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Early onset sepsis in Suriname

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General Introduction and Thesis Outline

A COMMON CASE OF SUSPECTED EARLY ONSET SEPSIS IN SURINAME

A day prior to giving birth the mother had taken a boat from her village downstream the *Suriname* River to the nearest mission post in *Debike*[1]. She had been pregnant for eight full moons. Her water had broken a few days earlier, but the baby had not arrived yet. The friendly *datra*[2] at the mission post phoned somebody in the city of *Paramaribo* and spoke *Bakratongo*[3]. People in the village had talked about the new *at'oso*[4] for babies. Many women went there to give birth and they brought her there too. After six hours she arrived and spent the night in a room with four other women. She felt like she had *korsu*[5].

Her daughter was born the next day and although she was crying loudly they still took her to the baby hospital. Doctors and nurses were standing around a glass box that held her daughter. The doctors seemed confused. One of the nurses spoke her *tongo*[6] and explained that her baby was doing fine but could have an infection. They had taken her daughter's blood to see if it was infected. Depending on her daughter's condition and the test results they were going to decide whether to continue the antibiotics they had started. The nurse said her daughter could suffer from sepsis, *wan takru siki fu brudu*[7].

In the next few days she spent many hours next to the glass box in the spacious baby room. To her, her daughter seemed healthy and the same as her four earlier children. After three days, the doctors used a *nanai*[8] to take her *brudu*[9] for the second time. The nurse told her the results were fine. However, they were still going to finish her treatment with more antibiotics. Finally, after a total of seven days they started their long journey home.

In this thesis, I focus on newborns admitted to the only neonatal intensive care unit (NICU) in Suriname, which is located in Paramaribo, with a specific focus on dilemmas of Early Onset Sepsis – from epidemiology and prediction towards changes in vascular endothelial integrity, principles of leukocyte-endothelial interaction, and novel diagnostic methodologies for its timely recognition or exclusion.

Rens Zonneveld, M.D.
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[1] Village located along the Suriname River in the district Sipaliwini in the interior of Suriname.
Translated from the Surinamese language (*Sranan Tongo*)
[2] physician;
[3] Dutch;
[4] hospital;
[5] fever;
[6] language;
[7] a serious infection of the blood;
[8] needle;
[9] blood.

EARLY ONSET SEPSIS

Early onset sepsis (EOS) is defined as onset of sepsis in newborns within 72 hours after birth [1]. When intra-uterine infection is present, the fetus can become infected due to increased permeability of the skin and mucosa for bacterial invasion. EOS is also caused by vertical transmission of pathogens in the vaginal canal from mother to fetus during labor.

EOS is a leading cause of morbidity and mortality amongst newborns [1-6]. In Western (i.e., North American and European) countries incidence of blood culture proven EOS ranges from 0.01 to about 1.2 per 1000 live births. Incidence rates of EOS increase with decreasing gestational age and birth weight, with the highest incidence (i.e., 26 per 1000 live births) and mortality (i.e., 50-60% of blood culture proven cases) amongst infants with a birth weight below 1000 grams (2-4). EOS is associated with colonization of the birth canal (about 30% of mothers in Western countries) with Group B *Streptococcus* (GBS) [1]. In Western countries over 45% of all cases of culture proven EOS GBS (45%) is the responsible pathogen, followed by *Escherichia coli* (*E.coli*) (25%) (5,6). Other bacteria that cause EOS include *Listeria Monocytogenes*, gram-negative enteric bacilli (i.e., *Enterobacter spp.*, *Klebsiella spp.*) and *Enterococcus spp.* [1]. Viruses (predominantly entero and herpes simplex virus) are also identified causes of EOS [1].

After the introduction of intrapartum antibiotics as prophylaxis for GBS, incidence of EOS has decreased about 10-fold over the last 20 years in many Western countries and South Africa [7]. However, recent data indicates that, while incidence of EOS due to GBS is decreasing, incidence of EOS with *E.coli* increases, probably due to altered resistance patterns of *E.coli* strains [1,5,8]. Additionally, GBS prevention approaches may have contributed to the rise of multi resistant gram-positive strains, such as Methicillin resistant *Staphylococcus aureus*, as causes for EOS [1,9-11]. Maternal GBS vaccination to further reduce maternal GBS colonization and incidence of EOS, while preventing antibiotic exposure, is currently under investigation [12].

