2) Diagnosis at ICU admission.
3) Reason for ICU admission
4) Co-morbidities as described in data collection sheet
5) Severity of the clinical condition at study recruitment was evaluated using the injury severity score (ISS). Presence of organ dysfunction was determined with the sequential organ failure assessment (SOFA) score
6) The following was recorded daily:
    a. Vital signs
    b. Ventilation status (patient ventilated or not)

c. Any routine blood tests done e.g. full blood count, liver function tests, renal function tests and CRP
d. Any microbiology culture and antibiotic sensitivity results
e. Source of sepsis if known.
f. Infectious complications e.g. bacteraemia, pneumonia, urinary tract infections.
g. All antibiotics given daily to the patient with dosages.

In addition, all patients in the intervention group had a PCT done at study recruitment and then every 48 hours until antibiotics were discontinued. In the control group the PCT was done according to the existing standard of care and was left to the discretion of the attending doctor. A copy of the data collection sheet can be found in Appendix A.

3.6 Laboratory procedure

The procalcitonin (PCT) was measured by the chemistry laboratory using patient serum measured on the ADVIA Centaur ®BRAHMS PCT assay. The assay has a measurement range of 0.02 - 75µg/L and analytical sensitivity of 0.02µg/L.

Microbiological specimens were processed in the microbiology laboratory. Identification and antimicrobial susceptibility testing (AST) of cultured organisms was done using the Vitek®2 (bioMérieux) instrument. Alternatively, AST was performed by disc diffusion testing or E-test® (bioMérieux). All AST results were interpreted according to the current Clinical and Laboratory Standards Institute (CLSI) criteria.

3.7 Data analysis

All the data was coded after it had been collected prior to being entered into a database. Comparisons were made between the two groups using mean (±standard deviation) and t-test for continuous variables. The p-value was determined by a chi square but if the number of items constituting a variable was less than 10 then the p value was calculated using the Fisher's exact test. Statistical significance was considered for two sided $p < 0.05$. Categorical variables were compared using percentages.

Diversity between study groups was determined using chi square test and Fisher's exact test as appropriate. Risk ratio for death and infectious complications (relapse) were calculated at

the 95% confidence interval. Kaplan-Meier survival curves were evaluated by the log-rank test.

A multivariate analysis was not undertaken due to the small number of study subjects. Data was analysed using Statistica™ version 13.2.

3.7.1 Presentation of data

The data is presented as tables, bar graphs, pie charts and curves. Tables were used to present variables such as baseline characteristics. Bar graphs and pie charts were used to present differences between groups. A Kaplan-Meier survival curve was used to demonstrate differences in mortality between groups.

3.8 Limitations of the study methodology

The study sample size was small which may have reduced potential differences noted in the study that did not reach statistical significance.

The patients were not assigned to either study group using randomization. This may have potentially introduced a sampling bias in the study.

3.9 Ethical considerations

3.9.1 Access to Charlotte Maxeke Johannesburg academic hospital

An application to conduct research in the hospital was granted by the hospital chief executive officer (CEO). The head of the trauma ICU at the hospital granted permission to carry out research in the unit.

3.9.2 Informed consent from study participants

All study participants had to give written informed consent to participate in the study. Relatives were approached for written informed consent for patients who could not consent. Once the patient was awake and able to give consent they were approached to give new written informed consent. If consent was declined the patient was not included in the study.

3.9.3 Ensuring confidentiality and anonymity of study participants

The data collection sheet did not contain the patient names so as to maintain patient confidentiality. Each patient was assigned a unique study number that was later linked to the hospital number in a code book.

3.9.4 Ensuring no harm comes to study participants

Clinicians taking care of patients were not obliged to adhere to the PCT algorithm to determine length of antibiotic treatment. They could use their own discretion to overrule the algorithm and continue antibiotics.

3.9.5 Ethics approval

The research protocol was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand. A copy of the ethics clearance certificate can be found in Appendix B.

3.10 Funding

The procalcitonin assay was measured every 48 hours which is routine practice in the ICU where the study was carried out. Therefore, there was no need for extra funding from external sources.

3.11 Conclusion

A cross over prospective study was an adequate research strategy for the study. It eliminated potential clinical bias by preventing the intervention from being inadvertently implemented in the control group. The data collection tool was robust and ethical considerations were implemented before undertaking the study. The next chapter presents the study findings.

CHAPTER - 4. RESULTS

4.1 Introduction

This chapter presents the study findings. The data is presented in the form of tables, bar graphs, pie charts, box and whisker graphs and survival curves. Where the data was normally distributed, clinical significance was tested using t-tests, chi square and log rank regression analysis where appropriate.

4.2 General characteristics of the study population

The two groups, control and intervention, were well matched in terms of baseline demographics as shown in table 4.1 below. There was no significant difference in other markers of sepsis severity e.g. the SOFA score, baseline temperature, white cell count or the CRP. The intervention group however, had a worse injury severity score (ISS) and this difference was statistically significant (p=0.002)

There was a significant difference in the baseline PCT between the two groups but the number of patients in the control group who had a PCT level was low (n=10) hence the wide confidence interval in the control group. There were more patients in the intervention group who had underlying infection with human immunodeficiency virus (HIV) compared to the control group.

Table 4.1: General characteristics of the study population

Characteristic	**Control group (n=40)**	**Intervention group (n=40)**	**p value**
Age in years (mean ±SD)	36.1±14.7	36.0 ±12.1	0.96
Gender, n (%)			
Male	39 (97.5%)	33 (82.5%)	
Female	1 (2.5%)	7 (17.5%)	
Mechanical ventilation type, n (%)			

Synchronized intermittent mechanical ventilation (SIMV)	26 (66.7%)	27 (69.2%)	-
Continuous positive airway pressure (CPAP)	13 (33.3%)	12 (30.8%)	-
SOFA score (mean ±SD)	7.3±2.92	7.1±2.98	0.70
ISS score (mean ±SD)	20.3±10.18	26.8±8.17	0.002
GCS score (mean ±SD)	7.1±3.68	6.1±3.02	0.21
Sepsis markers (mean ±SD)			
Temperature ^{o}C	37.5±0.89	37.1±5.94	0.70
Total white cell count ($x10^{9}$/L)	14.5±8.92	15.4±6.45	0.6
CRP (mg/L)	227.8±119.89	263.1±91.26	0.14
PCT (µg/L)	91.0±159.62 (n=10)	29.2±58.13 (n= 40)	0.04
Co-morbid illnesses, n (%)			
None	34 (85%)	31 (77%)	-
Cardiac	2 (5%)	1 (2.5%)	-
Neurologic	2 (5%)	1 (2.5%)	-
HIV	1 (2.5%)	6 (15%)	-
Chronic lung	1 (1%)	0	-
Endocrine	0	1 (2.5%)	-
Received antibiotics prior to study inclusion, n (%)			
Surgical prophylaxis	5	2	-
Sepsis	4	2	-

Reason for ICU admission, n (%)			
Mechanical ventilation	22 (55%)	15 (37.5%)	-
Haemodynamic instability	5 (12.5%)	3 (7.5%)	-
Major surgery	3 (7.5%)	1 (2.5%)	-
Severe injury	8 (20%)	21 (52.5%)	-
Sepsis	2 (5%)	0	-
Source of first episode sepsis, n (%)			
Pulmonary	16 (40%)	18 (45%)	-
SSTIs	9 (22.5%)	5 (12.5%)	-
Abdominal	8(20%)	3 (7.5%)	-
Urinary tract infection (UTI)	1(2.5%)	4 (10%)	-
Primary Bloodstream	3 (7.5%)	8 (20%)	-
Catheter related blood stream infection	0	2 (5%)	-
Unknown	3 (7.5%)	0	-

4.3 The first sepsis event:

Hospital acquired infections (HAIs) accounted for 65% of all first episodes of sepsis (n=52) while the rest (35%) were classified as community acquired infections (n=28).

A breakdown of organisms isolated from cultures of relevant specimens is shown in figure 4.1 below.

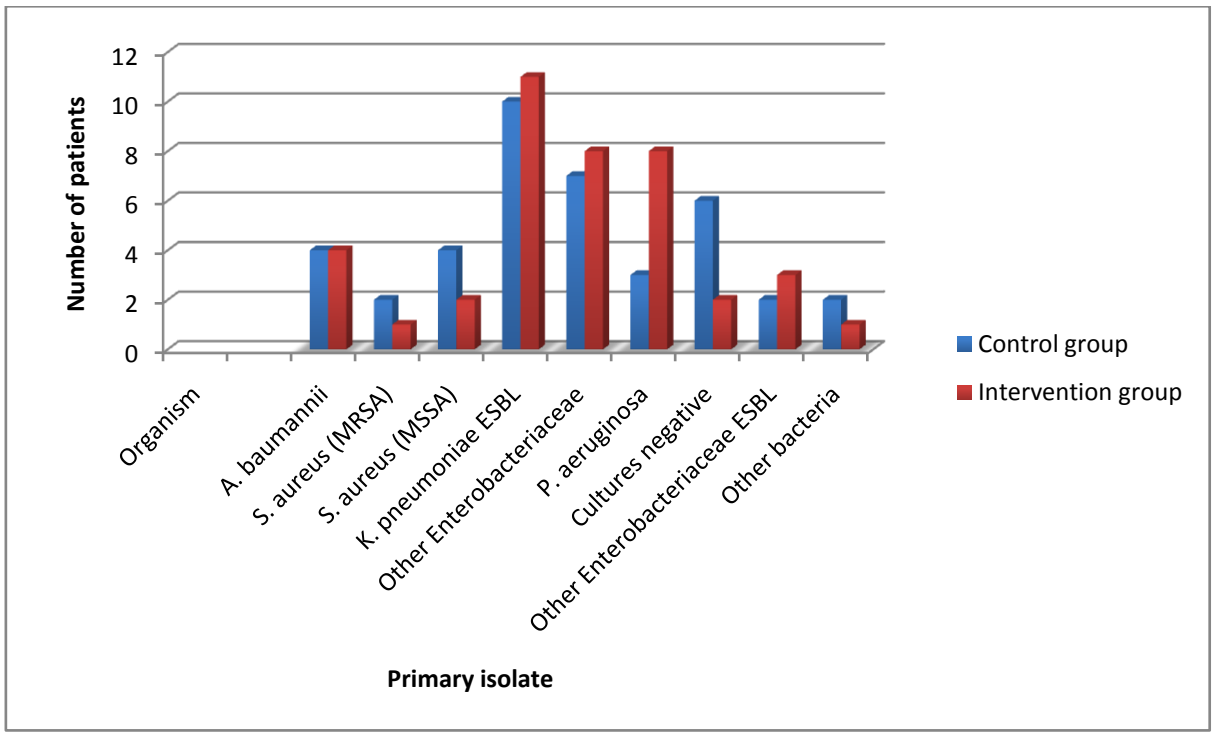

Figure 4.1: Primary organism isolated from culture for the first episode of sepsis

The most commonly isolated organism in both groups of patients was *Klebsiella pneumoniae* ESBL. The control group had a higher number of patients where cultures were negative (6 patients vs. 2 patients). The intervention group had a slightly higher number of *Pseudomonas aeruginosa* infections (3 patients vs. 8 patients).

