UiT The Arctic University of Norway

Faculty of Health Sciences

Metabolomics in neonatal sepsis

A systematic review

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Abstract

Background: The clinical signs of neonatal sepsis are nonspecific and therefore antibiotic treatment is often initiated in clinically suspected cases. This approach causes concern in regard to possible overuse of antibiotics in newborns.
Metabolomics is an emerging field of focus for neonatologists due to its potential phenotypical insight into cellular and metabolic processes, contributing to or resulting in disease in addition to having the potential to improve diagnosis.

Objectives: The purpose of this systematic review is to summarize current knowledge on metabolomics in neonatal infections, with a particular focus on how this method can contribute to identify sepsis in preterm and term infants. The main objective of the review will be on urine and blood metabolomics and the use or possible use of urine/blood metabolomics in clinical practice.

Methods: A systematic literature search was performed in the databases MEDLINE and EMBASE up to the 1st of August 2020. We included studies that assessed neonatal sepsis on the following outcomes; (1) change in the metabolism compered to healthy neonates and/or (2) metabolomics compared to traditional diagnostic tools of neonatal sepsis. The screened abstracts were independently considered for eligibility by two researchers. The study is registered in an international prospective register of systematic reviews; PROSPERO ID: CRD42020164454.

Results: The search identified in total 703 articles. 524 articles were screened after duplicates and triplicates were removed. 15 articles were assessed for eligibility. We included 3 studies, including a total of 71 newborns, that met the inclusion criteria. One study was included from the reference list of a literature review. The study did not conduct statistical analysis on the small neonatal group (n = 7), but had a large group of infants from 1 month up to one year (n = 46). This group of infants was considered to have a metabolomic profile likely to be comparable to the neonates, so it was included in the qualitative analysis of the systematic review. The studies used different diagnostic criteria and had small study samples. Three studies conducted untargeted metabolomics, while one study conducted both untargeted and targeted metabolomics. There was a significant difference in the metabolomic profile in septic

neonates and infants compared to controls. All included studies found alteration in the glucose and lactate metabolism.

Conclusion: The identified biomarkers in the included studies have yet to be validated in large-scale multicentre studies. In regard to neonatal sepsis, more large-scale standardised studies are needed in both untargeted and targeted metabolomics. In addition, future studies should consider alternative methods like the hybrid approaches of NMR/MS.

Abbreviations

AAP	American Academy of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
AMR	Antimicrobial Resistance
ANC	Absolute neutrophil count
BW	Birth weight
CBC	Complete blood count
CRP	C - reactive protein
CSF	Cerebrospinal fluid
CoNS	Coagulase-negative *Staphylococci*
CVC	Central venous catheters
EOS	Early-Onset Neonatal Sepsis
E. coli	*Escherichia coli*
GA	Gestational age
GBS	Group B *Streptococcus*
GC-MS	Gas chromatography mass spectrometry
H-NMR	Proton nuclear magnetic resonance
IAP	Intrapartum antibiotic prophylaxis
LB	Live born
LC-MS	Liquid chromatography mass spectrometry
LOS	Late-Onset Neonatal Sepsis
MeSH	Medical Subject Headings

MS	Mass spectrometry
NLR	Neutrophil to lymphocyte ratio
NMR	Nuclear magnetic resonance
PCT	Procalcitonin
PCR	Polymerase chain reaction
PROM	Prolonged rupture of membranes
S. aureus	*Staphylococcus aureus*
VGS	Viridans group streptococci
VLBW	Very low birth weight
WBC	White blood count
1D ^{1}H NMR	One-dimensional (1D) ^{1}H nuclear magnetic resonance
2D NMR	Two-dimensional nuclear magnetic resonance

1 Introduction

Neonatal sepsis is most commonly viewed as a clinical syndrome in infants up to 28 days of life. The syndrome can manifest as systemic signs of infection. Often also isolation of a pathogen from the bloodstream can be obtained, but an undisputable uniform definition for neonatal sepsis is still lacking (1).

Neonatal sepsis and other severe infections (e.g. meningitis) accounted for an estimated 430 000 of the 2.8 million global neonatal deaths in 2013 (2).

Neonates are born with an immature immune system. The maturation of the immune system commences in the early embryonic stages, but bares signs of the semi-allogenic sterile environment in which the immune system develops (3, 4). The intrauterine environment is a contrast to the rich microbial environment the neonate is exposed to from the time of delivery (4). Neonates are equipped with passive protection through the transferred maternal antibodies, but this protection has a an estimated duration of 3 - 4 months for common infectious agents that can infect newborns (5). In addition to the passive protection, the neonates' immune system undergoes an accelerated maturation in the first 3 months of life. This protects most newborns from infections, but infection susceptibility is highly influenced by different genetic and environmental factors (3-5).

Neonatal sepsis is often dived in two sub-groups based on the onset of the clinical symptoms; *Early-Onset Neonatal Sepsis* (EOS) and *Late-Onset Neonatal Sepsis* (LOS). The two conditions are separated by the different modes of transmission, causative pathogens and guidelines and recommendations for treatment (6, 7).

1.1 Early-onset neonatal sepsis

One common definition of EOS is bloodstream infections occurring within the first 72 hours of life (8-10). The American Academy of Pediatrics (AAP) reports that there are also some experts that define EOS as the onset of symptoms occurring in the first 7 days of life (11). In the western world the incidence of EOS lies between 0.5 – 1.2 per 1000 live born (LB) infants (8, 12), and the majority of these paediatric patients have a gestational age (GA) ≥ 30 weeks and a birth-weight (BW) ≥ 1500 g (9, 13, 14).

The main cause of EOS is vertically transmission of pathogens from the mother to the neonate during delivery. Neonates can be colonised by maternal bacteria, most commonly Group B *Streptococcus* (GBS) or *Escherichia coli* (*E. coli*), in the birth canal or through aspiration of infected amniotic fluid (15).