EARLY ONSET SEPSIS IN THE NON-WESTERN WORLD

Studies of EOS in low resource settings in the non-Western world are severely underrepresented in the literature [13-16]. The vast majority of data on EOS are from upper-middle to high-income countries in North America and Europe. Despite the lack of detailed data on EOS in the non-Western world, there is a strong indication that over 90% of global neonatal deaths due to EOS occurs in these low-to-middle income countries [17,18]. Large meta-analyses revealed incidence of EOS in low-income countries at least similar to Western countries [13,15,16]. However, in these analyses low-income countries represented only 5-10% of the total data leaving the true global impact of EOS underestimated. Additionally, underdiagnosing (i.e., due to lack of resources and logistic or financial constraints) and underreporting of EOS are common issues in low-resource settings further enhancing underestimation of the true global impact of EOS [19,20]. Furthermore, due to limited local availability of proper laboratory facilities, studies from these countries often lack blood culture confirmed results. As a result, the spectrum of bacterial pathogens involved in EOS in the non-Western world remains relatively unclear. More data on incidence, causative organisms, morbidity and mortality from non-Western countries remain critical before proper

prevention strategies and clinical management of suspected EOS can be achieved. Additionally, since there is strong indication that incidence rates of culture proven EOS are substantially higher in the non-Western world versus the Western world, studies from non-Western countries may contribute immensely to our knowledge on basic and pathophysiological principles of EOS.

EARLY ONSET SEPSIS IN SURINAME

Suriname is small developing country on the Northeastern corner of South America with a multiethnic population of about 550,000 people [21]. About half of the population of Suriname lives in its capital, the city of Paramaribo. Medical care is provided by four hospitals in Paramaribo, namely the Academic Hospital Paramaribo, 's Lands Hospital, Diakonessen Hospital and St. Vincentius Hospital, and the Streekziekenhuis in Nickerie. Suriname has an annual birth rate of approximately 10,000 births. Over 90% of these births take place at the maternity wards of the hospitals in Paramaribo. In rural parts of Suriname Medical Mission Posts provide primary health care to the inhabitants, including basic obstetric care.

The earliest data on neonatal mortality in Suriname dates back to the detailed documentations by Dr. Paul Christiaan Flu (1884 (Paramaribo, Suriname) - 1945 (Leiden, The Netherlands)) from the early 20th century. In his seminal, yet forgotten, work Flu describes the poor socio-economic circumstances after over three centuries of slavery and its effect on neonatal and pediatric care and mortality rates [22]. Between 1900 and 1909, 9,259 live births were recorded of whom 474 died within the first 14 days of life, making a high average death rate of 51.2 per 1000 live births for that age category. Over half (N=284) of these deaths were the result of pre- and dysmaturity, yet about one third (N=110) of these deaths were from unknown cause and potentially following neonatal infection.

Currently, neonatal death rate, defined as death within the first month of life, in Suriname has decreased, but remains high with 12.9 per 1000 live births [23]. Early neonatal death (i.e., death within the first 7 days of life) is estimated at 16 per 1000 live births [24]. Preliminary data from the Suriname Perinatal and Infant Mortality Survey estimates contribution of infection to early neonatal mortality at 24% (4 per 1000 live births) of all early neonatal deaths [23]. In contrast, in The Netherlands incidence of EOS alone was 0.19 per 1000 live births in 2014 [25].

These numbers indicate a high burden of neonatal infection in Suriname. About 40 newborns die each year of infection. Despite the overall idea of the impact of infectious disease in Surinamese newborns, detailed information regarding incidence, type of infection (i.e., EOS versus LOS), microbial causes, mortality and morbidity, antibiotic treatment (type and duration), and exact epidemiological determinants are currently unavailable. In **Chapter 2** of this thesis we explore the epidemiology and outcomes of newborns admitted to Suriname's neonatal care facility at the Academic Hospital Paramaribo. This facility was established in 2008 and renewed in 2015 with expansion of intensive care capacity, training of personnel and new equipment. For this chapter we hypothesized that tertiary function and morbidity and mortality rates of treated newborns would improve after the transition to the renewed neonatal care facility. Additionally, the impact of EOS on mortality of Surinamese newborns is explored.