Table 1 shows that the main source of sepsis in both groups was pulmonary. Since almost all patients were ventilated, ventilator associated pneumonia (VAP) was assumed to be a major source of sepsis in both groups of patients. The control group had more patients with source of infection in the abdomen and skin & soft tissue infections compared to the intervention group.

There were 8 patients (20%) in the control group who needed inotrope support for the first episode of sepsis compared to 5 patients (12.5%) in the intervention group.

The first sepsis event occurred approximately a day earlier in the control group (3.85 ICU days) compared to the intervention group (5.05 ICU days) as can be seen from the group means in figure 4.2 below.

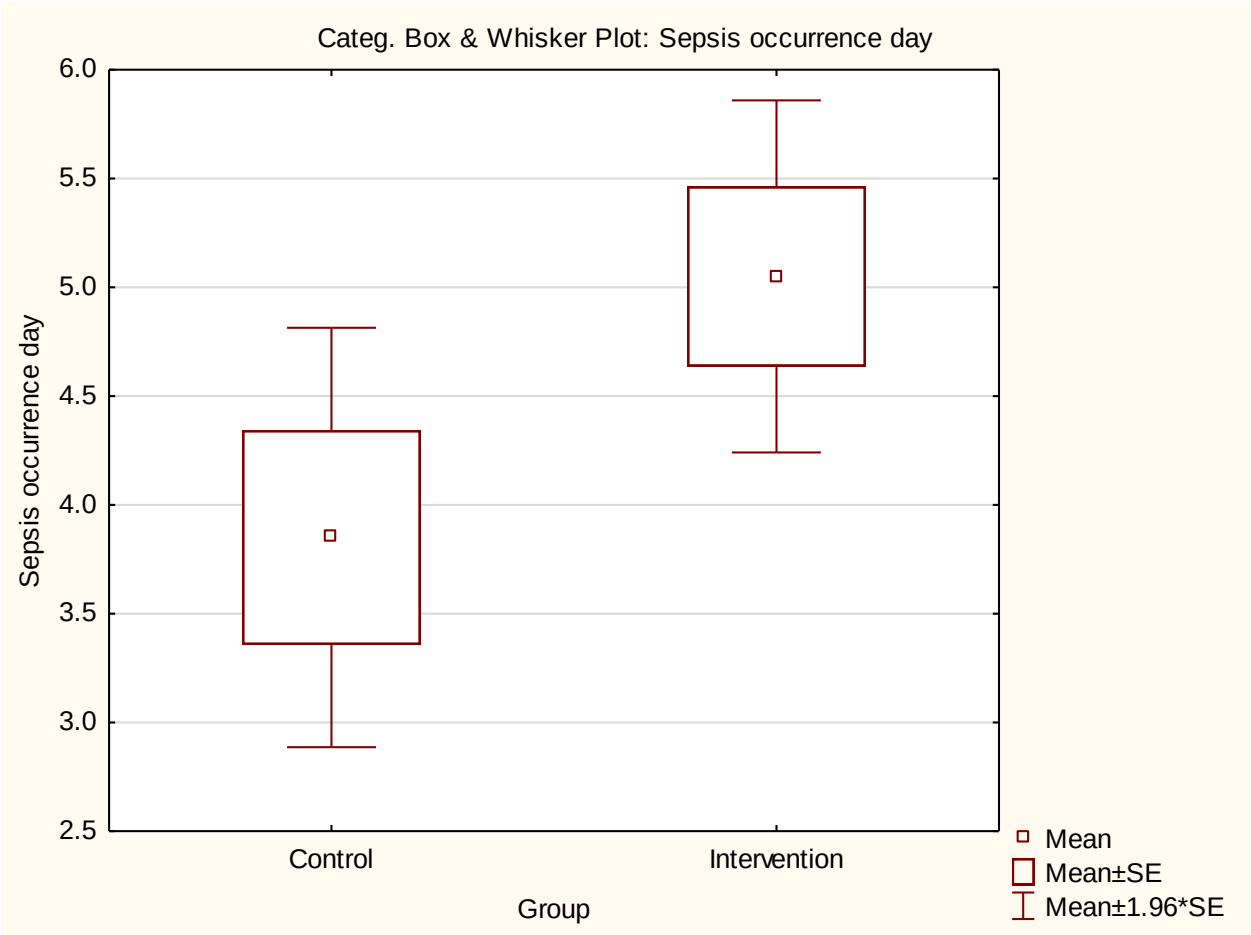

Figure 4.2: Sepsis occurrence day for control group and intervention group

4.4 Treatment of the first episode of sepsis

4.4.1 Empiric antibiotics

The most commonly used empiric antibiotic was piperacillin-tazobactam (piptaz) There were 16 patients in the control group and 36 patients in the intervention group who received piptaz as the empiric antibiotic. Carbapenems were more likely to be given empirically in the control group compared to the intervention group. A breakdown of empiric antibiotics used is shown in table 4.2 below.

Table 4.2: Empiric antibiotics prescribed for the first sepsis event

Empiric antibiotic	Control group, n (%)	Intervention group, n (%)	Row totals. n
Carbapenem	9 (22.5%)	1 (2.5%)	10
Piperacillin-tazobactam	16 (40%)	36 (90%)	52
Co-amoxiclav	12 (30%)	2 (5%)	14
Third generation cephalosporin	1 (2.5%)	0	1
Vancomycin	0	1 (2.5%)	1
Other	2 (5%)	0	2
Total	40 (100%)	40 (100%)	80

When empiric antibiotics were assessed in terms of appropriateness to the cultured organism it was found that an equal number of patients in each group received appropriate empiric treatment (16 patients in each group). There were more patients in the intervention group who received inappropriate empiric antibiotics (22 patients) compared to the control group (17 patients) but the difference was not statistically significant (p=0.59). Figure 4.3 below presents these findings.

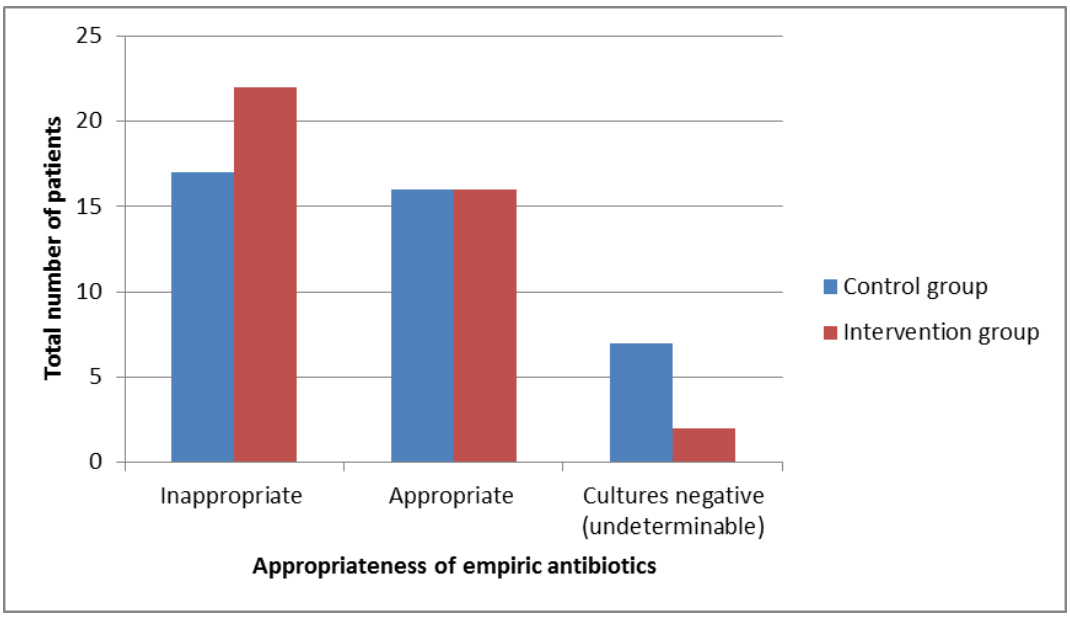

Figure 4.3: Appropriateness of empiric antibiotics for the first sepsis event

4.4.2 Definitive antibiotics

The most commonly used definitive antibiotic was a carbapenem for both the control group (13 patients) and the intervention group (16 patients). The breakdown of antibiotics used for empiric treatment is presented in table 4.3 below.

