Early procalcitonin kinetics and adequate empiric antibiotic therapy in critically ill

PhD Thesis

Domonkos Trásy M.D.

University of Szeged - Faculty of Medicine
Doctoral School of Multidisciplinary Medicine

Supervisor:
Prof. Zsolt Molnár MD, PhD
Department of Anaesthesiology and Intensive Therapy

Szeged

2016

Introduction

One of the most challenging tasks in critical care medicine is the treatment of serious infection related multiple organ dysfunction, termed in general as sepsis, severe sepsis, and septic shock. Despite improved awareness of critical care practitioners and the implementation of international guidelines, the mortality ranges between 28-41% in North America and Europe alike and still the leading cause of death among critically ill patients worldwide. However, sepsis means a very heterogeneous patient population, which varies in etiology and severity; therefore, universally applicable diagnostic criteria and treatment algorhythms are difficult to be defined. This heterogeneity proved to be one of the most difficult hurdles that most prospective randomized trials could not concur; hence, they failed to show either clear survival benefit or positive results of single center studies that were later contradicted by large multicenter trials. Nevertheless, sepsis has become a very important health economic issue all around the world.

Furthermore, treating sepsis is a multidisciplinary task. Early recognition and immediate start of initial steps which

stand on three main pillars of: resuscitation parallel with source control and adequate antimicrobial therapy undoubtedly are inevitable to give the best possible chance for survival, received strong recommendation by the Surviving Sepsis Campaign guidelines, which has to be started on the primary care level: outside the hospital, in the emergency department or on the wards. In the absence of adequate initial management, providing even the highest level of intensive care would be in vain. There is firm evidence that delaying appropriate antibiotic treatment increases mortality regardless from the severity of organ dysfunction.

However, in almost 30% of cases empirical antibiotics proved to be inadequate in the hospitals in general and on intensive care units (ICU) as well. To improve efficacy, empirical antibiotic therapy is guided by local protocols based on international guidelines in most centers. For microbiological proof of infection, although the gold standard of the diagnosis, unfortunately results often only become available 24–48 hours at the earliest after sending the specimen to the laboratory, and negative result do not necessarily rule out infection. So until then there is very little to help the clinician whether the administered empirical antibiotic treatment is effective or not.

However, while recognizing organ failure via objective signs is relatively easy, diagnosing infection as possible underlying cause remains a challenge. Due to the non-specific properties of conventional signs of infection, such as body temperature and white blood cell count, biomarkers have been searched to aid diagnosis for decades.

One of the most studied biomarker is procalcitonin (PCT). Its role in assisting antibiotic therapy has been studied extensively. with contradicting results. There are positive studies showing that a PCT-guided patient management reduced antibiotic exposure and length of antibiotic therapy without affecting patient outcomes. There are also negative studies, which could not show this benefit at all. However the fact that PCT is a reliable sepsis marker with short half life but its role in predicting bacterial infection and early decision making in assisting antibiotic therapy is undiscovered.

Aims

There are three fundamental questions to be answered when treating patients with suspected or proven infections: 1) is there infection, should we start empirical antibiotic therapy; 2) is the commenced antibiotic effective; and finally 3) when should we stop antibiotic treatment? We decided to give exact answers to these questions with the help of PCT as it is a fundamental problem in our daily practice in the ICU.

As this has not been investigated before, we performed a prospective observational study with 3 goals: a) to describe early kinetics of PCT measured 8 hourly after starting empirical antibiotic therapy within the first 24 hours, b) to investigate if the observed kinetics shows any difference in patients in whom the antibiotic treatment eventually proved to be appropriate versus those in whom it proved to be inappropriate, and c) to determine the cut-off value of PCT with highest discriminatory power.

As a spin off study, in a post hoc analysis those patients in whom PCT values were available from the previous day we investigated whether the absolute value or the change in PCT was a better indicator of infection.

Materials and methods

All patients over 18 years with suspected infection on admission or during their stay on the ICU were screened for eligibility. Patients were enrolled when the attending intensive care specialist suspected infection, decided to send microbiological tests and start empirical antibiotic therapy.

We recorded the value of PCT levels and changes from the day before (t_{-1}) to the day when infection was suspected (t_0), and after starting empirical antibiotic therapy 8 hourly (t_8, t_{16}, t_{24}) then daily ($day_{2\text{-}5}$). Demographic, outcome data, parameters of vital organ function and choice of antimicrobials were also registered.