EARLY ONSET SEPSIS: A DIAGNOSTIC AND THERAPEUTIC DILEMMA

EOS can present with relatively mild symptoms resulting in late discovery with high risk for mortality and morbidity. Furthermore, clinical symptoms of EOS are extremely diverse and difficult to distinguish from physiologic symptoms of neonatal transition from intra-to-extrauterine life and other non-infectious neonatal disease [3,9,26]. This complicates clinical decision-making on start and duration of antibiotic treatment leading to significant overtreatment. For example, in the European Union almost 8% of newborns are treated with antibiotics for suspected EOS, while incidence rates of bacterial culture proven EOS range from 0.01 to 0.53 per 1000 live births in those countries [3].

Blood culturing is considered the golden standard diagnostic test for EOS and takes several days to become positive. Upon suspicion of EOS, newborns are observed and treated empirically for EOS with antibiotics for at least 48 hours until results of blood culturing are known [1]. However, blood cultures are only positive in 0.01 to 1.2 per 1000 live births in countries in the European Union and North America. Contributing to this low prevalence may be false negativity due to low yield of bacteria in low sample volumes or low-density bacteremia in general. Nonetheless, over 60% of newborns empirically treated with antibiotics for suspected EOS are treated for longer than 72 hours even when blood cultures are negative [27]. Antibiotic stewardship is necessary to reduce this overtreatment [28].

These dilemmas in the management of EOS pose a huge cost and socioeconomic threat, especially in non-Western countries [1,6,16]. Moreover, it is becoming clear that prolonged treatment of newborns with antibiotics also can negatively and severely impact early and long-term neurodevelopment, growth, the developing immune system, and gut microbiome resistance patterns [29-32].

CURRENT APPROACHES IN PREDICTION OF EARLY ONSET SEPSIS

Since clinical presentation and blood culturing have poor specificity for EOS, additional approaches to aid clinical decision-making whether to start and/or continue antibiotic treatment have been developed in the recent decade. Approaches that are commonly used in the clinic include maternal risk factor stratification and serial measurement of C-reactive protein (CRP) levels and leukocyte counts. Each of these has limitations in clinical utility, as will be discussed below.

Maternal Risk Factor Stratification

Maternal risk factors for EOS (i.e., presence and duration of prolonged rupture of the membranes, intrapartum fever or administration of antibiotics, and presence of maternal GBS colonization, as the most common cause of EOS in Western countries, have been used to predict presence of EOS in newborns. In an attempt to overcome the problem of antibiotic overtreatment amongst near and at term newborns with a gestational age equal or above 34 weeks, a risk stratification strategy based on these factors and neonatal clinical findings has been developed in 2010 by Escobar et al., which was revised in 2014 (33). This EOS calculator (available online at https://

neonatalsepsiscalculator.kaiserpermanente.org) provides a quantitative estimation of EOS risk along with a recommendation whether to start antibiotic treatment. Since its inception, two retrospective studies revealed that application of the EOS calculator might help to reduce antibiotic therapy with 50% (34,35). Additionally, the EOS calculator uses local incidence rates of EOS as a variable, which still have to be established in many non-Western countries.

Correlation of results of the EOS calculator with biomarkers of inflammation in the newborn may be helpful in further increasing its clinical utility. Therefore, the study in **Chapter 3** explores the relationship of results from the EOS calculator with results of serial measurement of CRP and leukocyte counts in a cohort of Dutch near and at term newborns. For this study we hypothesized that higher EOS calculator result, indicating higher risk for EOS, corresponds with an increase in CRP and low leukocyte counts.