Table 4.3: Definitive antibiotics used for first sepsis event

Empiric antibiotic	**Control group, n (%)**	**Intervention group, n (%)**	**Row totals, n**
Carbapenem	13 (32.5%	16 (40%)	29
Piperacillin-tazobactam	8 (20%)	12 (30%)	20
Co-amoxiclav	9 (22.5%)	1 (2.5%)	10
Third generation cephalosporin	3 (7.5%)	2 (5%)	5
Vancomycin	3 (7.5%)	1 (2.5%)	4
Cefepime	1 (2.5%)	2 (5%)	3
Other	3 (7.5%)	6 (15%)	9
Total	40 (100%)	40 (100%)	80

4.4.3 Treatment duration

When duration of therapy for the first sepsis episode was compared between groups, the intervention group had a shorter duration of treatment (mean 9.3±5.67 days) compared to the control group (10.9±2.62 days). This difference however, did not reach statistical significance (p= 0.10)

4.4.4 Clinician compliance to PCT algorithm

There were 15 patients (37.5%) in the intervention group where the clinician did not comply with the PCT algorithm to stop antibiotic treatment. Antibiotics were prolonged for a range of between 1 and 4 days beyond the recommended stop as shown in table 4.4 below:

Table 4.4: Number of days that antibiotics were prolonged

Number of days antibiotics were prolonged after recommended stop	**Number of patients (n=15)**
One day	4
Two days	3
Three days	5
Four days	3
Total	15

Treatment duration was 9.73 ± 2.37 days in those in whom the study algorithm was overruled compared to 9.08 ±2.78 days in those patients where the PCT algorithm was followed. (p=0.45)

The reasons for not stopping antibiotics are shown in figure 4.4 below:

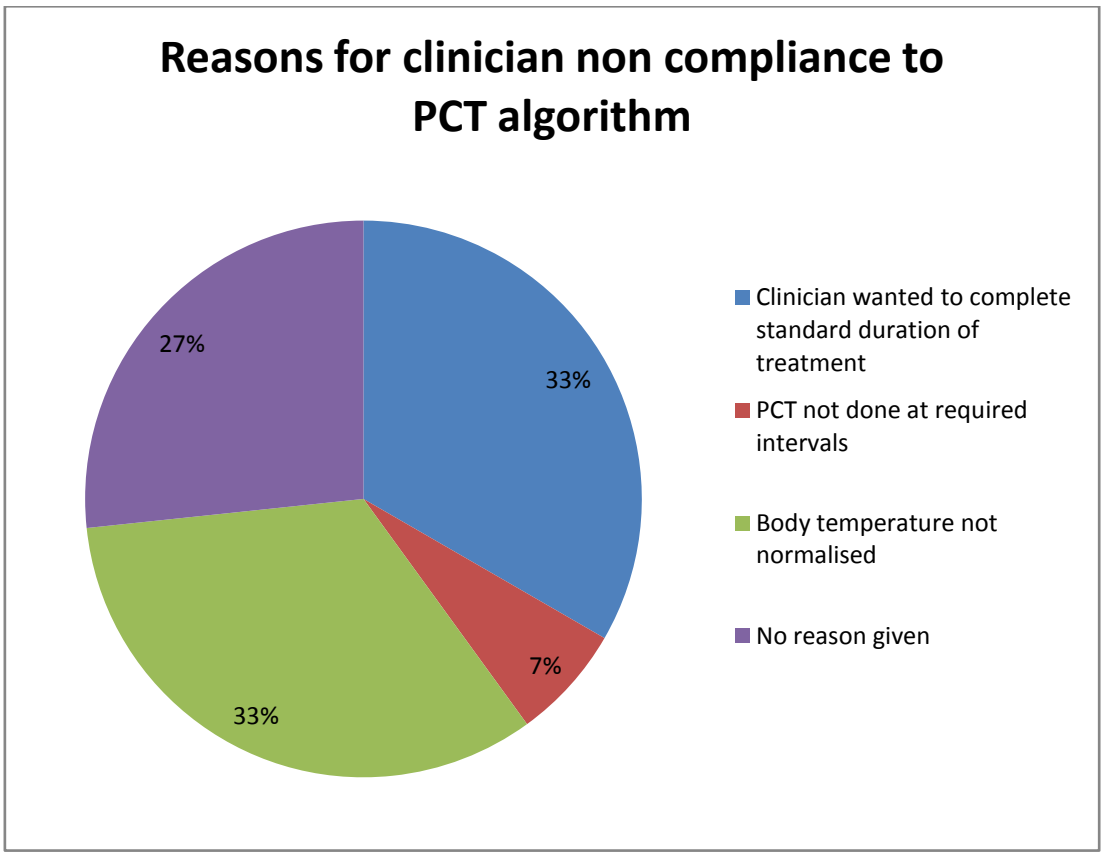

Figure 4.4: Reasons for non-compliance to PCT algorithm

The baseline PCT value had no influence on the duration of treatment for a first episode of sepsis. (p=0.8).

Patients with bacteraemia (primary or secondary) had longer duration of treatment (mean 11.6 days) compared to patients with negative blood cultures (mean 8.84 days). The difference is shown in figure 4.5 below and was statistically significant (p value=0.003).

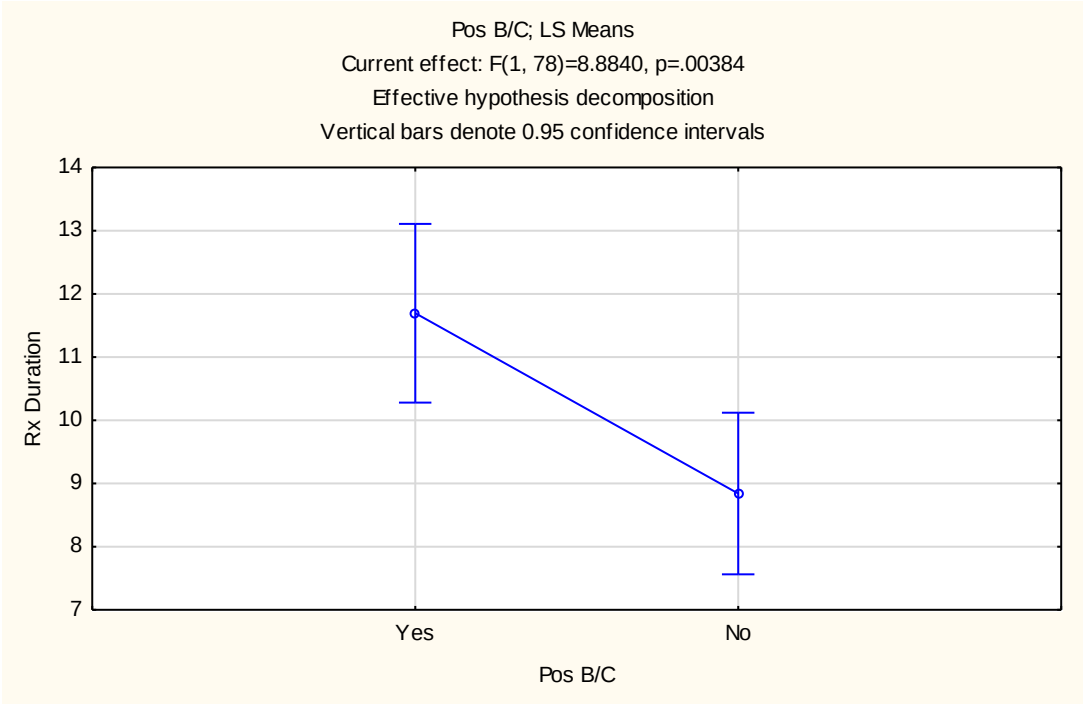

Figure 4.5: Treatment duration for patients with and without bacteraemia

4.5 Antibiotic free days

The total number of days that patients stayed antibiotic free was calculated for both groups and is illustrated in figure 4.6 below. Patients in the intervention group had more antibiotic free days alive (mean 7.7±6.57 days) compared to the control group (mean 3.8±5.22 days) and the difference was statistically significant (p=0.004) n=80.

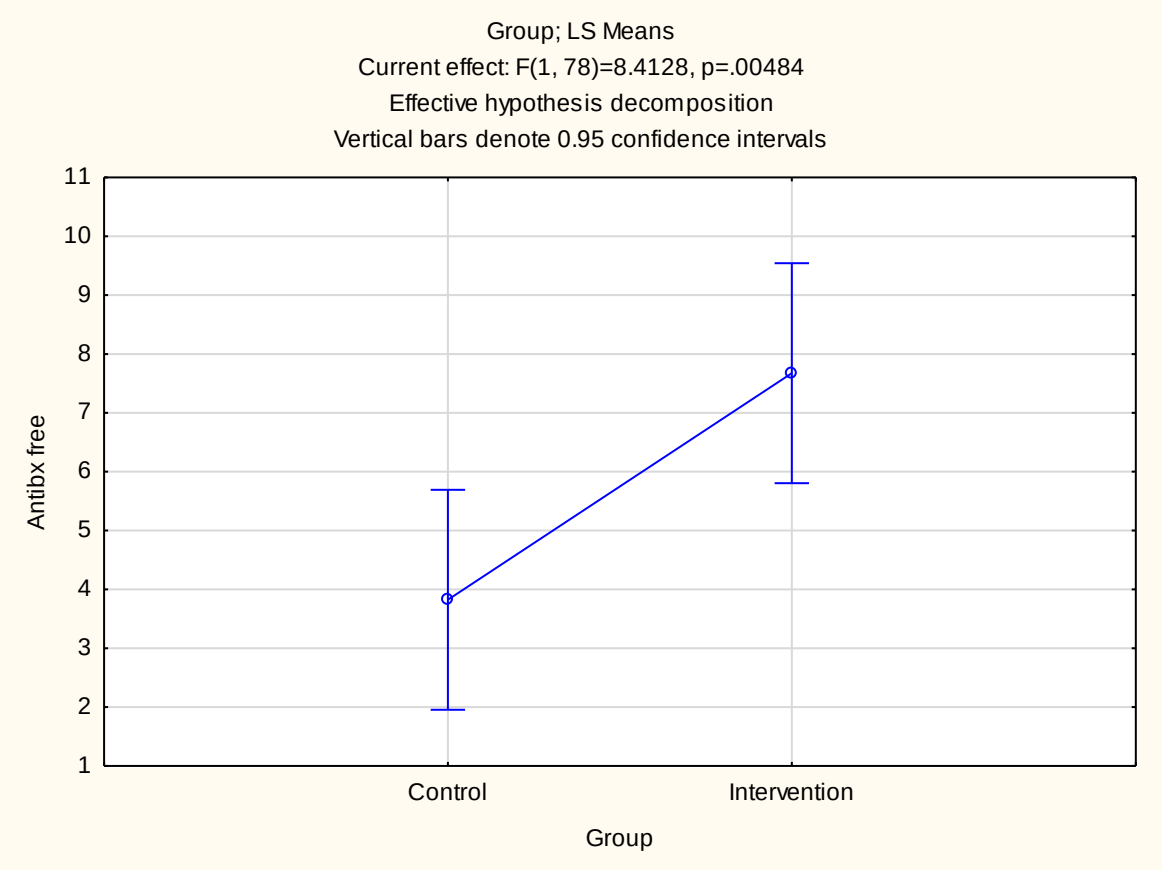

Figure 4.6: Antibiotic-free days alive in the control and intervention groups

4.6 Admission period

The period of admission was compared between the control group and the intervention group.