An American multicentre surveillance during 1995 to 1996 reported an incidence of 3.5 EOS cases per 1000 LB infants, and the most frequent causative bacteria were GBS (40 %) and *E. coli* (approx. 18 %) (16). *Stoll et al. 2011* published a prospective surveillance study from the period 2006-2009 and found a decreased incidence of 0.98 EOS cases per 1000 LB infants. The most frequently isolated bacteria were GBS (43 %) and *E.coli* (29 %) (9). Recently a new prospective surveillance study, that included a cohort of infants from the period 1st of April 2015 to 31st of March 2017, was published by *Stoll et al. 2020*. The incidence of EOS was 1.08 cases per 1000 LB infants, and the most frequent pathogens were *E. coli* (36.6 %) and GBS (30.2 %)(17). The incidence of EOS increases with the decrease of GA(12, 13, 17), with the highest incidence among infants with a GA of 22 to 28 weeks (18.47 EOS cases per 1000 LB infants) (17).

The introduction of intrapartum antibiotic prophylaxis (IAP) and maternal screening for vaginal carriage of GBS has reduced the GBS EOS in the USA (17, 18). The American Centers for Disease Control and Prevention (CDC) has been responsible for the American guidelines for prevention of neonatal GBS disease up to 2019 (19, 20). In 2019 the American College of Obstetricians and Gynecologists (ACOG) took over the role of updating the guidelines. The guidelines from ACOG continued the focus on IAP administration in women with a positive rectal-vaginal GBS culture (culture-based approach) rather than solely on predefined maternal characteristics associated with EOS (risk factor-based approach). They implemented in the guidelines that all pregnant women at 36+0 to 37+6 weeks of GA should be offered a GBS rectovaginal screening culture, with the exception of pregnant women with GBS bacteriuria during the current pregnancy and women who previously gave birth to an infant with invasive GBS disease (21). The traditional risk factor-based approach includes evaluating risk factors such as intrapartum fever ≥ 38°C, delivery before 37+0 weeks of GA, rupture of membranes ≥18 hours, previous delivery of an infant affected by GBS disease and GBS bacteriuria in the current pregnancy (21, 22).

Though GBS and *E. coli* are the two most frequent bacteria causing EOS, there are other less common bacterial and non-bacterial agents associated with EOS and LOS. The less common bacterial agents associated with EOS are *Klebsiella spp.*, *Enterobacter* spp., *Listeria monocytogenes*, enteric Gram-negatives, non-enteric Gram-negatives (e.g. *Hemophilus influenzae* and *Neisseria meningitidis*), Viridans group streptococci (VGS), *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS) (23). Non-bacterial agents that can be associated with EOS are *Herpes simplex virus* (24), enterovirus and parechovirus (25) and *Candida* (26).

EOS is associated with complications such as retinopathy of prematurity, intraventricular haemorrhage, bronchopulmonary dysplasia and periventricular leukomalacia in VLBW infants. The morbidity and mortality associated with EOS is therefore considerably high (27). Studies indicate that there might be a higher mortality rate associated with Gram-negative EOS, though GA seems to be a confounding factor (9, 17). *Stoll et al. 2020* reported a total case fatality rate of 29 % for preterm infants born at 22 to 36 weeks of GA. Further the study reported that preterm infants infected with GBS had a case fatality rate of 24 %, but for those infected with *E. coli* the case fatality rate was 40 %. The study has its limitations because of the small numbers, so there could be confounding factors effecting the results (9, 17).

1.2 Late-onset neonatal sepsis

AAP reports that similar to EOS there are some experts that define LOS as the onset of symptoms occurring ≥ 7 days of life (11). Another common definition is bloodstream infections occurring after the first 72 hours of life (2, 28).

LOS is associated with horizontal transmission through the postnatal nosocomial or community environment (29). Advances in neonatology have increased survival of premature VLBW infants, but the increased survival rate causes challenges seen as an increased incidence of LOS (12, 29). The incidence rate of LOS in England is reported to be 3 per 1000 LB infants, but is significantly influenced by the BW. LOS effects between 10 to 30 % of VLBW infants, with a peak of onset reported to be between 11 - 22 days (8, 29-32).

The majority of LOS cases are caused by Gram-positive bacteria (57.9%) compared to the Gram-negative bacteria (32.6 %) (31). Coagulase-negative staphylococci (CoNS), predominantly *Staphylococcus epidermidis*, are the predominant pathogens associated with

LOS. They are the causative pathogens in 35.5 – 47.4% of LOS cases in some developing regions, while they account for 53.2 – 77.9% of LOS cases in industrialised countries (30-32).

Other pathogens associated with LOS are *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp., *Acinetobacter* spp. and *Candida* spp. The distribution of these infectious agents varies depending on demographic characteristics of the patients, colonisation of the nosocomial environment and the policy regarding antibiotic usage at the hospital (31).

Though decreased GA and VLBW are strongly associated with LOS, another important risk factor is the use of percutaneous catheters, central venous catheters (CVC) and umbilical catheters. These indwelling catheters provide a passageway for nosocomial bacteria, such as CoNS, and provide a surface for the development of biofilms. The longer the duration of the catheter use, the higher is the risk of infection (33, 34). Other risk factors are long-term use of mechanical ventilation and parenteral nutrition, hospitalisation, surgery, underlying respiratory and cardiovascular diseases and late introduction of enteral feeding with breast milk (29, 31).

LOS is a significant cause of mortality in preterm neonates, and treatment of sepsis is not always successful in protecting the infants from the long-term neurodevelopmental impairments (30, 35). It is strongly argued that preventing LOS is the preferable strategy rather than solely focusing on novel treatment options (35). *Bion et al. 2013* reported a 47.3 % decrease in bloodstream infections from venous catheters in 19 paediatric ICUs by implementing proper hand hygiene, full-barrier precautions, 2% chlorhexidine skin antiseptics, avoiding the femoral route and promptly removing unnecessary catheters (36). In the recent years there have been studies on the potential benefits of prophylactic probiotics, but the results have been inconsistent in regard to nosocomial sepsis. Metanalyses have shown no significant reduction of the incidence of sepsis with the use of probiotics, though heterogeneity among trials might significantly influence the results (37, 38). Early initiation of enteral feeding in VLBW infants causes concerns because of the possible implication in the pathogenesis of necrotising enterocolitis (NEC) (39, 40), but human milk feeding within the first 72 h after birth is associated with a significant (approx. threefold) reduction in the risk of LOS (41). Lactoferrin is an important glycoprotein in human milk, that plays an important component in the innate immune defence against infections. The trials involving the protein

and preterm infants had been promising (35, 42), but a recent Cochrane systematic review including 12 randomized controlled studies found low evidence that lactoferrin supplementation decreases the incidence of LOS (43).