C-reactive Protein

CRP is an endogenous acute phase reactant synthesized by the liver upon infection [36]. Serum CRP in newborns always represents endogenous synthesis since it passes the placenta in extremely low quantities [37]. CRP is constitutively present in serum of newborns at very low concentrations and its levels are dependent on gestational age and birth weight. CRP synthesis starts immediately after an inflammatory stimulus by chemokines, such as interleukin (IL)-1, and IL-6, with serum concentrations rising above the usual laboratory threshold of 5 mg/L after 6 hours and peaking after 48 hours. This delayed synthesis results in poor sensitivity of CRP levels during early EOS. In most practices, in the newborn suspected and treated with antibiotics for EOS, a repeat CRP level below the laboratory threshold measured between 24 to 48 hours after start of antibiotics has negative predictive value of 99% for EOS, yet only in case of a negative blood culture plus a clinically improved newborn [37]. However, in clinical practice, despite this strong negative value, the repeat CRP also leads to even more testing, culturing, and longer treatment duration and hospital stay (38).

Leukocyte Counts

Inflammation and infection causes release of leukocytes from the bone marrow into the circulation. Leukocyte counts (both total and subset, predominantly neutrophil, counts) have been widely used to assess EOS [1,3]. However, both leukocyte and neutrophil counts lack specificity for prediction of EOS [39,40]. Their numbers are dependent on many perinatal factors such as gestational age, birth weight, type of delivery, and post partum age [41]. Neutropenia has shown the most specificity for EOS [42]. However, as discussed above, due to low prevalence of positive blood cultures, clinical decision-making on start and duration of antibiotic treatment is often based on non-specific clinical symptoms and repeated measurement of CRP. Serial measurement of low immature-to-total granulocyte (I/T) ratio has been showen to have a negative predictive value for blood culture positive EOS of 99% [42]. **Chapter 4** explores the relevance of a one-point automated I/T ratio determination in prediction of duration of antibiotic therapy in a retrospective cohort of Surinamese newborns with suspected EOS. For this study, we hypothesized that early

establishment of a one-point low I/T ratio is associated with short duration of antibiotic treatment in suspected EOS. This may prevent start of unnecessary antibiotic treatment, which may help to reduce the antibiotic burden in developing countries.

EARLY ONSET SEPSIS: A NEED FOR NOVEL DIAGNOSTIC STRATEGIES

The approaches described above have been used for over 20 years and have remained virtually unchanged. A recent international survey established that in practice only 31% of clinicians use CRP levels and leukocyte counts as arguments for the decision to start antibiotics [43]. Many other biomarkers have been investigated, but have not made it into the clinic for various reasons such as poor specificity, short half lives of biomarkers, lack of reproducibility, or technical issues [44]. At this point, serial measurement of procalcitonin, an acute phase reactant similar to CRP, is showing promise in negative prediction of EOS and reduction of antibiotic treatment in Western countries [45]. However, novel and practical approaches for early and prompt confirmation or exclusion of EOS remain necessary to reduce antibiotic overtreatment, while improving outcomes. Elements of the vascular pathophysiology may be relevant for development of these novel approaches, which will be discussed below.

THE VASCULAR PATHOPHYSIOLOGY OF EARLY ONSET SEPSIS

The diagnostic and therapeutic dilemmas of EOS occur, at least in part, because its pathophysiology remains poorly understood. Endothelial inflammatory activation and leukocyte-endothelial interactions are key processes in sepsis pathophysiology. **Part 3** is aimed to provide more insight into these processes in newborns to unravel aspects of EOS pathophysiology and provide novel concepts for its timely diagnosis and management.

LEUKOCYTE-ENDOTHELIAL INTERACTIONS: SHEDDING OF ADHESION MOLECULES IN EARLY ONSET SEPSIS

Leukocyte-endothelial interactions are involved in any infectious pathophysiology [46]. A body of evidence is indicating that aberrant leukocyte, mostly neutrophil, activation and recruitment towards the endothelium plays a pivotal role in breakdown of the vascular endothelium, which, in turn, is associated with organ failure and death [47,48]. Bacterial derived lipopolysaccharide (LPS) drives release of cytokines, such as tumor necrosis-α and interleukins, known as the 'cytokine storm'. Additionally, the endothelium becomes activated and increased presence of LPS in the vasculature is associated with increased expression of endothelial cell adhesion molecules (CAM) P-selectin, E-selectin, vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule (ICAM-1) and platelet and endothelial cell adhesion molecule-1 (PECAM-1) [49]. These adhesion molecules orchestrate tethering, rolling and firm adhesion of leukocytes on and transmigration across the endothelium [50]. During sepsis, soluble isoforms of adhesion molecules (sCAMs) accumulate in the bloodstream due to shedding [51]. Shedding represents removal of CAMs from cell surfaces