4.6.1 Length of ICU stay

The intervention group had a shorter ICU stay (mean 16.1±8.31 days) compared to the control group (mean 17.6±13.84 days) but this difference was not statistically significant (p=0.5) n=80. Figure 4.7 below illustrates the findings described.

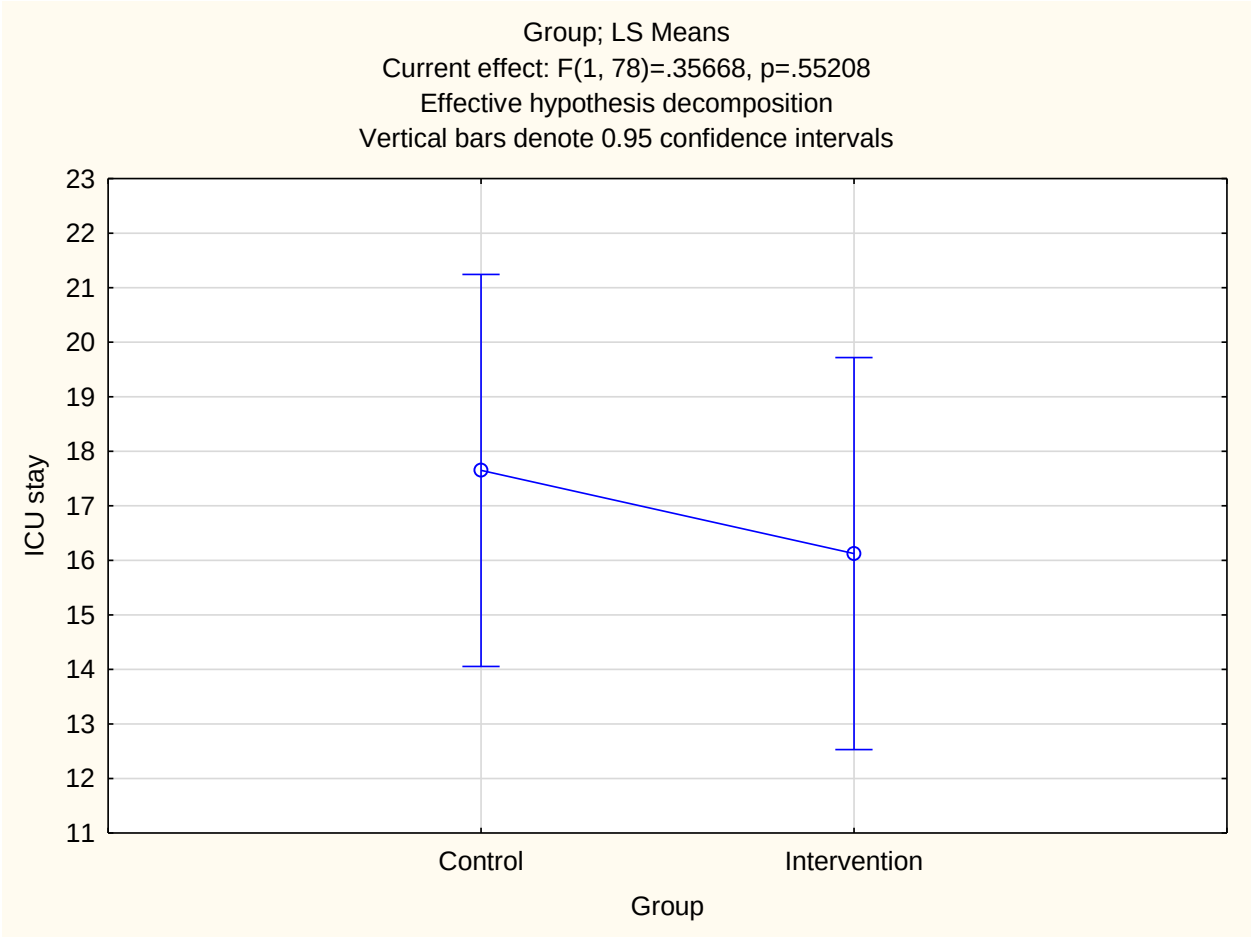

Figure 4.7: Mean ICU stay (in days) for control group and intervention group

Patients who had positive blood cultures had longer ICU stay (mean 19.9 days) compared to those with negative blood cultures (14.3 days) and the difference was statistically significant (p=0.02). The mean ICU stay compared to bacteraemia is shown in figure 4.8 below.

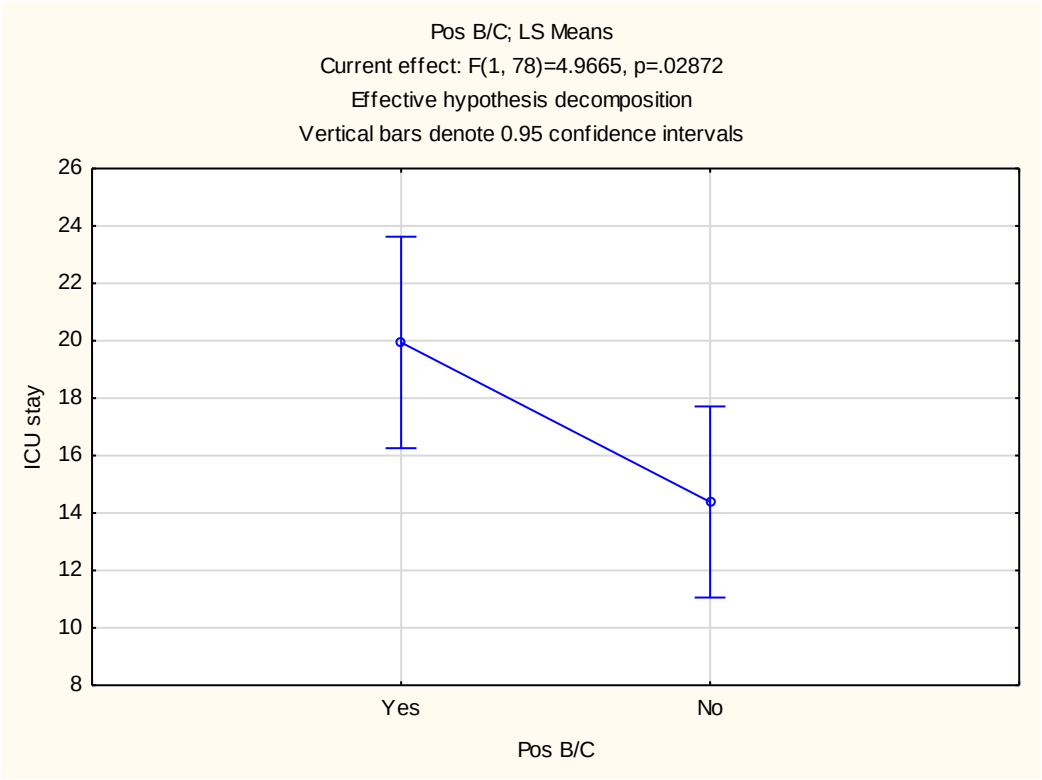

Figure 4.8: Mean ICU stay (in days) in patients with and without bacteraemia.

4.6.2 Hospital stay

The intervention group had a slightly longer mean hospital stay (25.4±8.32 days) than the control group (24.5±17.03 days) but the difference was not statistically significant (p=0.76). The mean hospital stay for both groups is illustrated in figure 4.9 below.

Figure 4.9: Mean hospital stay (in days) for the control and intervention groups

4.7 In-hospital mortality and survival

4.7.1 Hospital mortality in the two study groups

Hospital mortality was compared between the two groups. The intervention group had fewer deaths (6 patients) compared to the control group (12 patients). There were more patients who were discharged from hospital in the intervention group compared to the control group (19 patients vs. 11 patients). Final outcome measurements are shown in figure 4.4 below.

Table 4.5: Outcome measures for the control group and intervention group

Outcome **n=80**	**Control group, n (%)**	**Intervention group, n (%)**	**Totals, n**
Deceased	12 (30%)	6 (15%)	18
Alive, still admitted	17 (42.5%)	15 (37.5%)	32
Discharged home	8 (20%)	12 (30%)	20
Transferred out	3 (7.5%)	7 (17.5%)	10
All groups	40 (100%)	40 (100%)	80