Diagnosis of infection and appropriateness of the empirical antimicrobials were established as a retrospective analysis evaluated by two experts blinded for the PCT. Based on these results, patients were then grouped into Infectious (I) -, and Noninfectious (NI) - groups. Patients who had infection were further divided into Appropriate (A) - and Inappropriate (IA) - antimicrobial treatment groups.

Results

Over the study period 209 patients were enrolled of whom 76% had proven infection. PCT at t_0 was significantly higher in the I- compared to NI-group (p=0.024), respectively. In the I-group 23% of the patients antimicrobials proved to be inappropriate.

Regarding demographics there were no differences between the A-, and IA-groups but ICU-, and hospital-survival was significantly higher in the A-group. These patients also required less vasopressors and renal replacement therapy.

In both groups the increase in PCT levels continued after the initiation of empirical antimicrobial treatment (t_0) until 16 hours (t_{16}). In the IA-group there was a significant increase from t_{16} to t_{24}, while in the A-group there was a significant decrease. By t_{24} the PCT reached significantly higher levels in the IA-group and remained higher the following day compared to the A group. In the A-group PCT levels peaked at t_{16}, while in the IA-group the peak was at t_{24}. From t_{24} until the 5^{th} day PCT levels decreased in both groups.

The Receiver operating characteristic (ROC) analysis revealed that a PCT elevation from t_0 to t_{16} had an Area Under the Curve (AUC) of 0.73 (95% Confidence Interval (CI) 0.63-

0.83; p<0.001), from t_0 to t_{24} 0.86 (95% CI 0.77-0.94; p<0.001). According to the Youden index, the best cut off for PCT increase from t_0 to t_{16} was 69.2%, and from t_0 to t_{24} it was 73.5%.

Out of the 209 patients 114 cases were included in the post hoc analysis, of whom 75% were identified as having proven infection the others had highly unlikely.

PCT absolute values were similar at t_{-1}, but by t_0 in the I-group levels were significantly higher compared to the NI-group and there was also a significant increase from t_{-1}, while there was no such change in the NI-group.

PCT had a significant predictive value, but with a poor AUC. However, PCT's AUC for both percentage and delta changes had a significantly better performance for predicting infection.

The best cut-off values for the PCT absolute value it was 0.84 ng/ml with a sensitivity of 61 % (95% CI 50-72) and specificity 72 % (95% CI 53-87) to indicate infection in the ICU. Regarding the percentage change a PCT increase of >88% from t_{-1} to t_0 had a sensitivity of 75% (95% CI 65-84) and specificity of 79% (95% CI 60-92) and a PCT delta change of >0.76 ng/ml had a sensitivity of 80% (95% CI 70-88) and specificity of 86% (95% CI 68-96) to indicate infection.

Discussion

The most important finding of the current study is to show the superiority of PCT kinetics over the absolute values to indicate new onset infection on the ICU. We observed significant difference in the PCT levels between patients with and without proven infection in contrast to C-reactive protein and temperature, suggesting that PCT is superior as a marker for initiating antibiotic treatment in the critically ill. However, the interpretation of PCT measurements, especially the absolute values on their own may be misleading. Therefore, evaluating PCT kinetics and an aetiology-based approach may prove more appropriate.

Early identification and adequate antibiotic treatment of septic patients is of pivotal importance as any delay in starting effective antibiotic therapy is associated with increased in-hospital mortality although such therapy is a common feature in the ICU, reportedly as high as 25-30%. The main reason for this high rate of inadequacy may be due to the fact that reliable clinical and biochemical signs of bacterial infections are lacking, and the microbiological proof becomes available well after the antibiotic therapy was commenced. Once inappropriate antimicrobials are initiated, it often takes days (until organism

isolation and sensitivities are produced) to correct them. In our study 23% of patients received inappropriate antimicrobials. This high incidence may be due to the lack of fast and reliable diagnostic tests for bacterial infections, and to the subsequent delay in microbiological results. Earlier recognition of potential inappropriate microbial therapy may allow an opportunity to substantially improve outcome.