1.3 Immunopathology of neonatal sepsis

Contrary to the traditional understanding of sepsis as an in initial hyper-inflammatory phase followed by hypo-inflammatory responses, recent adult studies suggest that sepsis simultaneously induces both hyper- and hypo-inflammatory responses. Furthermore the studies find a correlation between early deaths and an acute hyper-inflammatory phase, whereas late deaths are associated with a prolonged immunosuppression and recurrent infection (44, 45). However, when it comes to neonatal sepsis it still remains unknown whether the associated morbidity and mortality is due to hyper-inflammation and/or immunosuppression (46).

"Immunometabolism" is an emerging field, that recognizes the complex interactions between the metabolism and the immune system. The amino acid pathway, fatty acid synthesis, fatty acid oxidation, glycolysis and the tricarboxylic acid cycle (TCA, also known as the Krebs Cycle) are all metabolomic pathways that promote innate immune cell survival or growth, function, and activation (47, 48). During inflammation, glycolysis is an ineffective, but rapid pathway of generating the essential chemical energy substrate adenosine triphosphate (ATP). ATP drives many processes in living cells from muscle contraction to chemical synthesis. However, oxidative phosphorylation in the mitochondria (in the Krebs Cycle) is more effective than glycolysis in generating ATP (49, 50). High levels of ATP can dangerously prolong the immune response during sepsis (51), but through the hydrolyzation of ATP to adenosine diphosphate (ADP) and adenosine monophosphate (AMP), adenosine levels rise. Unlike ATP, adenosine reduces pro-inflammatory/Th1-polarizing immune responses (47, 52). Compared to adults, neonatal blood contains higher levels of adenosine, that may promote an anti-inflammatory immunological status (53, 54).

1.4 Traditional diagnostic tools

Neonatal sepsis often presents with subtle and non-specific clinical manifestations, but there are some symptoms that seem to have a significant association with LOS. These are symptoms like respiratory distress, prolonged capillary refill time (> 2 seconds), pallor and

lethargy (55, 56). However, isolation of a pathogen in a microbiological culture of blood or cerebrospinal fluid (CSF) is the "gold standard" of diagnosing neonatal sepsis, while adjunctive tests include C-reactive protein (CRP) and procalcitonin (PCT) and a haematological panel. Mortality increases with delayed treatment of sepsis, and as a result a more conservative clinical approach is used in diagnosing neonatal sepsis. Empirical treatment with antibiotics usually commences without confirmed clinical and microbiological finding of sepsis (57-60).

1.4.1 Microbiological cultures

Microbiological blood cultures have some limitations, like contaminations by skin microbiota. In preterm infant there are challenges with small blood volumes, low colony count and exposure to empiric antibiotic therapy. In turn this may lead to uninfected neonates receiving unnecessary prolonged antibiotic therapy, which is associated with an adverse effect on the gut microbiota and provides pressure on antimicrobial resistance (AMR) (29, 60). The previous reported average amount of blood collected in neonates was 0.5 mL (61). This amount has been demonstrated to be insufficient in detecting bacteria in low count colony sepsis with a 60 % risk of false negative result. During a moderate to high grade of bacteraemia 0.5 mL can be adequate to detect bacteria, but one should try to obtain a minimum of 1 mL blood (57, 62, 63). A positive blood culture requires 12 - 48 hours in order to expand microbial numbers, this leads to empirical antibiotic treatment of neonates. Initiated antibiotic treatment before blood draw is a significant challenge as it reduces bacterial density, and hinders sensitivity (64, 65). Though blood cultures have significant shortcomings in diagnosing neonatal sepsis, the method is crucial for isolating bacteria for antibiotic susceptibility testing as microbiological independent techniques like PCR, cannot distinguish between live or dead bacteria (66).

The initial clinical signs of meningitis are subtle and might overlap with sepsis, and lumbar puncture remains the most important tool for diagnosing meningitis. The incidence of neonatal meningitis varies from 0.8 - 6.1 per 1000 LB infants in low income countries, while in high income countries the incidence is reported to be 0.3 per 1000 LB infants (67, 68). Though difficult to diagnose solely based on a lumbar puncture, it is an important differential diagnosis in regard to neonatal sepsis as meningitis affects the antibiotic treatment type, dosage and duration of treatment. It is reported that at least 15 % of neonates with meningitis

may present with a negative blood culture, and the question has been raised whether lumbar puncture should be considered a part of the routine investigation of LOS (69).

1.4.2 The use of biomarkers

The liver produces acute phase reactants that can activate the complement system, enhance phagocytosis modulate pro-inflammatory cytokines and reduce tissue damage. The majority of studies on sepsis biomarkers have focused on the acute phase proteins CRP and PCT, mostly due to their inexpensive assays and ease in which these analyses can be performed. CRP and PCT are non-specific acute phase proteins that are influenced by the maturity of the liver and the progression of organ dysfunction associated with sepsis (70, 71). CRP is the most commonly used adjunctive indicator for sepsis, as it elevates in response to IL-6 and other pro-inflammatory cytokines approximately 4 - 6 hours after onset of infection and/or inflammation. The protein has been extensively studied in regard to neonatal sepsis, but results vary depending on the definition of sepsis, EOS or LOS, sampling time, study population, sample size and cut-off values (71-73). CRP sensitivity of neonatal sepsis is reported for most studies to be between 50 - 77%, while the specificity is between 78 - 100 %. There is an increased sensitivity associated with CRP measurements during the first 24 - 72 hours of suspected neonatal sepsis cases, but non-infectious causes like foetal distress and maternal fever can also increase CRP and thereby decrease sensitivity (73, 74).