4.7.2 Survival curves for both study groups

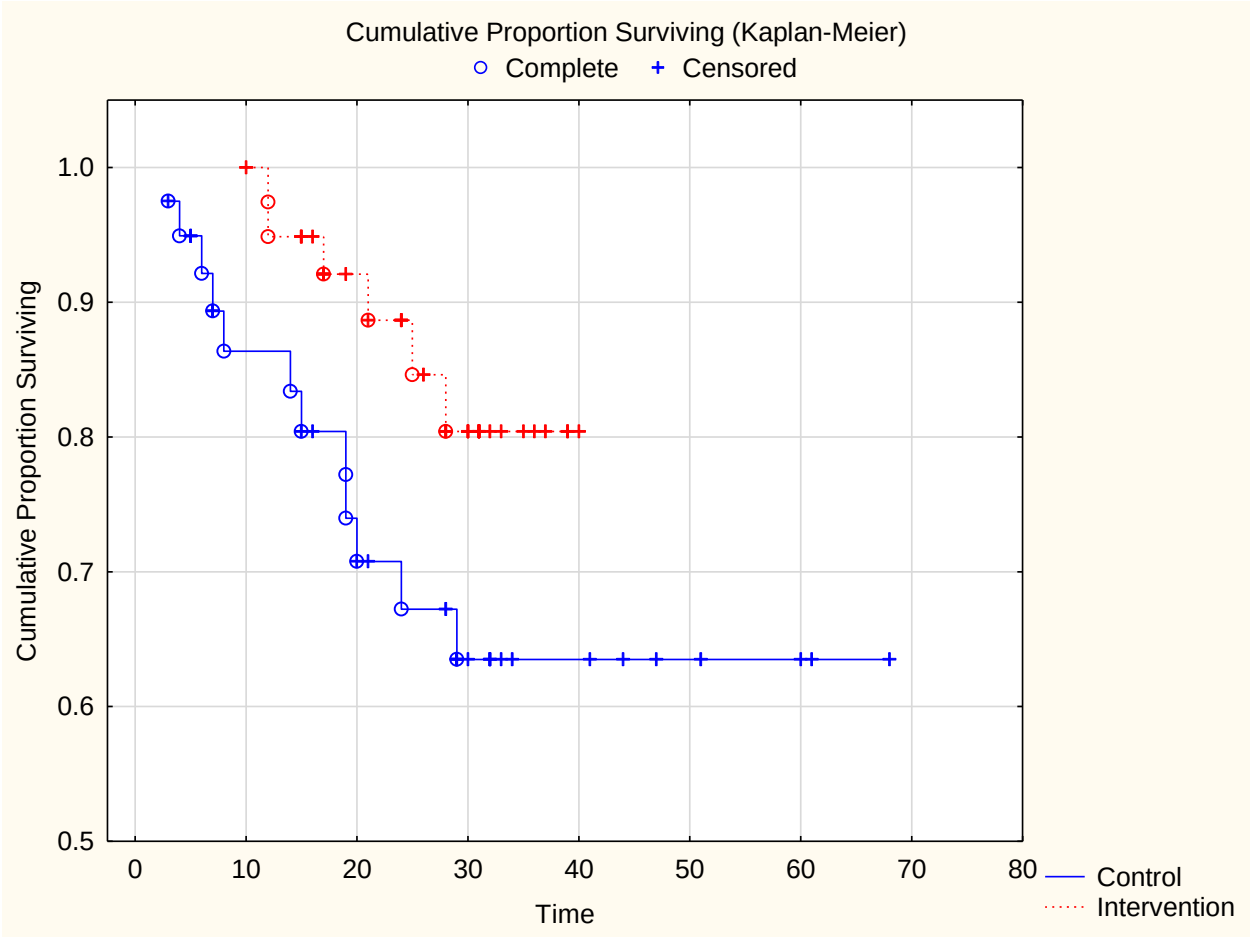

Figure 4.10: Kaplan-Meier survival curves for intervention group and control group

Survival between the two groups was compared using Kaplan-Meier analysis as shown in figure 4.10 above. The complete cases are the patients who suffered a death event. The censored cases are patients who are alive and did not suffer the event (death). The intervention group had improved survival compared to the control group (Wilcoxon log rank analysis had a p value of 0.045).

4.7.3 Procalcitonin measurements compared to outcomes

A total of 50 patients had a baseline PCT obtained at the onset of sepsis (40 in the intervention group and 10 in the control group).When outcomes were compared to the mean baseline PCT hospital mortality was highest in those patients with the highest mean PCT value (119.8 µg/l). Patients with the lowest mean PCT values were either discharged home or to a primary level hospital (mean PCT values of 7.2 µg/l and 11.9 µg/l respectively). The results are shown in table 4.5 below.

Table 4.6: Profile of PCT measurements compared to patient outcomes

Outcome	PCT mean (µg/l)	Total number of patients (n=50)	Standard deviation
Alive (still admitted in hospital)	35.48	19	71.80
Deceased	119.84	10	152.92
Transferred to primary care facility	7.29	9	11.19
Discharged home	11.98	12	19.60
Total (all groups)	41.64	50	89.39

4.7.4 SOFA score compared to final outcome

Patients who demised had a mean SOFA score of 10.2 while those who were discharged home or transferred to a primary care facility had the lowest mean SOFA scores (5.6 and 5.9 respectively). The results are shown in figure 4.11 below.

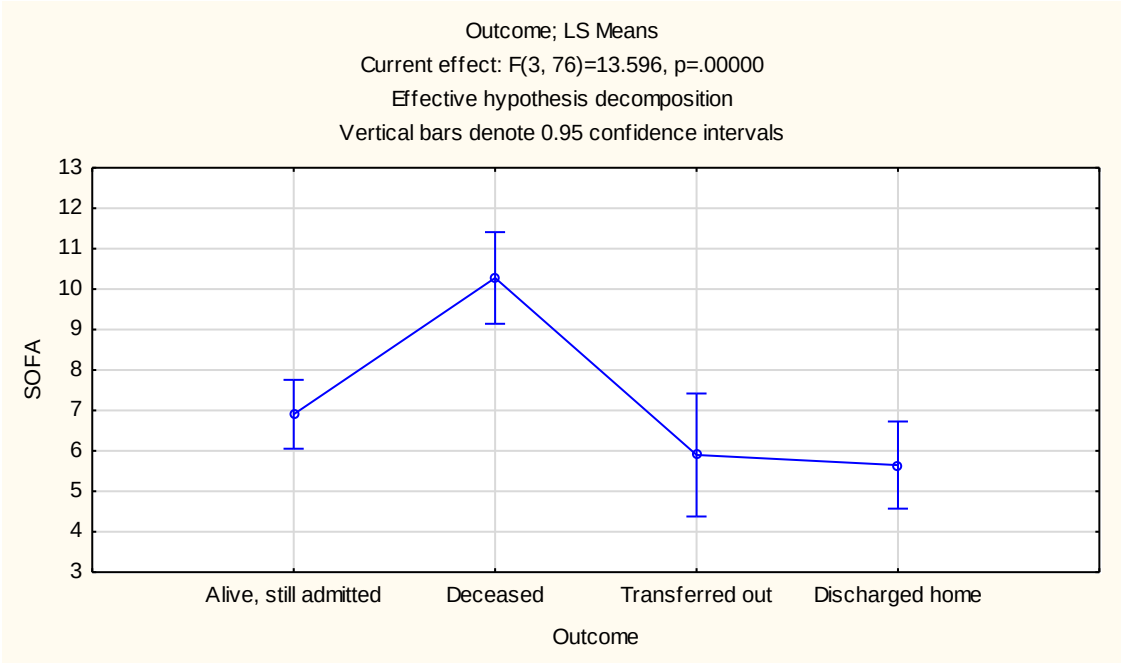

Figure 4.11: Baseline SOFA compared to patient outcomes

4.7.5 Presence of bacteraemia compared to outcomes

Hospital mortality was equal in patients with bacteraemia at any time point and those without bacteraemia (9 cases each) but patients who were bacteraemic were less likely to be discharged home than non-bacteraemic patients (5 patients versus 15 patients). The results are shown in figure 4.12 below. Out of those patients who had bacteremia and died 6 patients

were from the control group and 3 patients were from the intervention group. None of the three patients in the intervention group who died had their antibiotics discontinued. They died while still on antibiotics.

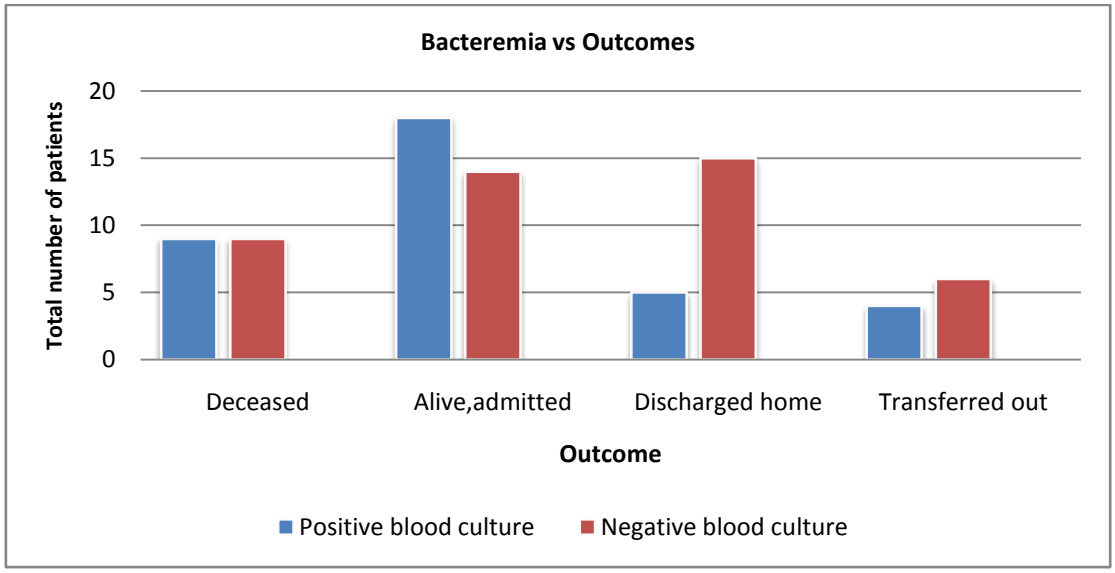

Figure 4.12: Presence of bacteraemia compared to patient outcomes

4.7.6 Outcomes of patients in whom PCT algorithm was overruled

There were more patients who were transferred to a primary care facility in whom the PCT algorithm was overruled compared to those in whom the PCT algorithm was followed. There was only one patient who died in hospital where the study algorithm was overruled compared to 5 patients in whom the PCT algorithm was followed. Final outcomes in this subgroup are presented in table 4.6 below.

Table 4.7: Outcomes in patients when PCT algorithm was followed compared to patients where PCT algorithm was overruled

Patient outcome at study completion	**Compliant with PCT algorithm (n=25)**	**Non-compliant with PCT algorithm (n=15)**
Alive, still admitted, n (%)	9 (36%)	6 (40%)
Deceased, n (%)	5 (20%)	1 (6.6%)
Discharged home, n (%)	9 (36%)	3 (20%)
Transferred out, n (%)	2 (8%)	5 (33.3%)
Total	25 patients	15 patients

4.8 Subsequent episodes of sepsis

4.8.1 Relapse of infection

Only 2 patients (5%) in the intervention group had a relapse of infection whereas in the control group 9 patients (22.5%) suffered a relapse of infection after antibiotics were discontinued for the first episode of sepsis (p=0.02). The results are shown in figure 4.13 below.

In the patients who suffered a relapse there was one hospital death in the control group but none of the relapses in the intervention group died in hospital.

