Editorial

The NeoPIns study: a step towards a rational use of antibiotics in early-onset sepsis in term neonates

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We read with interest the results of the NeoPIns trial, published this year in *The Lancet* by Stocker and colleagues and assessing the effect of a procalcitonin (PCT) guided algorithm in early-onset neonatal sepsis in term infants (1).

Early-onset neonatal bacterial sepsis (EOS), defined as sepsis occurring within the first seven days of life in term infants, has become infrequent in developed countries but still remains a major cause of morbidity and mortality (2). Moreover, diagnosis of EOS in neonates is a challenging issue. Since microbial documentation is rare and delayed, diagnosis of EOS in neonates is mainly based on a neonatal sepsis risk assessment (3). Thus, many newborns are started empirically on broad-spectrum antimicrobial treatment as recommended (4). Consequently, many neonates receive unnecessary antibiotic treatment in their very first days of life. Immediate deleterious effects of antibiotics have been described: emergence of multi-drug resistant organisms, invasive candidiasis, necrotizing enterocolitis, etc. (5). Early initiation of antibiotic treatment in neonates may also have lifelong consequences. The concept of the interaction between the microbiota and the shaping of the immune system is well described (6). An early prescription of antibiotics, during the "window of opportunity" of the 2 first weeks of life may interfere with the development of a normal bacterial colonization and have severe consequences on further immune development of the neonate.

In the objective of a rationalized use of antibiotics, biomarkers are increasingly used in sepsis and PCT is the most promising one. PCT is the precursor of calcitonin produced in the thyroid and involved in calcium homeostasis. In inflammatory states, particularly during infections, local PCT production rises without further transformation outside of the thyroid, resulting in the rise of serum levels of untransformed PCT. Specific cut-offs in the 72 first hours of life of neonates have been described and used in clinical studies (7). PCT measurements have been used with three different aims. First, as a diagnostic tool: to help physicians decide whether to initiate antibiotics and spare unnecessary treatment. Second, PCT has been tested as a marker of disease severity to guide an escalation therapy—without proof of a better outcome in ICU patients, so far (8). Third, PCT has been extensively studied and proved its efficacy in different settings as a de-escalation tool, using sequential measurements to shorten length of treatments (9,10).

In *The Lancet* this year, Stocker and colleagues reported the results of the NeoPIns trial (1), a clinical trial testing a PCT-driven de-escalation therapy in suspected EOS in neonates.

The investigation by Stocker and colleagues represented another important study to determine the potential role of PCT in the fight of reducing antibiotic consumption, a public health priority (11).

NeoPIns is a randomised open-labelled controlled trial conducted in 18 hospitals in four high-income countries (The Netherlands, Switzerland, Canada and the Czech Republic). The study involved 1,710 neonates (>34 weeks

of gestational age) suspected with an EOS and started on antibiotics by the physician in charge. Neonates were stratified into four risk categories and randomized either to be treated according a PCT-guided algorithm or either to standard care-based following the risk stratification. In the PCT group, 12 neonates had a proven infection (1%), 85% a probable infection (10%), 405 a possible infection (47%) and 350 an unlikely infection. Repartition was alike in the standard group (2%, 9%, 46%, 43%, respectively). Overall, this pragmatic study showed a reduction in antimicrobial treatment duration (intention to treat: 55.1 *vs.* 65.0 h, P<0·0001; per protocol: 51.8 *vs.* 64.0 h; P<0.0001). PCT-based algorithm was also associated with a slight shorter in-hospital length of stay by 3.5 h [123 h (113–134.5 h) in the PCT group *vs.* 126.5 h (117.5–144.3 h) in the standard group]. However, non-inferiority for re-infection or death could not be shown due to the low occurrence of re-infections and absence of study-related death.

The strengths of the study were the design, the large sample size, inclusion of multiple centers, rigorous statistical analysis, and the complete follow-up. Thus, the authors should be congratulated with the efforts to report such a well-conducted study. Despite the undeniable merits of this NeoPIns study we would like to discuss two limitations: the lack of a global antibiotic stewardship in the control group and the significance of the results produced.

