Procalcitonin use for shorter courses of antibiotic therapy in suspected early-onset neonatal sepsis: are we getting there?

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Antibiotic overuse and subsequently infections caused by antibiotic resistant pathogens are a worldwide problem that according to the 2014 WHO report "*threatens the achievements of modern medicine*" (1). In the Neonatal Intensive Care Units (NICUs), antimicrobial use does undoubtedly influence the types of pathogens involved in neonatal sepsis as well as their resistance patterns (2). In addition to that, there is now overwhelming and accumulating evidence that antibiotic treatment in early life affects the neonatal microbial flora and leads to long-term consequences. The Centers for Disease Control and Prevention has initiated in 2011 a campaign to prevent antimicrobial resistance in healthcare settings (3) with emphasis on antimicrobial stewardship interventions. Antimicrobial stewardship is recognized as a critical patient safety and quality imperative which aims at optimizing clinical outcomes while minimizing the emergence of antimicrobial resistance and preserving the activity of the existing agents (4). Several antimicrobial stewardship strategies in NICUs have been proposed (5,6) and include interventions for improvement in the diagnosis of neonatal sepsis. The signs and symptoms of sepsis in infants are non-specific and may mimic the presentations of a non-infectious process but it is difficult not to treat with antibiotics for suspected sepsis when these symptoms appear. In addition, culture-negative sepsis is a common reason for antibiotic prescribing in NICUs. The use of biomarkers (7-9) such as C reactive protein (CRP), procalcitonin (PCT), interleukin

6 (IL-6), as well as the sampling with adequate blood volume for culture [at least 1 mL recommended from the American Academy of Pediatrics (10)] could aid the earlier and more accurate diagnosis of neonatal sepsis as well as the judicious use of antimicrobials by reducing the total treatment duration. Of note, it is estimated that currently the prevalence of culture-proven early-onset neonatal sepsis in countries with established surveillance systems is less than 0.1% of life births which implies that the majority of neonates are treated with antibiotics unnecessarily (11-13). Therefore, it is of paramount importance on the one hand to identify those that are at risk at the earliest possible and on the other hand to withhold antibiotics accurately where not needed.

Amongst the biomarkers used for earlier diagnosis and exclusion of neonatal sepsis, both PCT and CRP have been studied extensively during the last decades (14-16). Both of them have demonstrated various sensitivities, specificity, positive and negative predictive values in different studies. The use of PCT though appears to demonstrate a higher negative predictive value meaning that neonates with normal PCT levels most likely don't have an infection. It is important to mention here that in healthy neonates PCT levels increase gradually after birth, reach peak values on day 1 of life (mean 1.5–2.5 ng/mL) and then decrease gradually to normal values (<0.5 ng/mL) by day 2 to 3 of life. Perinatal factors such as chorioamnionitis, perinatal asphyxia and maternal pre-eclampsia could account for

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the PCT postnatal increase (17). The latter should be taken into consideration when interpreting PCT levels in neonates and different cut-off values have been suggested for neonates for the first few days of life compared to the ones used for children and adults.

The majority of the studies for the value for PCT in the field of neonatal sepsis so far were small prospective non-randomized or cross-sectional, i.e., observational studies (including both early-onset neonatal sepsis and late-onset) and did not have a uniform definition for sepsis (both microbiologically confirmed as well as probable sepsis were included) (16,18). Moreover, there were interpretation difficulties of these studies due to heterogeneous groups, different times at blood sampling and methodology used in general. A recent meta-analysis has concluded that PCT has high sensitivity but low specificity in the diagnosis of neonatal sepsis which is somehow acceptable given the fact that for a life threatening disease such as neonatal sepsis a biomarker should maintain a low false negative ratio (18). Apart from early identification and antibiotic administration, the ideal biomarker should also guide the duration of treatment. The latter is in fact one of the core elements of antimicrobial stewardship. A single-center randomized intervention study including 121 neonates (gestational age ≥34 weeks) has shown that serial PCT measurements resulted in shorter courses of antibiotics but the sample size was insufficient to assess safety (9).

In a recent article published in the *Lancet* (19), Stocker and colleagues, on behalf of the Neonatal PCT Intervention Study Group (NeoPIns), provided evidence from an international multicentre randomized intervention study on the efficacy and safety of PCT-guided treatment. The investigators enrolled 1,700 neonates and aimed primarily to address the clearly focused question as to whether PCT-guided decision making for early-onset neonatal sepsis could reduce the duration of antibiotics given for that purpose (superiority aspect of the trial) without an increase in the re-infection or death rates in the first month of life (non-inferiority aspect).