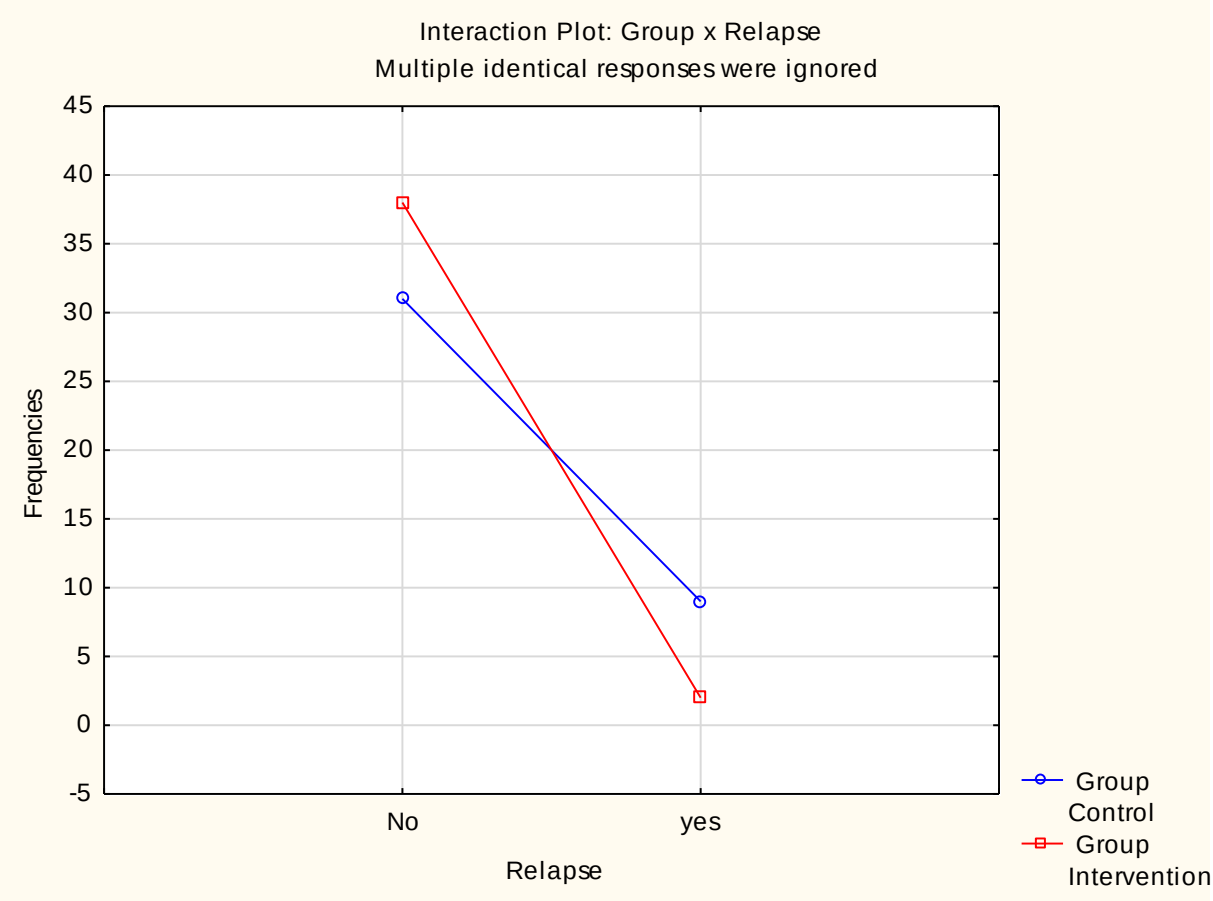

Figure 4.13: Interaction plot between relapse of infection and patient group (control versus intervention

4.8.2 Second episode of sepsis

There were 16 patients (40%) in the control group who had a second episode of sepsis as compared to 15 patients (37.5%) in the intervention group but the difference was not statistically significant (p=0.76).

After completion of treatment for the first episode of sepsis, patients were evaluated for colonisation or infection with MDR bacteria cultured from any site. The control group had 22

patients (55%) who cultured an MDR organism from any site compared to 12 (30%) patients in the intervention group.

4.8.3 Duration of treatment of second episode of sepsis

Out of the total patients who had a second episode of sepsis, an almost equal number of patients in the control group versus the intervention group received antibiotics for the second episode of sepsis (14 patients versus 15 patients).

For patients who were treated for a second episode of sepsis, there were 11 patients in the control group versus 4 patients in the intervention group that had the second course of antibiotics started immediately after stopping the first course of antibiotics i.e. within 24 hours of stopping antibiotics.

The mean duration of treatment for the second episode of sepsis was 12.0±4.62 days in the control group (n=14) and 9.6±2.61 days in the intervention group (n=15) but the difference did not reach statistical significance (p=0.09). The results are shown in figure 4.14 below.

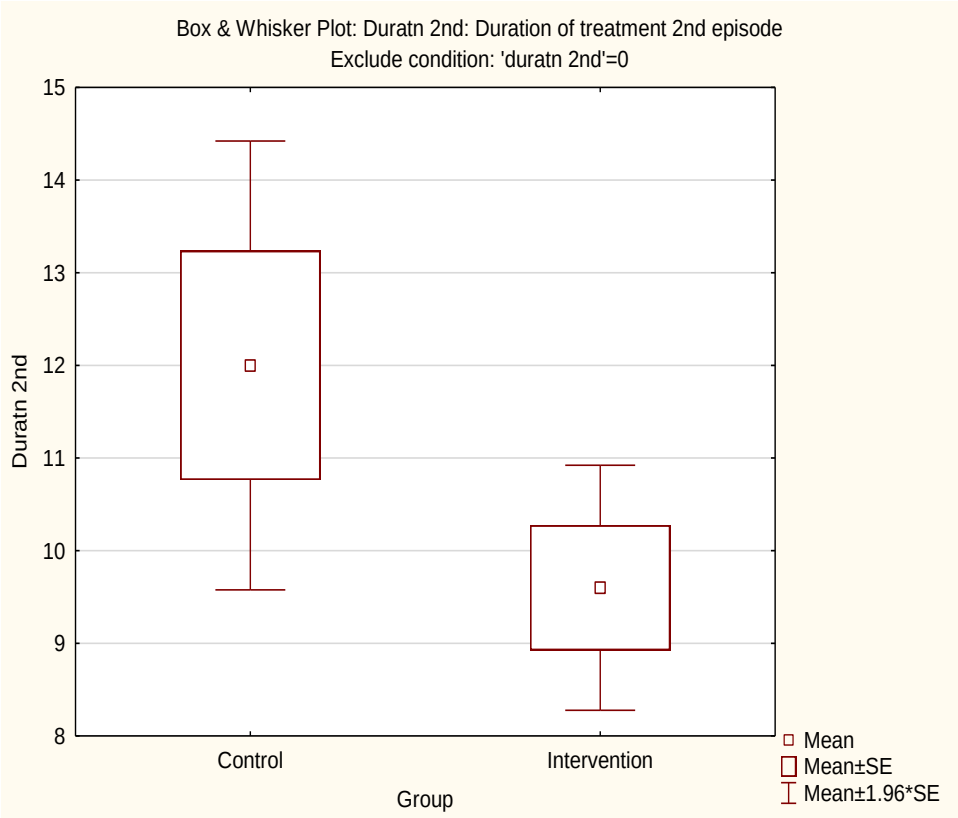

Figure 4.14: Duration of treatment for the second episode of sepsis for the intervention and control group

4.9 Conclusion

The results from this study show that procalcitonin-guided antibiotic discontinuation reduced antibiotic duration of treatment and increased the number of antibiotic free days in the intervention group without an increase in adverse outcomes. The next chapter discusses the study findings in relation to findings from other authors and concludes the study.

CHAPTER - 5. DISCUSSION AND CONCLUSION

5.1 Introduction

This chapter discusses the study findings of a PCT-guided algorithm to guide discontinuation of antibiotic treatment in trauma patients. It explains the findings in relation to background literature, concludes the study and makes recommendations based on the study findings.

5.2 Discussion

5.2.1 Primary outcomes

In this single centre study there was an observed benefit in using a procalcitonin-based algorithm to guide the duration of antibiotic treatment. The intervention group had shorter duration of treatment for both the first and second episode of sepsis compared to the control group. The most impressive reduction occurred for the second episode of sepsis which may reflect increasing clinician familiarity and compliance with the PCT algorithm. Hochreiter et al. (2009), Nobre et al. (2007), Albrich et al. (2012) and Haddad et al. (2018) are amongst the many authors who have found that use of a PCT-based antibiotic algorithm reduces duration of antibiotics in critically ill septic patients. Wirz et al. (2018) found that reduction in antibiotic duration was only moderate in ICU patients and depended on the SOFA score and site of infection. They found that PCT guidance did not reduce antibiotic duration in patients with abdominal infection compared with other sites of infection. This may partly explain why our results did not reach statistical significance.

In our study reduction of antibiotic duration of treatment translated into a significant increase in antibiotic free days alive at 28 days in the intervention group. Stolz et al. (2009) had similar findings. They randomized 101 patients to either a procalcitonin group or a control group. They found that at 28 days the PCT group had more antibiotic-free days alive (13 days) compared to the control group (9.5 days). Agarwal and Schwartz (2011) systematically reviewed six ICU studies and similarly found that there was a 23-37% increase in antibiotic free days alive in the PCT group compared to the controls.

Our study found a trend towards reduced ICU stay in the intervention group but the difference did not reach statistical significance. The effects of a PCT-based algorithm on length of ICU stay are not very clear when compared across different studies. Nobre et al. (2007) found a significantly shortened ICU stay in the PCT group compared to the control group. Jensen et

al. (2011) however, found that length of ICU stay was one day longer in patients in the PCT arm compared to the standard-of-care arm. This study differs from other studies because it used an algorithm of PCT-guided antibiotic escalation which prolonged ICU admission without improving survival. Prkno et al. (2013) performed a meta-analysis of seven studies comprising 1,075 patients with septic shock or severe sepsis which compared PCT-guided antibiotic treatment to standard of care. The ICU length of stay was reported in five studies and there was no appreciable difference between the PCT and the control groups. The effect of a PCT-based antibiotic algorithm on length of ICU stay is therefore still open to debate.