To our knowledge, this is the first study to show that the early kinetics of PCT measured within the first 24 hours may help clinicians to evaluate the appropriateness of empirical antimicrobial therapy in critically ill patients. The rationale for measuring successive PCT levels within this timeframe came from the assumption that by giving appropriate antibiotics this may slow the inflammatory response within hours, and that this could be detected by serial measurements of PCT.

A PCT increase of ≥69.2% during the first 16 hours or a PCT increase ≥73.5% during the first 24 hours were the best cut off values to indicate inappropriate antimicrobial treatment. It is known that PCT increases within hours after an infectious insult and levels halve daily once the infection is controlled by the host immune system and/or by appropriate antibiotic therapy. This feature explains the significant difference found in the PCT kinetics between the A-, and IA-groups during the first 24 hours.

Measuring PCT on commencement of antimicrobials (t_0) and then at 16 and 24 hours, by evaluating the percentage change rather than the absolute values the clinicians may have some additional early help when there is nothing else to follow but the clinical picture. In those cases where there is a "large" increase within the first 16-24 hours, may indicate inappropriate antimicrobial therapy, while a lower grade increase or a decreasing tendency after 16 hours would support appropriate antimicrobial therapy. Within the first 16 hours, followed by further increase after that indicates that antibiotic therapy may need adjusting; in the case of a lower grade increase till 16 hours followed by a decreasing tendency may mean adequate empirical antibiotic therapy. However, it is important to note, that one should never treat one single parameter, and PCT also has to be dealt with in the context of the full clinical picture and other biochemical and microbiological results. The clinical importance of our findings is emphasized by the significant difference in hospital mortality between the A-group and the IA-group (37% versus 61%).

Conclusion

In our study PCT kinetics within the first 24 hours after commencing empirical antimicrobial therapy showed a significant increase in patients in whom therapy proved to be inappropriate, while in the appropriate group, after a brief increase at 16 hours, there was a significant decrease by 24 hours. Applying this approach may be helpful in quickly tailoring antimicrobial therapy for the patient's specific needs.

The main finding of the spinoff study was that an increase in PCT levels from the day before (t_{-1}) to the day when infection was suspected (t_0) predicted infection, while in patients with no proven infection PCT remained unchanged. Based on the data presented spot PCT may not be adequate to differentiate infection from non-infectious inflammatory response. The clinical implication of these results are that daily PCT measurements in patients with high risk of infection would give the opportunity to evaluate PCT kinetics, which may improve our diagnostic accuracy and rationalize antibiotic therapy on the ICU.

Summary

In this deadly battle of fighting the burden of serious infections on the ICU, we often keep missing the point. Although sepsis exists, just like critical illness, but precisely defining it is probably impossible due its diversity in etiology, pathomechanism and clinical manifestation. PCT is definitely one of the most reliable inflammatory markers in the critically ill to date, and there is also convincing evidence that its use to guide antibiotic therapy can rationalize starting, escalating and stopping antibiotic therapy. Furthermore, PCT may also become cost effective, by not starting at all, or stopping antibiotic therapy early. However, starting or stopping antibiotic treatment is more complex than just treating one single figure or even the kinetics of PCT values. A multimodal, individualized concept, consisting of: recognizing organ dysfunction, identifying the possible source, following the clinical picture and taking PCT and PCT-kinetics into account, is necessary to make the most out of your PCT and to do the best of your patients in your everyday practice.

Key message of the study

- Early PCT kinetics within the first 24 hours after commencing empirical antimicrobials are different in patients receiving appropriate as compared to patients on inappropriate antimicrobial therapy.
- In case of appropriate therapy PCT peaks around 16 hours after commencing empirical antimicrobials and by 24 hours it already shows a decline.
- In patients on inappropriate antimicrobials PCT levels show a continuous increase within the first 24 hours during empirical antimicrobial therapy.
- Although absolute values showed several fold difference in medical as compared to surgical patients with suspected infection, but kinetics in those receiving appropriate as compared to those who received inappropriate antimicrobials were similar to that of reported in the whole sample.

Key message of the spin off study

- Kinetics of PCT values based on daily measurement are superior to absolute values only in diagnosing infection on the ICU.
- Absolute values of PCT may be of limited use in diagnosing infection on the ICU.
- Both absolute values and kinetics of C-reactive protein and body temperature are poor indicators of infection on the ICU.