by enzymes called sheddases, in particular matrix metalloproteinase-9 (MMP-9) and neutrophil elastase (NE), released from tertiary granules in neutrophils [51]. Both MMP-9 and NE prepare the extracellular matrix underlying the endothelium to allow transmigration of leukocytes into inflammatory sites. The activity of MMP-9 is tightly regulated by sheddase antagonist tissue-inhibitor of metalloproteinases-1 (TIMP-1) to reduce damage to host-tissues and an increased TIMP-1/MMP-9 ratio was associated with severity and outcome of sepsis in adults [52,53]. **Chapter 5** reviews mechanisms for changes in levels of circulating adhesion molecules and their sheddases during sepsis and age-dependency of their levels in newborns, children and adults. For **Chapter 6** we applied the concept of simultaneous measurement of circulating adhesion molecules and their sheddases in a cohort of healthy newborns and newborns with suspected EOS. We hypothesized that higher circulating levels of adhesion molecules sP-selectin, sE-selectin sVCAM-1, sICAM-1 and sPECAM-1, coincide with higher levels of sheddases MMP-9 and NE, and sheddase antagonist TIMP-1 in newborns with culture proven EOS versus healthy controls.

ENDOTHELIAL INTEGRITY DURING EARLY ONSET SEPSIS: THE ANGIOPOIETINS

Endothelial integrity is maintained by the Angiopoietin/Tie2 Receptor Tyrosine Kinase - system, which consists of the endothelial restricted receptor Tie-2 and its ligands Angiopoietin (Ang)-1 and Ang-2 [54]. In health, Ang-1 is present in human serum at higher levels than Ang-2 and promotes endothelial stability through continuous endothelial Tie-2 receptor phosphorylation [55]. Inflammation leads to higher circulating levels of Ang-2 that is being release from endothelial cells. Circulating Ang-2 dose-dependently inhibits Tie-2 signaling and acts as an antagonist of Ang/Tie-2, driving vascular permeability. Emerging clinical evidence indicates a positive correlation of high Ang-2 levels, and subsequent high Ang-2/Ang-1 ratio with presence, severity, and outcome of pediatric and adult sepsis [56,57]. It was recently suggested that the Angiopoietins may be relevant as biomarkers of EOS [58]. Additionally, investigating the dynamics of Ang-1 and Ang-2 in healthy and infected newborns may unravel changes in their levels during EOS. In **Chapter 7**, these changes are explored in a large cohort of healthy newborns and newborns with suspected and culture proven EOS. For this study, we hypothesized that low Ang-1 and high Ang-2 levels are associated with presence of bacterial culture positive EOS.

NOVEL ASPECTS OF NEUTROPHILS IN SEPSIS

Manual microscopic analysis of neutrophils and their counts have been part of the clinical assessment of bacterial infection for over a century [59]. However, manual analysis of counts and morphology is time consuming, requires experienced laboratory technicians, and lacks reproducibility. Novel methods allow for measurement of several aspects of neutrophils, in particular morphology, mechanics and motility. Flow-based automated hematology analysers (AHAs) are able to determine leukocyte subsets and different granulocyte fractions [42]. Additionally, recent developments in the performance of these AHAs have enabled measurement of neutrophil size and scatter properties and determination of neutrophil cell surface markers with

immunofluorescence, each with their own sensitivity for presence of sepsis in patients. **Chapter 8** and **Chapter 9** discuss basic and clinical aspects of neutrophil morphology, mechanics and motility during sepsis, along with current evidence and future possibilities for the use of these parameters into the management of sepsis.

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