In the current study the intervention group had a slightly prolonged mean total length of hospital stay compared to the control group but the difference did not reach statistical significance. There were certain confounders for increased length of stay e.g. significantly worse injury severity scores (ISS) at baseline. These confounders were not analysed in a multivariate analysis. Different meta-analysis have assessed the hospital length of stay (Prkno et al. 2013, Lam et al. 2018) and found no difference between the procalcitonin and the standard of care groups. Bouadma et al. (2010) and de Jong et al. (2016) similarly found no difference between groups for length of hospital stay.

Similar to other studies, patients in our intervention group had lower hospital mortality compared to the controls. Schuetz et al. (2018a, 2018b) performed an individual patient data meta-analysis for patients with acute respiratory tract infections. They found that PCT testing was associated with lower 30 day mortality compared with controls. A landmark study by Bouadma et al. (2010) concluded that mortality in the PCT group was non-inferior to that in controls. The largest PCT-guided antibiotic study to date was conducted by de Jong et al. (2016) in 1575 critically ill ICU patients. They found lower 28 day mortality in the PCT group compared to controls. The authors speculate that the reduction in mortality may be due to earlier focused search for an alternative diagnosis if the PCT remains low and critical review of antibiotics if the PCT remains high. In contrast to these findings, a meta-analysis of 15 randomized clinical trials (Lam et al. 2018) found the pooled short term all-cause mortality was similar between procalcitonin guided and standard of care groups.

A major concern while using a PCT algorithm to discontinue antibiotics is the potential for relapse if infections are inadequately treated. In our study this phenomenon was not observed. In fact, there was a lower relapse rate in the intervention group (2 patients) compared to the control group (9 patients). Patients in the intervention group may have benefited from a more focused assessment and vigorous source control leading to the lower relapse rate. Antibiotics

discontinuation guidance was provided by a more objective measure in the intervention group compared to the control group. A study by Nobre et al. (2007) found a similar infection recurrence rate in the PCT and the control group. De Jong et al.(2016) however found that re-institution of antibiotics for relapse was more common in the PCT group than in the control group but the numbers were small in both instances (5% versus 3%). Schuetz et al. (2012) conducted a meta-analysis of 14 trials where patients were assigned to receive antibiotics based on a PCT algorithm. They found decreased risk of treatment failure in patients assigned to a PCT group.

In our study we also analysed outcomes in the subset of patients in the intervention group where the PCT algorithm was overruled compared to patients where the PCT algorithm was adhered to. Interestingly, there were fewer hospital deaths in the subset of patients in whom the PCT algorithm was overruled. However, there were no deaths in the intervention group attributed to relapse of infection. Since the increased hospital mortality cannot be attributed to relapse of infection, it is difficult to speculate as to why there was lower hospital mortality when the study algorithm was overruled. The numbers are so low however, that it is probably not relevant. Patients in whom the PCT algorithm was overruled tended to be transferred to primary care facilities rather than be discharged home. Since these patients were originally admitted to the trauma ICU from other facilities it may explain the reluctance of clinicians to actively intervene with an algorithm to reduce antibiotic use in patients who would eventually be transferred back to the admitting hospital. Hospital mortality in this subgroup may also have been under-estimated if it occurred after patients were transferred back to the primary care hospital.

In our study there were an almost equal number of patients in the intervention and the control groups who were treated for a second, new episode of sepsis. We can conclude that patients in the intervention arm did not have an increased number of infection relapses, new episodes of sepsis or higher mortality compared to the control group. This proves the efficacy and safety of a PCT algorithm as a tool for antibiotic stewardship.

5.2.2 Secondary outcomes

Almost all patients in both study groups were mechanically ventilated and the most common source of sepsis was pulmonary. The current study therefore supports the use of PCT-guided therapy to reduce antibiotic duration in trauma patients including those who may have ventilator-associated pneumonia. Sepsis occurred earlier in our cohort amongst controls compared to the intervention group (mean 3.9 days versus 5.0 days). Polytrauma patients have

raised levels of other biomarkers making it difficult to differentiate injury from infection. The monitoring of PCT trends in the intervention group may have provided a more objective assessment of sepsis and prevented premature institution of antibiotic treatment. The onset of sepsis occurred much earlier in our study cohort compared to reports from other authors. In a study of 119 trauma patients by Balci et al. (2009) sepsis occurred on average at day 7 (±3SD) after trauma. We can only speculate at the reasons for this difference. Patients in our study cohort may have developed sepsis earlier due to lack of established care bundles to prevent sepsis but these findings need to be investigated further.

In our study, patients who died in hospital had higher mean SOFA score than those who were discharged from hospital. Hospital mortality was higher in patients with higher mean PCT values (119.8 µg/L) compared to those who were still alive at the end of study follow-up and those who were discharged home. Stolz et al. similarly found that patients who died in hospital had significantly higher SOFA scores (9 versus 6) and higher PCT values (1.29 versus 0.58 µg/L) than those who survived. These findings are corroborated by other authors. Sakran et al. (2012) found that increased mortality in critically ill trauma patients was associated with a PCT level of ≥5 ng/ml. Meisner et al. (2005) correlated PCT and CRP levels to outcome in multiple trauma patients in ICU. They found that in non-survivors PCT levels were significantly higher than in survivors in the first week after trauma. Furthermore, patients with high PCT levels had longer ICU stays than patients who had low PCT levels following trauma. These authors could not establish a link between CRP concentrations and survival. Wojtaszek et al. (2014) also monitored the PCT values in 45 multiple trauma patients. They found that patients who survived had lower mean PCT values compared to non-survivors. Meisner (2014) emphasizes that depending on the success of treatment, an increased mortality risk is associated with high PCT levels. Persistently high PCT or a failure to decrease is associated with high mortality while continuously declining levels offer a better prognosis. Unlike the CRP, the peak PCT level at onset of sepsis may be used as a prognostic indicator to predict adverse outcomes in trauma patients. The SOFA score can also be used as a prognostic indicator in septic trauma patients.

Our study assessed for the absence or presence of primary and secondary bacteraemia during the first episode of sepsis. Patients with bacteraemia had longer mean duration of treatment and longer ICU stays which suggests that bacteraemic patients were generally more ill than non-bacteraemic patients. However, mortality was the same in patients who had bacteraemia compared to those without bacteraemia. Bacteraemia could therefore be used to predict which

patients would stay longer in ICU but could not be used to predict hospital mortality. Since the presence of bacteraemia correlated with prolonged antibiotic treatment it may have impacted on treatment duration in the intervention group which had more episodes of total bacteraemia compared to the control group (25% versus 7.5%).

There were 11 patients in the control group versus 4 patients in the intervention group who had no break between treatment of the first and second episodes of sepsis i.e. the second course of antibiotics was started the next day after stopping treatment. Clinicians who were treating patients in the intervention group had the advantage of knowing the PCT trends in the patient and would have been more confident in rejecting a diagnosis of a second episode of sepsis in the intervention group. This may explain the longer antibiotic free period in the intervention group compared to the control group in the follow-up period.

There was reduced emergence of multidrug resistant (MDR) bacteria for the second episode of sepsis in the intervention group compared to the control group. This may be a direct result of reduced antibiotic exposure in the intervention group. However, routine surveillance cultures for colonisation with MDR bacteria were not done. This would have been more accurate in detecting emergence of MDR pathogens so we cannot draw firm conclusions from our findings. Broyles (2017) found that hospital *C. difficile* rates were significantly reduced by 64% four years after implementation of a PCT algorithm in a hospital antimicrobial stewardship program. In contrast, Bouadma et al. (2010) evaluated emergence of MDR pathogens and found no significant difference between the PCT group and the control group. Due to mixed findings, the impact of PCT algorithms on hospital MDR rates needs further study.

Clinician compliance to the PCT algorithm in our study was 62.5%. The main reasons for non-compliance were raised patient body temperature or wanting to complete the standard duration of antibiotic treatment. De Jong et al. (2016) found adherence to stopping advice was 44% for stopping within 24 hours and 53% for stopping within 48 hours after reaching the stopping threshold. Bouadma et al. (2010) had a compliance rate of 47% to the PCT algorithm. Other authors have had better clinician compliance rates. Shuetz et al. (2009) found clinician compliance to a PCT-guided algorithm to be 90.8%. Lam et al. (2018) speculate that non-compliance with a PCT algorithm may be due to usual care practice and may bias study findings towards no difference between groups. Clinicians will need continuous education about the safety and efficacy of a PCT-guided algorithm so as to improve compliance.

5.2.3 Study limitations

Our study had several limitations; firstly, it was a single centre, non randomized study. The results of this study may be biased by non-randomization and may not be extrapolated to patients with a different background. However, since this was a single centre study a crossover design was best suited to the study aims. Secondly, the sample size was calculated to have sufficient power to detect a between group difference of at least two days in antibiotic duration of treatment. It is likely that a larger sample size would have detected a statistically significant difference between groups with the results that we obtained. Despite these limitations our study found an appreciably reduced antibiotic duration of treatment in the intervention group for all episodes of sepsis. Thirdly, poor compliance by clinicians to a PCT algorithm may have resulted in a conservative bias and reduced the potential benefits of a PCT-guided algorithm. Fourthly, our definition of relapse was defined using microbiologic criteria. Patients who were discharged home or transferred out may have suffered a late relapse that was underestimated in our study. However, the reduced relapse rate in our intervention group supports the safety of PCT based antibiotic algorithms. Fifthly, this study was not powered to detect a mortality difference. Few patients had post mortems done or microbiologic specimens submitted at the time of death so we could not attribute mortality to sepsis. Finally, our study did not measure the actual reduction in antibiotic costs associated with a PCT algorithm. Schroeder et al. (2009) estimated that the antibiotic costs had a 17.8% reduction in their PCT group compared to the control group. Hohn et al. (2013) conducted a retrospective analysis on duration of antibiotic treatment in severely septic patients over a five year period. These were patients admitted in a surgical ICU over five years following the implementation of a PCT-guided algorithm. Between 2005 and 2009 there was an average reduction of one day per year in antibiotic treatment duration but this did not significantly reduce antibiotic costs.

5.3 Conclusion

The current study has shown the benefits to be gained in using a procalcitonin-guided antibiotic regimen. Procalcitonin has the potential to reduce the duration of antibiotics for patients with suspected and confirmed sepsis. It is an important biomarker that can be used in patients with multiple trauma in whom other biomarkers may be persistently raised as a result of trauma. The benefits observed could be increased through better compliance of clinicians to a PCT-based antibiotic algorithm.