List of full papers related to the subject of the thesis

I. **Domonkos Trásy**, Krisztián Tánczos, Márton Németh, Péter Hankovszky, András Lovas, András Mikor, Ildikó László, Edit Hajdú, Angelika Osztroluczki, János Fazakas, Zsolt Molnár: Early procalcitonin kinetics and appropriateness of empirical antimicrobial therapy in critically ill patients. *Journal of Critical Care* 2016; Aug;34:50–55. **IF: 1.997**

II. **Domonkos Trásy**, Krisztián Tánczos, Márton Németh, Péter Hankovszky, András Lovas, András Mikor, Edit Hajdú, Angelika Osztroluczki, János Fazakas, Zsolt Molnár: Delta Procalcitonin is a Better Indicator of Infection than Absolute Procalcitonin Values in Critically Ill Patients. J Immunol Res. 2016;2016:3530752. **IF: 2.812**

III. Ildikó László, **Domonkos Trásy**, Zsolt Molnár, János Fazakas: Sepsis: From Pathophysiology to Individualized Patient Care. *J Immunol Res*. 2015;2015:510436. **IF: 2.934**

List of book chapters relating to the subject of the thesis

I. János Fazakas, **Domonkos Trásy**, Zsolt Molnár: Interpreting procalcitonin at the bedside. Jean-Louis Vincent (ed.) Annual Update in Intensive Care and Emergency Medicine 2016. Springer Verlag, Berlin-Heidelberg, 2016. pp. 3-15.

Other papers not related to the subject of the thesis

I. Krisztina Szabadfi, Bese Danyadi, Peter Kiss, Sridharan Manavalan, Robert Gabriel, Dora Reglodi, Andrea Tamas, **Domonkos Trasy**, Istvan Batai: Preconditioning with volatile anaesthetic sevoflurane in ischemic retinal lesion in rats. *J MolHist* (2012) 43:565–569. **IF: 1.484**

II. András Lovas, **Domonkos Trásy**, Márton Németh, Zsolt Molnár: Lung recruitment can improve oxygenation in patients ventilated in continuous positive airway pressure/pressure support mode. *Front Med (Lausanne)* 2015 Apr 21;2:25. **IF: 0**

III. András Mikor, **Domonkos Trásy**, Márton F. Németh, Angelika Osztroluczki, Szilvia Kocsi, Ildikó Kovács, Gábor Demeter, Zsolt Molnár: Continuous central venous oxygen saturation assisted intraoperative hemodynamic management during major abdominal surgery: a randomized, controlled trial. *BMC Anesthesiology* 2015 Jun 4;15:82. **IF: 1.33**

IV. Krisztián Tánczos, Márton Németh, **Domonkos Trásy**, Ildikó László , Péter Palágyi, Zsolt Szabó, József Kaszaki: Goal directed resuscitation aiming cardiac index masks residual hypovolemia. *Biomed Res Int*. 2015;2015:160979. **IF: 1.579**

V. Péter Hankovszky, **Domokos Trásy**, Nándor Öveges, Zsolt Molnár: Invasive Candida Infections in the ICU: Diagnosis and Therapy review. *The Journal of Critical Care Medicine* 2015;1(4):129-139 **IF: 0**

VI. Péter Hankovszky, **Domonkos Trásy**, Zsolt Molnár: Editorial Commentary: Which Patients Would Benefit From Antibiotic Prophylaxis: A "Burning" Question? *Clin Infect Dis* 2016 Jan 1;62(1):67-8. **IF: 8.886**

Acknowledgement

First, and foremost I would like to express my sincere gratitude to my supervisor Professor Zsolt Molnár for his continuous support of my scientific work, for his patience, motivation, enthusiasm, and immense knowledge, for initiating my scientific career and for providing me with the opportunity to carry out my scientific work in the Department of Anaesthesiology and Intensive Therapy under his scientific guidance.

I would like to thank the help all of the co-authors of the publications related to my thesis, this work could not have been completed with the selfless assistance of them.

I express my special thanks for the help of the doctors and nurses and all of the employees from the Department of Anaesthesiology and Intensive Therapy without which this study could have not been completed.

Special thanks for my family members for their patience and constant support throughout the past years. I am indebted to thank my parents for all their love and encouragement, for financial support during my long study years and also supporting me spiritually throughout my life.