With regards to the methodology, the assignment of neonates to treatments was randomized in a 1:1 ratio but was not blinded as the attending physicians and nursing staff were aware of the intervention given. There were two groups: the PCT group, where antibiotics were stopped when two PCT values were within normal hourly values post-birth, and the standard group, where antibiotics were stopped following clinical examination and routine laboratory investigations. The included neonates were

at low risk for infection (unlikely or possible infection) and were classified as such based on a well-defined risk stratification incorporating a combination of risk factors, clinical symptoms and laboratory findings. Neonates who were considered high risk (infection probable or eventually proven with positive blood culture) were not assigned to any group. Therefore, the population recruited was a priori low risk for infection and this is the area where an ideal biomarker could be useful by decreasing the unnecessary and prolonged antibiotic use. In those neonates who are very ill, with or without any risk factors, none would argue against the use of antibiotics and PCT-guided treatment would be of limited value. Hence, the investigators targeted the right group for intervention in this trial. Moreover, the two groups were similar at the start of the trial and neonates were analysed in the group to which they were initially randomised. Last but not least, the study recruited a large number of neonates—in fact the largest in any of the trials conducted so far in that field—and it was adequately powered to reach statistically significant results.

As for the results, the primary outcome was clearly specified and PCT-guided decision making resulted indeed in a statistically significant reduction of the duration of treatment with antibiotics between the two groups both in the intention-to-treat (median difference of –9.9 hours) and in the per-protocol (median difference of –12.2 hours) analysis. This reduction was present even if the so called non-adherent to the protocol cases were taken into account. In particular, in around 25% of the cases in the per-protocol analysis, the attending physician decided not to comply with the guidance suggested by the investigators and either stopped earlier or continued antibiotics more than indicated from the study design. In the comparison between the adherents versus non-adherent cases in the PCT group a further reduction in the duration of antibiotics was shown as one might expect.

With regards to the non-inferiority aspect of the trial for re-infection or death, this was not shown due to the low incidence of the above events in the study group. There were a total of 8 cases of suspected re-infection after completion of therapy (5 in the PCT group) and one death within the first month of life in the standard treatment group due to perinatal asphyxia. Of note, none of the re-infections had a culture-confirmed infection. Hence, the safety of the PCT-guided decision making could not be demonstrated in this study. It is worth, however, mentioning at this point that in a similar randomized controlled trial enrolling 1,575 critically ill adults, apart from the shorter

duration of antibiotics there was also a reduction in the overall mortality in the PCT-guided treatment group compared to the standard care group (20). In addition to that, in a meta-analysis of 14 trials from 4,221 patients with respiratory tract infections, the use of PCT to guide initiation and duration of antibiotic treatment was not associated with higher mortality rates (21).

The secondary outcome was the duration of hospital stay which was found to be significantly shorter in the PCT group. Although statistically significant, the difference between the two groups was not as striking as the difference shown between the two groups concerning the primary outcome. This could be explained by other factors, apart from infections, accounting for prolonged hospitalization in the preterms including primarily feeding difficulties. The authors well point out in the discussion section that their study was not originally designed to assess the effect of the PCT-guided decision making in a neonatal population with reasons for inpatient stay other than suspected infection. Ideally, a study looking into the duration of hospital stay in the neonatal units should take into consideration other factors apart from antibiotic treatment which are various and indeed very common.

The authors rightly and carefully acknowledge that this study, as a pragmatic one, has several limitations including the gestational age of the eligible neonates which was more than 34 weeks. In addition, the majority of participating centers were from high-income countries with a low background incidence of early-onset neonatal sepsis. Therefore, one should consider carefully the applicability of the study findings in a different neonatal setting. Another limitation addressed by the authors is the risk stratification assessment tool used which was not validated. However, this tool was based on a combination of perinatal risk factors, clinical symptoms and laboratory findings and reflects the rational and the everyday approach of the majority of neonatologists.

Overall, the NeoPIns study brings a better insight in the use of PCT. The study design and methodology are very thoroughly presented. The study findings undoubtedly demonstrate that PCT-guided decision making was superior to standard care in shortening antibiotic treatment courses for early-onset neonatal sepsis. This is the first interventional study in the field recruiting such a large number of neonates. Given the paucity of high quality data and the fact that the vast majority of published so far studies are observational, this randomized trial bridges a huge scientific gap. Based on the results of this trial, a

large number of low risk neonates could benefit from less exposure to antibiotics. The NeoPIns intervention targets the right population to reduce unnecessary antibiotic prescribing, a cornerstone of antimicrobial stewardship. Future high quality research is certainly needed to investigate further the value of PCT as a diagnostic tool for sepsis especially in neonates from low income countries or/and higher background infection rates. However, when available, serial PCT measurements could offer an additional piece of information which can aid the neonatologist to discontinue antibiotics in neonates at low infection risk. There is undoubtedly though a need for more studies to confirm the safety of this approach in various neonatal settings and to investigate in depth country-specific cost-effectiveness issues.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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