5.3.1 Primary outcomes

Reduced duration of antibiotic treatment was observed for both the first and the second episode of sepsis during ICU admission in the intervention group. The intervention group also had a significant increase in antibiotic free days alive. This reduction in antibiotic usage has the potential benefit of reducing costs directly through reduced antibiotic usage but also by reducing the number of ICU days which is the main cost driver.

Procalcitonin-guided regimens have not found a place in developing countries possibly due to their perceived costs. However, the procalcitonin can be measured on alternate days or other determined intervals to reduce costs while still retaining the benefits discussed above.

The potential of procalcitonin guided regimens to reduce mortality and increase survival is difficult to quantify in terms of cost benefit and needs to be explored in further studies. This is especially important in critically injured patients in whom sepsis has potentially fatal outcomes.

The intervention group had fewer relapses of infection compared to the control group which proves the safety of PCT based algorithms.

5.3.2 Secondary outcomes

The most common source of sepsis in both study groups was pulmonary infections. The most commonly isolated bacterial species was *Klebsiella pneumoniae* ESBL and collectively the ESBL-producing *Enterobacteriaceae* made up the majority of infections. Less than half of all patients in both study groups received appropriate empiric antibiotics for these organisms.

Emergence of MDR bacteria subsequent to the first episode of sepsis was noted to be lower in the intervention group compared to the control group. No firm conclusions could be drawn but reduced antibiotic exposure may correlate with reduced acquisition of MDR bacteria.

Patients with the highest peak PCT levels at the onset of sepsis had the highest hospital mortality. Therefore, in our study cohort of septic ICU patients the procalcitonin level had prognostic value.

Compliance with the PCT algorithm was low for the first episode of sepsis. In comparison to patients where clinicians complied, patients in whom the clinician did not comply had longer duration of antibiotic treatment, were more likely to be transferred to a primary care facility than be discharged home but were less likely to die in hospital.

5.4 Recommendations

5.4.1 Recommendations to the trauma ICU, Charlotte Maxeke academic hospital

In our study, PCT measurements were done every 48 hours starting from the first day of sepsis. Hayashi and Paterson (2011) argue that daily measurement of PCT may be potentially wasteful and expensive. Our study shows that it is possible to use a PCT algorithm to reduce the duration of antibiotic treatment without the need for daily PCT measurements.

There were many patients where the empiric antibiotic cover was inadequate to treat the cultured pathogen. Since the most commonly isolated pathogen was ESBL producing *Klebsiella pneumoniae* the trauma ICU needs to formulate antibiotic protocols with empiric antibiotics that will cover these pathogens.

5.4.2 Recommendations for application of PCT based algorithms for antibiotic stewardship

Our study shows the potential value of implementing PCT based antibiotic algorithms to guide the duration of antibiotics in septic trauma patients. Such an algorithm has been proven in the current study to reduce the duration of antibiotic treatment for all episodes of sepsis in the ICU. Antibiotic algorithms based on PCT can increase the number of days that patients remain antibiotic free which potentially reduces antibiotic pressure and selection for MDR bacteria.

5.4.3 Recommendations for further research

Hayashi and Paterson (2011) recognized that all studies on PCT based antibiotic algorithms have a significant geographical publication bias. To date all published studies had been from Europe hence there is a need to expand our knowledge to other countries. To our knowledge, this is the first study from Africa reporting on the use of a PCT based algorithm to reduce antibiotic use in hospitalized patients.

There is need for more studies from Africa and the developing world to evaluate the applicability and cost-effectiveness of PCT based algorithms for antibiotic stewardship in critically ill patients.

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APPENDICES

APPENDIX A: DATA COLLECTION SHEET

Patient study number……

Contact telephone number

Age in years…….

Gender A. Male B. Female

Date of admission to ICU……..Date of discharge from ICU…….

Date of Discharge from hospital……

Reason for admission to
ICU…….

……
…….

……

Co -morbid illnesses

1. Heart failure (NYHA III/IV)
2. Insulin dependent diabetes (uncontrolled)
3. Chronis renal failure requiring dialysis
4. Advanced HIV infection with CD4 <100 cells/µL
5. Liver cirrhosis
6. Other
   (specify)……
   ……..

If female, are you pregnant? A. Yes B. No

Patient admitted while already on antibiotic treatment?

A. Yes B. No

If yes, state the antibiotic and duration given in days/hours

ANTIBIOTIC	DOSE	DURATION OF TREATMENT

Reason(s) why antibiotics started prior to ICU admission

……

……..

……

……

- SOFA score……

- Injury Severity Score……

- Glasgow Coma Scale……

- Vital signs

  Blood pressure (mmHg)……

  Temperature^{o}C…….

  Pulse rate/min…….

  Respiratory rate/min……..

Oxygen Saturation……

Need for mechanical ventilation A.Yes B.No

Patient qualifies for study enrolment A. Yes B. No

If No, why does patient not fulfill study criteria?.....

……

……

Date of recruitment into study……..

SEPSIS RECORD OF PATIENT

Date	Day in ICU	Suspected Source of Sepsis	White cell count and Differential	Urea/creatinine	Specimen type	Isolate(s) cultured	Susceptible drugs	Resistant drugs	Other Tests

ANTIBIOTIC RECORD OF PATIENT

DATE	PCT LEVEL	PCT/BASELINE as percentage	TEMP ºC	PULSE RATE/ MIN	ANTIBIOTIC 1		ANTIBIOTIC 2		ANTIBIOTIC 3		ANTIBIOTIC 4		ANTIBIOTICS STOPPED (Y/N)	REASON ANTIBIOTICS NOT STOPPED
					DOSAGE	DOSES GIVEN	DOSAGE	DOSES GIVEN	DOSAGE	DOSES GIVEN	DOSAGE	DOSES GIVEN		
TOTAL ANTIBIOTIC DAYS														

APPENDIX B. ETHICS CLEARANCE CERTIFICATE

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130860

NAME: (Principal Investigator)	Dr Rispah Chomba
DEPARTMENT:	Clinical Microbiology & Infectious Diseases National Health Laboratory Services
PROJECT TITLE:	Prolacitonin-Guided Antibiotic for Suspected and Confirmed Sepsis in Patients in a Surgical Trauma Intensive Care Unit, A Prospective, Two-Period Cross-Over, Interventional Study
DATE CONSIDERED:	30/08/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Warren Lowman
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 12/09/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

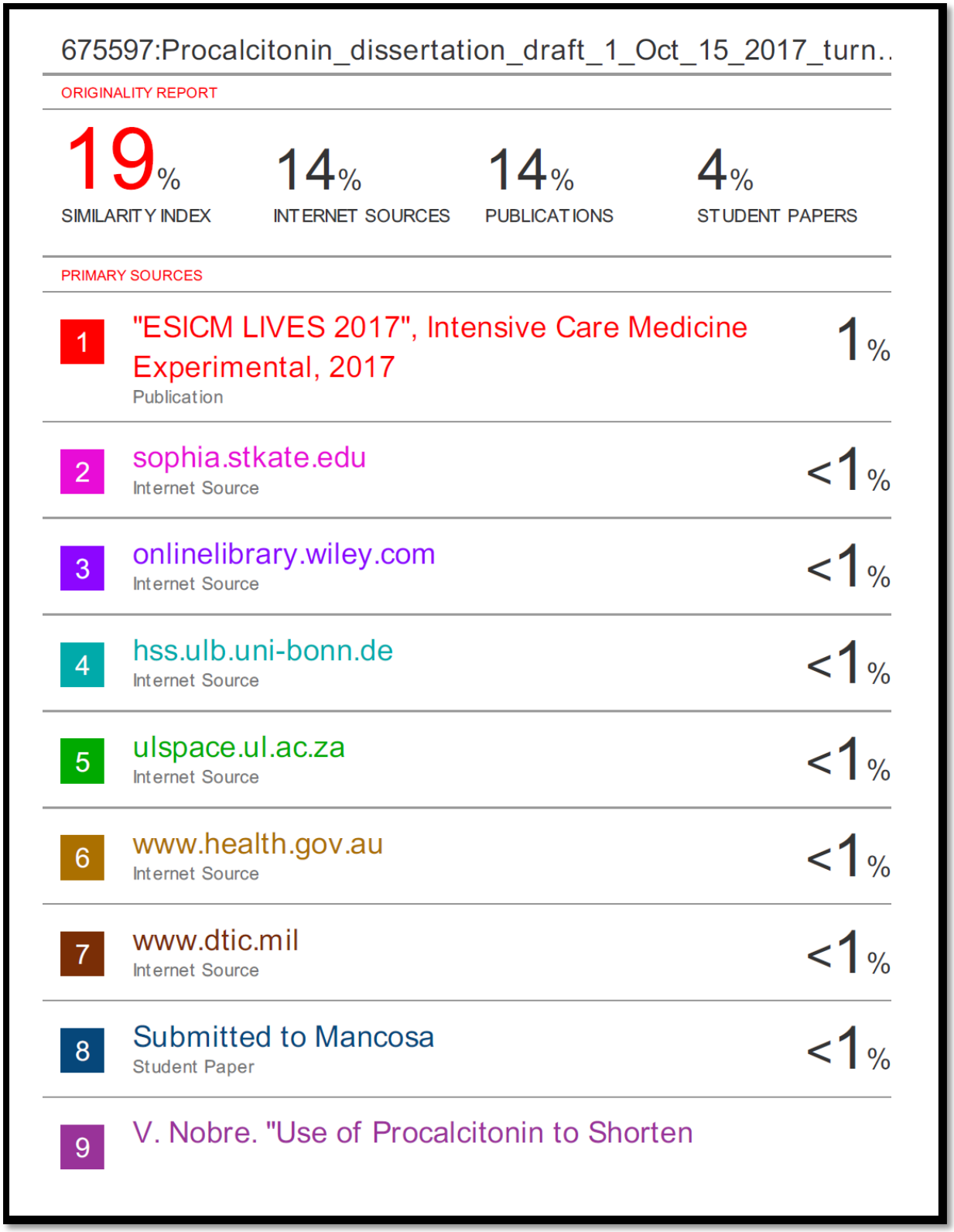
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

14·09·2013
M130860Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C: TURN-IT-IN REPORT



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