The authors state that compliance with antimicrobial stewardship is difficult to obtain and rarely reported in neonatology. It is not completely true, and it did not exempt the author from embracing the use of biomarker into a global antibiotic stewardship. The SCOUT study is a prospective observational interrupted time-series study in the level 3 NICU (12). After a baseline period of observation, continuation of empirical antibiotic therapy for ruled-out sepsis courses beyond 48 h, pneumonia, and "culture-negative" sepsis were selected as targets for antibiotic stewardship interventions. Empirical antibiotic therapy was set to discontinue after 48 h in the electronic medical record and the duration of therapy for pneumonia and culture-negative sepsis was limited to 5 days. A total of 2,502 infants were admitted to the NICU during the two study periods (1,607 in the baseline period and 895 in the intervention period). Antibiotic use declined from 343.2 days of therapy per 1,000 patient-days during the baseline period to 252.2 days of therapy per 1,000 patient-days in the intervention period (P<0.0001), representing an overall decrease of 27%. Importantly, no difference in safety outcomes was observed between the intervention and baseline periods. Moreover, in the SCOUT study, the antibiotic stewardship program allowed to discontinue the antimicrobial treatment within 48 h in almost all the rule-out sepsis courses and within 5 days in 75% of neonates treated for pneumonia. In the NeoPIns study, the neonates were at low risk of infection and a substantial fraction of the antibiotic courses should have been discontinued at 48 h. Instead of a discontinuation strategy, the duration of antibiotic therapy in the control group was 36–72 h in "infection unlikely" group and 5–7 days in "infection possible" group. In the absence of an antibiotic stewardship program to stop antimicrobial treatment the neonates in control group might have been over-treated. A huge variation of antibiotic consumption has been reported despite similar burden of infection in neonates. In a retrospective cohort study of 52,061 infants in 127 NICUs across California during 2013, overall antibiotic use varied 40-fold, from 2.4% to 97.1% of patient-days; median =24.5%. At all levels of care, it was independent of proven infection, necrotizing enterocolitis, surgical volume, or mortality. This study indicated that antibiotics were overused in NICU (13). To conclude, whether the NeoPIns study was a success related to the use of PCT or whether the antibiotic stewardship was inefficient or inexistent inherently is questionable. An antibiotic stewardship program in neonates should include at least the Core Elements of Hospital Antibiotic Stewardship Programs define by the CDC (https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html). From our perspective, the use of a sepsis biomarker such as PCT should be considered in view of a help when the use of antibiotics is still high despite a well-implemented antibiotic stewardship program. While we agree that PCT is the best sepsis biomarker so far, in our opinion it doesn't replace the need of a global stewardship approach.

The clinical implication of the main result of the NeoPIns study (i.e., the duration of antibiotic therapy was reduced by 9.9 h in the intention-to-treat analysis) is questionable as well. This result should be interpreted from two different perspectives: antibiotic consumption reduction and neonate's microbiome preservation. We are now heading towards extreme drug resistance and any effort to reduce antibiotic consumption is commendable and should be encouraged. Additionally, evidence is compelling that antibiotic treatment in early life disturbs the microbial flora that colonizes the neonate and might

be associated with health problems (6). From the point of view of reducing antibiotics consumption, the NeoPIns study is an obvious success. Use of sequential PCT dosage to customize antimicrobial treatment duration with no detrimental impact on outcomes has been shown in different populations. The NeoPIns study is of great interest because it designed a very useful PCT-guided decision-making algorithm in the particular setting of EOS in term neonates. The authors of the NeoPIns study should be congratulated on designing such a challenging algorithm. However, in a preliminary monocentric study using the same algorithm the authors reported a higher reduction of antibiotic duration by 22.4 h. This raises the question of the external validity of the study. Whether this tiny result (i.e., a reduction by 9.9 h) is realistic in inexpert center and outside of controlled study conditions remains to be proved. Indeed, results from RCTs may not unconditionally be generalized in daily practice. If compelling evidence suggests that every dose of antibiotics counts in increasing antibiotic resistance, a strategy which allowed antimicrobial treatment duration of 55.1 h on average in a context of unlikely or possible infection is not good enough to preserve neonates' microbiome. Indeed, our group showed that exposure to imipenem, as short as 1 to 3 days, is associated with a 5-fold increase in the risk of imipenem resistance in the gut microbiota of ICU patients (14). Since the incidence of EOS is declining, many neonates receive unduly an antimicrobial treatment. Consequently, to preserve neonates' microbiome, investigators should work on new approaches to avoid any antimicrobial treatment. For example, the usefulness of serial examinations to obtain a reliable assessment of the risk of EOS has been shown (3). Those were unfortunately limited in NeoPIns as only two hours separated birth from start of antibiotic therapy.

In conclusion, in NeoPIns, Stocker *et al*. showed that the use of a PCT-based algorithm may be of good help to shorten length of antimicrobial treatment in early-onset sepsis in term neonates. In the future, finding strategies to withhold antibiotics in low risk neonates may be a promising goal.

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Footnote

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

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