Another widely used indicator of neonatal sepsis is PCT, the prohormone of calcitonin. The protein is mainly produced by peripheral mononuclear cells and increases approximately 2 - 6 hours after infection and/or inflammation. The more rapid increase of PCT compared to CRP makes it a more practical biomarker for early detection of neonatal sepsis (72, 75). The PCT sensitivity and specificity is reported to be comparable to CRP, with sensitivity ranging from 67 - 98 % and specificity from 67 - 100 % (76, 77). There seem to be an increase of sensitivity when CRP and PCT are both included as adjuvant tests. However, the metanalysis conducted by *Ruan et al.* 2018 had limitations due to the heterogenous definitions of sepsis, and the included studies in the metanalysis used different techniques for detection of septic infants (77).

There has also been extensive research in other biomarkers (e.g. acute phase proteins and cytokines) besides CRP and PCT. The metanalysis of the cytokines TNF, IL-8 and IL-6 have

limitations mostly due to the heterogenicity of the included studies (78-80). Despite extensive research, there is still no single test, biological marker or panel of markers reported to more superior for the diagnosis of neonatal sepsis (29, 81, 82).

1.4.3 Haematological profiling

Other adjuvant tests routinely taken in the diagnosis of neonatal sepsis are complete blood count (CBC), which includes tests like white blood count (WBC), absolute neutrophil count (ANC) and immature-to-total neutrophil ratio (83, 84). The haematological profile showing an increase of immature compared to mature neutrophils (IT-ratio), abnormal WBC and/or a left shift in ANC (57, 81, 85). The CBC tests have wide ranges of sensitivity from 17 - 90% and specificity from 31 - 100 %. This is mainly due the broad abnormal ranges, slow time for positive result, restrictive sampling times and the influence of non-specific factors (57, 64, 83, 86, 87).

1.5 Metabolomics

The word *metabolite* has its origin from the ancient Greek word *metaboli*, meaning *change*. Metabolomics or metabonomics is derived from the same word and describes a modern profiling technique in medicine. The method can be used to investigate and detect a comprehensive set of molecules, like carbohydrates, lipids, vitamins and amino acids. These molecules can be located intracellular and/or in the extracellular matrix (88). In the recent years there has been extensive research in genomics, transcriptomics, proteomics and metabolomics. One way to differentiate the different methods in the field of medicine is to focus on what information they give us. Genomics informs us about the neonates' predispositions to sepsis, while transcriptomics relay information about transcriptional changes that occur during sepsis. Proteomics illustrates how protein expression is altered by sepsis, and finally metabolomics give us information about the metabolites produced as a result of sepsis (89, 90).

Sepsis causes a dysregulation of the metabolome by inducing hypoxia, oxidative stress and high energy demand. The novel field of research, metabolomics, can profile/characterise the products of the intricated interaction between the gut microbiome, host genome and environment. The method is important in order to characterise the normal state of neonates as

well as the metabolic state during sepsis, in the hopes of identifying novel biomarkers (89, 90).

The main techniques for analysing the metabolic state of an organism (Table 1) is through proton nuclear magnetic resonance spectrometry (H-NMR), gas chromatography mass spectrometry (GC-MS) and liquid chromatography mass spectrometry (LC-MS) (91, 92). Methods based on MS are reported to be time-consuming and expensive. MS-based methods involve an extensive sampling process and the data has to be pre-processed before analysing the data, which requires specialized hardware and software. NMR is reported to be less time-consuming compered to MS, and without the need of pre-processing the data before analysing. MS on the other hand is more sensitive and can detect low-abundance metabolites (Table 1) (93, 94).

1.5.1 Targeted metabolomics

In some studies, it is important to predetermine metabolites of interest and quantify the metabolites in biological samples. Other times there might be a library of metabolites available and researchers can use the library to predetermine metabolites of interest. These are examples of targeted or semi-targeted metabolomics. Statistical tools can then assess how successful the targeted metabolites contributed to the group differences observed between cases and controls (95). Correlations can then be evaluated further by studying the different variables in order to understand the underlying metabolomic differences between the groups (96).

There is extensive research in improving the methods of targeted metabolomics. 1D ^{1}H NMR is the most used method, but some studies have started using 2D NMR and others are looking into combining NMR and MS (97-101).

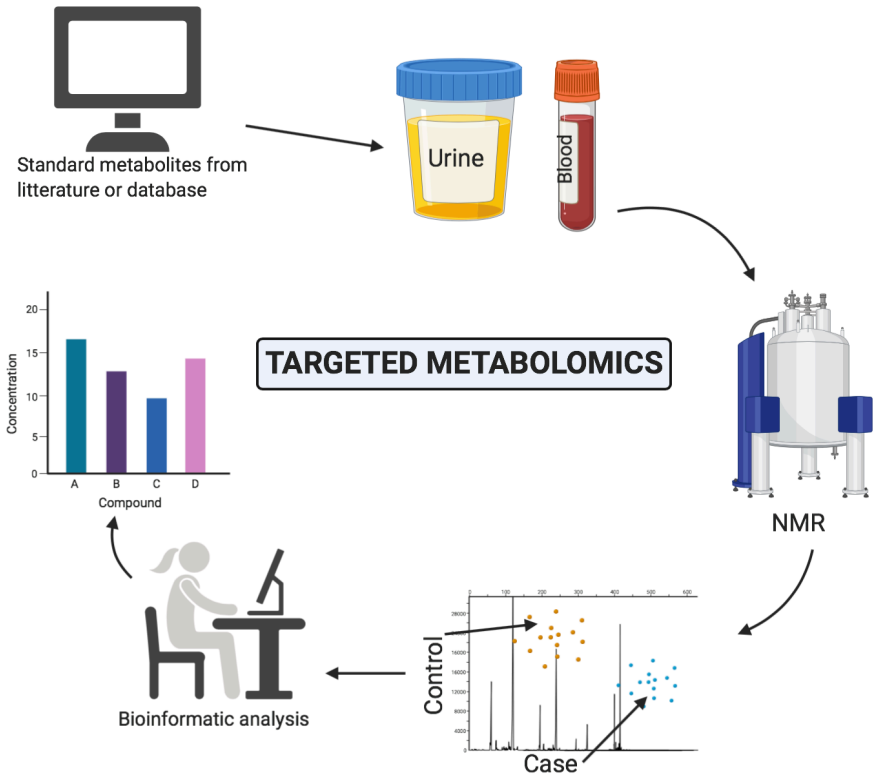

Figure 1 An example of targeted metabolomics with NMR.
This figure shows an illustration of targeted metabolomics. The process is hypothesis-driven, and identification of metabolites is already conducted. The method results in an absolute quantification of metabolites. ***Figure is created at BioRender.com.***

1.5.2 Untargeted metabolomics

Untargeted metabolomics relies on metabolomics databases for identification of the metabolites. These studies focus on the qualitative identification and relative quantification of metabolites in samples (100, 102, 103).

Untargeted metabolomics uses mainly MS techniques, NMR based techniques or MS/NMR hybrid techniques. In MS methods the fragmentation spectra of the unknown metabolites are compared to a set of standards for known chemical structures to find the best match (104-107). NMR methods compare processed experimental chemical shifts of the unknown metabolite against a quantum NMR chemical shift prediction (108, 109). In order to increase the power of these experiment, developments in hybrid MS/NMR is ongoing. The combination of the two methods increase the power of the experiment by combining two methods, instead of relying on a single technique (110-112).

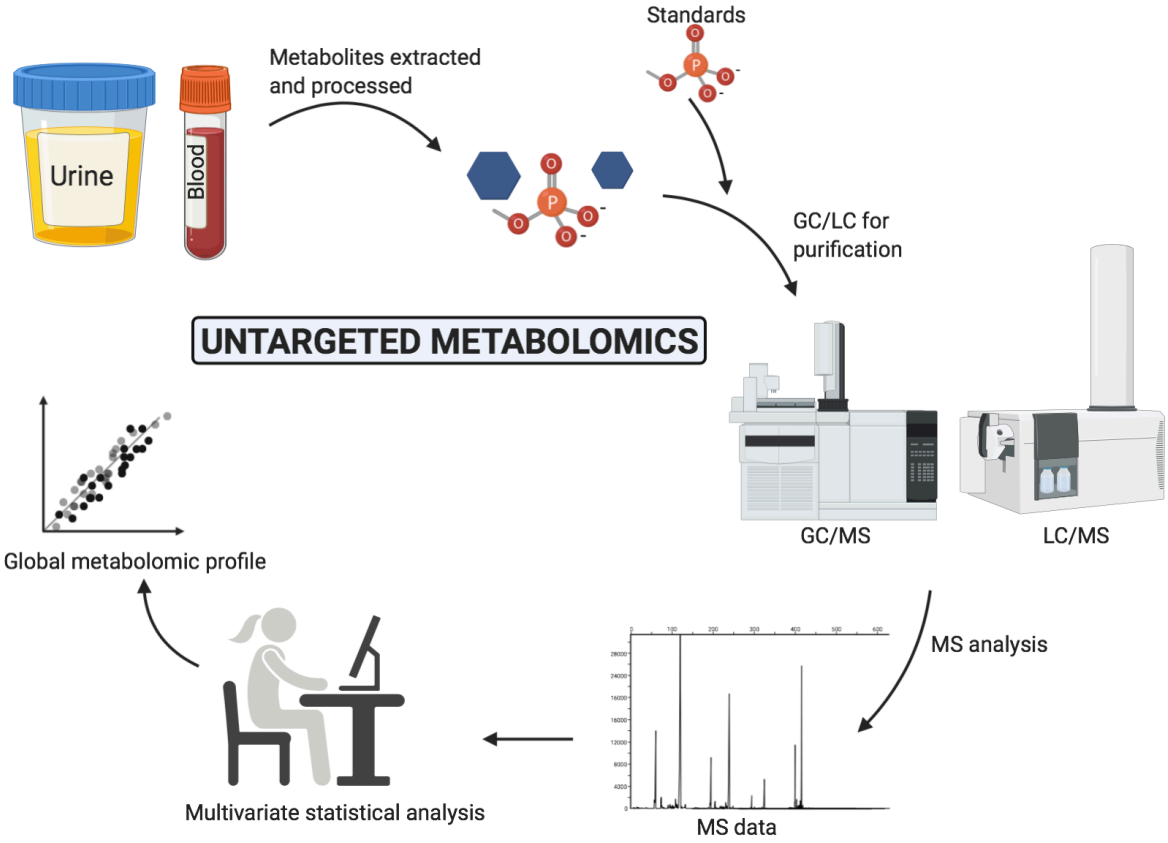

Figure 2 An example of untargeted metabolomics with GC/LC - MS.
This figure shows an illustration of untargeted metabolomics. This process is hypothesis generating, because of its global analysis and the qualitative identification of metabolites. The method results in a relative quantification of metabolites. ***Figure is created in BioRender.com.***

2 The aim of the thesis

The purpose of this systematic review is to summarize current knowledge on the use of metabolomics in neonatal infections, with a particular focus on how metabolomics can contribute to identify sepsis in preterm and term infants. The focus will be on urine and blood metabolomics and the use or possible use of metabolomics in clinical practice. We aimed to assessed neonatal sepsis on the following outcomes; (1) change in the metabolism compered to healthy neonates and/or (2) metabolomics compared to traditional diagnostic tools of neonatal sepsis.

3 Methods

3.1 PICO

Patient	Intervention	Comparison	Outcome
Neonates: first 28 days of life or preterm neonates up to 44 weeks postmenstrual age	**Metabolomics**: metabolic profiling using the methods nuclear magnetic resonance (NMR) or/and mass spectrometry (MS).[1]	**Traditional diagnostic tools**: e.g. blood culture, CRP, other inflammatory markers	**Detection of** **(1) Culture proven sepsis** **(2) Culture-negative sepsis**

Comparison:

Culture proven sepsis: The gold standard to confirm the diagnosis of neonatal sepsis is isolating a pathogenetic isolate from a blood culture.

[1] We also considered other methods that screen for multiple metabolites.

Culture-negative sepsis: An isolate is not always detected in a blood culture, but the neonates still present with a clinical course that is concerning for sepsis. This could be seen as ongoing temperature instability, ongoing respiratory distress, cardiocirculatory symptoms or neurologic symptoms that cannot be explained by other conditions. It can also be ongoing laboratory abnormalities suggestive of sepsis, like cerebrospinal fluid (CSF) pleocytosis or elevated IT-ratio, PCT or CRP.

In this systematic review we will include diagnostic tools for both culture proven sepsis (blood culture) and culture-negative sepsis (e.g. CRP).

3.2 Selection criteria

Searches were conducted with both Medical Subject Headings (MeSH) terms and without MeSH terms.

Search words:

NEONATAL SEPSIS (MeSH - Term)
• Neonatal sepses • Neonatal Late Onset Sepsis • Neonatal Late Onset Sepses • Neonatal Early Onset Sepsis • Neonatal Early Onset Sepses

METABOLOMIC(S) (MeSH - Term)
• **Metabolomic(s)** • Urine Metabolomic(s) • Blood Metabolomic(s) • Fetal blood Metabolomic(s) • Plasma Metabolomic(s) • Serum Metabolomic(s) • **Metabonomic(s)** • Urine Metabonomic(s) • Blood Metabonomic(s) • Fetal blood Metabonomic(s) • Plasma Metabonomic(s) • Serum Metabonomic(s) • **BIOMARKER (MeSH)** • Urine/Blood/Fetal blood/Plasma/Serum Biomarker(s) • Urine/Blood/Fetal blood/Plasma/Serum Biologic Marker(s) • Urine/Blood/Fetal blood/Plasma/Serum Biological Marker(s) • Urine/Blood/Fetal blood/Plasma/Serum Clinical Marker(s) • Urine/Blood/Fetal blood/Plasma/Serum Biochemical Marker(s)

Inclusion criteria: Human newborns (neonatal period = first 4 weeks of life or premature neonates up to 44 weeks postmenstrual age), use of metabolomics for studying sepsis. Metabolic profiling in urine and blood. Published in peer reviewed journals from 1st of January 1999 to 1st of August 2020.

Exclusion criteria: Animal studies. Research methods not including nuclear magnetic resonance (NMR) or mass spectrometry (MS) or screening for multiple metabolites. Publications older than 20 years. Descriptive or narrative review. Single case study.

3.3 Search strategy

The search for articles was performed in the databases MEDLINE and EMBASE (APPENDIX 2 and 3). All titles and abstracts of all articles citing metabolic testing in diagnosing neonatal sepsis, identified through Google Scholar and/or Scopus/Web of Science search engines, were also reviewed. The screened abstracts were independently considered for eligibility by two researchers.

3.4 Data collection

Data was exported to an excel spreadsheet from the databases EMBASE and MEDLINE. Management of the data was conducted in an excel spreadsheet. The studies identified by the search strategy were collated and duplicates/triplicates were manually removed.

Data was screened by medical research student Aline Bjerkhaug and checked by Associate Professor Hildegunn Norbakken Granslo. Potential eligible full-text articles were independently selected by Aline Bjerkhaug and Hildegunn N. Granslo according to predetermined inclusion and exclusion criteria.

All randomized control trial, clinical control trial, other research that has been randomized, observational studies (case-control studies, retrospective cohort studies, prospective cohort studies, cross-sectional studies, before-after studies, case-series), systematic review or meta-analysis meeting the inclusion criteria were considered. Descriptive or narrative review and single case study were not included.

Types of data that was extracted:

- Study name/article title
- Authors
- Year of publication

- Journal and full reference details
- Country
- Study design
- Participants
- Setting
- Interventions including metabolomics and traditional diagnostic tools
- Main results
- Statistical methods

The reference list and citations of included studies and relevant previous reviews was used to identify any additional eligible studies. Corresponding authors were contacted for additional data when necessary.

3.5 Analysis and synthesis

GRADE (Grades of Recommendation, Assessment, Development and Evaluation) is a tool to estimate the quality of evidence, from very low to high. This tool was used to rank the selected articles.

No individual patient data was reported. The data was not possible to meta-analyse, therefore a narrative (descriptive) synthesis was conducted.

3.6 Registration of the systematic review

The systematic review is registered in an international prospective register of systematic reviews; PROSPERO ID: CRD42020164454. The protocol is available at: https://www.crd.york.ac.uk/PROSPEROFILES/164454_PROTOCOL_20200116.pdf

4 Results

The systematic search in this review resulted in the inclusion of four peer-reviewed articles that are summarized in Table 2. There are in total n = 71 neonates included in this systematic review (93, 113, 114). Mickiewicz *et al* (2013) included in total n = 140 paediatric cases and controls; n = 60 septic shock, n = 40 Systemic Inflammatory Response Syndrome (SIRS) criteria and n = 40 healthy children. The decision was made to include the infant group (ages from 1 month up to 1 year, n= 46) in the qualitative analysis, based on the possibility that the neonates might share some of the characteristics in their metabolomic profile during sepsis.

Paper 1: Mickiewicz *et al* (2013) used NMR for metabolite profiling in venous blood taken from 7 neonates, where 5 neonates had septic shock and 2 neonates met the SIRS criteria. The neonatal group was significantly smaller than the other age groups, so the neonates were not considered in the predictive model analysis. However, the neonatal group could potentially share a metabolomic profile similar to the infant group. Mickiewicz *et al* (2013) reports decrease in the metabolites 2-Aminobutyrate, acetate, adipate and threonine in septic infants compared to healthy infants (Table 2). Furthermore, an increase in 2-Hydroxybutyrate, 2-Hydroxyisovalerate, 2-Oxoisocaproate, creatinine, glucose and lactate were reported in septic infants compared to healthy infants.

The level of evidence for main outcome, diagnostic value of metabolomics, was considered very low (GRADE).

Paper 2: Desi *et al* (2014) used GC-MS for metabolite profiling in urinary samples taken from 1 neonate with fungal sepsis and 13 healthy neonates. The study reports decrease of citric acid, hexadecanoic acid and octadecanoic acid in single case with fungal sepsis vs healthy controls. There is an increase of D-glucose, L-threonine, maltose, N-glycine and N-serine in single case with fungal sepsis vs healthy controls.

The level of evidence for main outcome, diagnostic value of metabolomics, was considered very low (GRADE).

Paper 3: Fanos *et al* (2014) used GC-MS and ^{1}H NMR for metabolite profiling in urinary samples from 9 neonatal sepsis cases and 16 healthy neonates. In addition, there were also able to conduct NMR in urinary samples from 7/9 neonatal sepsis cases and 14/16 healthy neonates. They reported a decrease in 2,3,4-trihydroxybenzoic acid, ribitol, ribnic acid and citrate in the neonatal sepsis cases vs healthy controls. They also found an increase of glucose, lactate and acetate in neonatal sepsis cases vs healthy controls.

The level of evidence for main outcome, diagnostic value of metabolomics, was considered very low (GRADE).

Paper 4: Sarafidis *et al* (2017) used H-NMR that was complemented with LC-MS/MS in urinary samples taken at symptom debut (day 0), day 3 and day 10. The population group was 16 neonatal cases with confirmed and possible LOS, and 16 healthy controls. Table 3 compares significant finding at the different time-points. H-NMR found 10 metabolites that were altered at day 0 in LOS cases compared to healthy controls, in particularly acetone, sarcosine, leucine and dimethylamine. There were no significant changes at day 3 and day 10. LC-MS/MS found differences in 17 metabolites at day 0 in LOS cases compared to healthy controls. There were much more subtle changes at day 3 and no significant changes at day 10 when comparing LOS cases with healthy controls.

The level of evidence for main outcome, diagnostic value of metabolomics, was considered low or very low (GRADE).

Summary of findings from the four studies: All four studies showed an alteration in glucose and lactate when comparing septic neonates/infants with healthy controls. The other metabolites described in the four studies vary. However, the metabolites may be connected to the same (dysfunctional) metabolomic pathways during sepsis, such as the mitochondrial oxidative phosphorylation, the pentose phosphate pathway and the glycolysis(93, 113-115). Table 3 shows the trend of the significant metabolites in the four studies. None of the studies included evaluated the diagnostic value of metabolomics compared to traditional diagnostic tools.

5 Discussion

5.1 Metabolomic markers for identification of neonatal sepsis?

The systematic search resulted in only four included articles. None of the articles evaluated metabolomics as a diagnostic tool for neonatal sepsis. Therefore, no conclusion can be made about the effectiveness of metabolomics compared to traditional diagnostic methods. The four included studies did report alteration in the glucose and lactate metabolism that could be viewed as a significant finding. In addition, the different studies detected different metabolites that could be connected to the same metabolomic pathway.

Three studies reported increase in glucose (93, 114, 115), while one study specified the finding as an increase of D-glucose (113). One study conducted metabolomics in serum, while the other three used urine. These are important results, because one of the significant changes in the metabolism of septic neonates is a change in plasma glucose. The disturbances in the metabolism can manifests clinically in preterm neonates as hypo- or hyperglycemia (114), though hyperglycemia or increased glucose is more often associated with neonatal sepsis than hypoglycemia (115). These alteration can be viewed as the redistribution of glucose consumption from mitochondrial oxidative phosphorylation to among other pathways, the lactate and the pentose phosphate pathway (93). The increased glucose levels in septic neonates and infants discovered in the four studies, indicates that glucose might be an interesting metabolite to quantify through targeted metabolomics in regard to neonatal sepsis. Three of the studies conducted untargeted metabolomics(93, 113, 115), though one of the studies conducted untargeted metabolomics using both GC-MS and ^{1}H NMR (93). It is not possible to exactly quantify metabolites through untargeted metabolomics, so we can only speculate about the role of glucose or the underlying cause of the change in the glucose metabolism in regard to neonatal sepsis.

Another interesting metabolite discovered in three of the studies was the alteration in the lactate pathway. Two studies found an increase of lactate (93, 115), while one study reported increased lactic acid (114). The study that did not report any changes in lactate, specifically chose a neonate with fungal sepsis (n = 1) (113). One study found elevation of lactate levels in all septic pediatric patients up to 11 years old (n = 60) (115). In a clinical setting, serum lactate levels are often incorporated in the clinical management of critically ill patients. Serum

lactate is particularly important in the cases of severe sepsis and septic shock (116-118). International guidelines have recommended that serum lactate values over 2 mmol/L should be considered a new criterion when clinically defining septic shock, despite adequate fluid resuscitation (118, 119).

Vincent *et al* (2016) conducted a systematic review that included 96 studies. The studies evaluated the capacity of serum lactate concentrations to predict outcome. Decreased blood lactate concentrations were associated with better outcome and the results were not limited to septic patients. The authors clarified the preferred term "lactate kinetics", which refers to greater lactate production than clearance. Lactate kinetics was found to be significant despite the initial value of lactate (120).

Increased lactate production is associated with activated immune cells through a possess called aerobic glycolysis. Aerobic glycolysis is essential for the immune system as it provides rapid energy production and precursors that can be utilized in the growth and proliferation of immune cells (121, 122). Aerobic glycolysis sustains the energy requirements for the activated immune cells, but recently this process has also been shown to alter the metabolism in a way that promotes changes in the immune cell's phenotype (123-127).

Other than the metabolites glucose and lactate there are no clear findings in the identified metabolites described in the four studies. We can only speculate on the discovered metabolites in light of the metabolomic pathway they might be a part of.

One study showed elevated levels of 2-oxoisocaproate and creatinine(115), while another study showed elevated levels of creatine and phenylalanine (114). Elevated levels of metabolites such as 2-oxoisocaproate, creatine, creatinine and phenylalanine are associated with decreased energy supply and organ failure during sepsis (128-130). There is a likelihood that the two studies illustrate the same metabolomic process, but have identified different metabolites. Another example of this is that one study reports increased levels of 2-Hydroxybutyrate and decreased threonine (115), while another study found increased levels of L-Threonine (113). 2-Hydroxybutyric acid, also known as alpha-hydroxybutyrate, is an organic acid. One of the metabolomic pathways of alpha-hydroxybutyrate is through hepatic tissue that catabolize L-threonine. L-threonine is the active form of the essential amino acid threonine and can be used in the production of alpha-hydroxybutyrate. Therefore, one could

consider the decrease of threonine and increase of L-threonine, as part of the metabolic process of producing alpha-hydroxybutyrate. Increased alpha-hydroxybutyrate is associated with increased lipid oxidation and oxidative stress. The metabolite has also been suggested as a potential early marker for insulin resistance (113, 131).

The road of metabolomic is not straightforward, it is first and foremost about understanding the network in which all of these identified metabolites interact with each other. The metabolites described in the four included articles, are part of an intricate system that involves several pathways. The screening of biomarkers can result in a potential fingerprint for syndromes like neonatal sepsis, or can be followed by targeted analysis to better understand the metabolites' role (132). The challenge with interpreting the data from these studies, is that all included studies have several limitations.

5.2 Limitations

As previously mentioned, there are three studies (93, 113, 115) that used untargeted metabolomics with the use of NMR, MS or NMR/MS, while one study (114) conducted untargeted metabolomics with NMR and then targeted metabolomics with LC-MS/MS in order to improve sensitivity, specificity, chemical coverage and the dynamic range (133, 134). One of the key limitations for all included studies, is the single method approaches. Though two studies use NMR and MS (93, 114); one study focuses on untargeted metabolomics (93) while the other conducts both untargeted and targeted metabolic profiling (114). Considering the limitations of MS and NMR approaches (93, 113-115), Sarafidis *et al* (2017) was the only study that attempted validation and absolute quantification through targeted metabolomics (114). By conducting untargeted and then targeted metabolomics, they eliminated the bias information from targeted metabolomics as the method only captures a limited part of the metabolome (132). However, they used a single method approach for the untargeted and targeted metabolomic profiling of the neonates. This review has previously mentioned the significant limitations to the single-approach method (110-112).

Furthermore, the results from the metabolomic profiling should be considered "snapshots" in the metabolomic status at the timepoint of which the sample is taken. Sarafidis *et al* (2017) illustrate this well by using different time points in their study (day 0, day 3 and day 10). The alteration in the metabolism is significant at the onset of symptoms (day 0), but they are not

necessarily significantly altered at the other time points (114). The dynamic metabolic process during sepsis and the ambiguous clinical presentation of neonatal sepsis, makes it challenging to standardize key variables. In order to be sure that the studies are using similar sampling time points, one should have a clear understanding and documentation of the diagnosing criteria utilized in the studies. Two studies provide adequate information about the diagnostic criteria for culture proven and culture negative neonatal sepsis, though one study involved only one neonatal fungal sepsis case (113, 114). There should also be information about whether there has been initiated a treatment regime before sampling, which one study proved along with the clinical response (113).

Another important factor to consider when collecting samples in cases and controls, is the circadian variation. The time of day one collects the sample could influence the metabolomic results. In addition, the neonate's nutritional status should be carefully considered in addition to GA at birth, when including patients in the study. An example of the importance of the neonate's nutrition is that plasma concentration of threonine are up to twice as high in formula fed infants compered to infants fed with breast milk (113, 135). One should also conduct quality checks for the sampling material and consider the metabolites stability over time (132).

The larger issue with the included studies is the small sample size of neonates. This was the case for all the included studies. The study by Mickiewicz *et al* (2013) reported that the metabolic profile in infants and toddlers are comparable, and that the significant changes are seen in the school age. We have used this as an argument to include Mickiewicz *et al* (2013) in the qualitative analysis of this systematic review, since we were not able to get in touch with the corresponding author. The neonates' serum was collected in this study and as far as we can interpret from the journal article so was the metabolomic screening. However, the neonates' metabolomic profile was not analysed with a predictive model. The study also included mixed cases of Gram-positive, Gram-negative and polymicrobial neonatal sepsis cases that makes the correlations challenging to evaluate (115). Three of the four studies have not validated the identified biomarkers with targeted metabolomics, while biomarkers identified in Sarafidis *et al* (2017) have not yet been validated in a large-scale multicenter study.

All of the mentioned limitations make the reproducibility of the studies challenging. Though one may argue that the three studies using NMR would have the possibility to replicate their studies, since the NMR method is non-destructive in the detection of metabolites. This review raises the question whether certain metabolites may be affected by the storage conditions, and thereby effecting the reproducibility of the studies even when using NMR method.

5.3 Strength and weaknesses

The strength of this systematic review is the search strategy protocol. Both Mesh terms and relevant keywords were used in different combinations. The articles were screened by two researchers independently. Still, there are always limitations to any literature search conducted. We discovered the article Mickiewicz *et al* (2013) when assessing relevant reviews. Mickiewicz *et al* (2013) included a large range of paediatric patients in their metabolomic study, including a neonatal group (n = 7). No statistical analysis was conducted on the neonatal group. Therefore, this article did not match the predefined search criteria. We also did not include articles that compered metabolomics with other -omics in regard to neonatal sepsis as this was not in the scope of this review. Unfortunately, none of the articles included evaluated the diagnostic value of metabolomics compared to traditional diagnostic tools. However, this systematic review provides important information to take into consideration when designing a future neonatal sepsis metabolomics study.

6 Conclusion

Precision medicine led by the fields of the -omics is reported to be the future of medicine, but there are still significant challenges to overcome. The lack of consensus in diagnosing neonatal sepsis limits the comparison in sepsis studies in neonates. The identified biomarkers in metabolomics have yet to be validated in large-scale multicenter studies. However, these studies have provided more knowledge about the pathophysiology of neonatal sepsis and gives researchers the opportunity to test hypothesis in regard to different metabolic pathways. To date there is a very low-certainty evidence for identifying markers for neonatal sepsis with metabolomics. In addition, there are no studies evaluating the diagnostic value of metabolomics compared to traditional diagnostic tools.

Figures and Tables

Figure 3 Prisma flow diagram of selected articles.

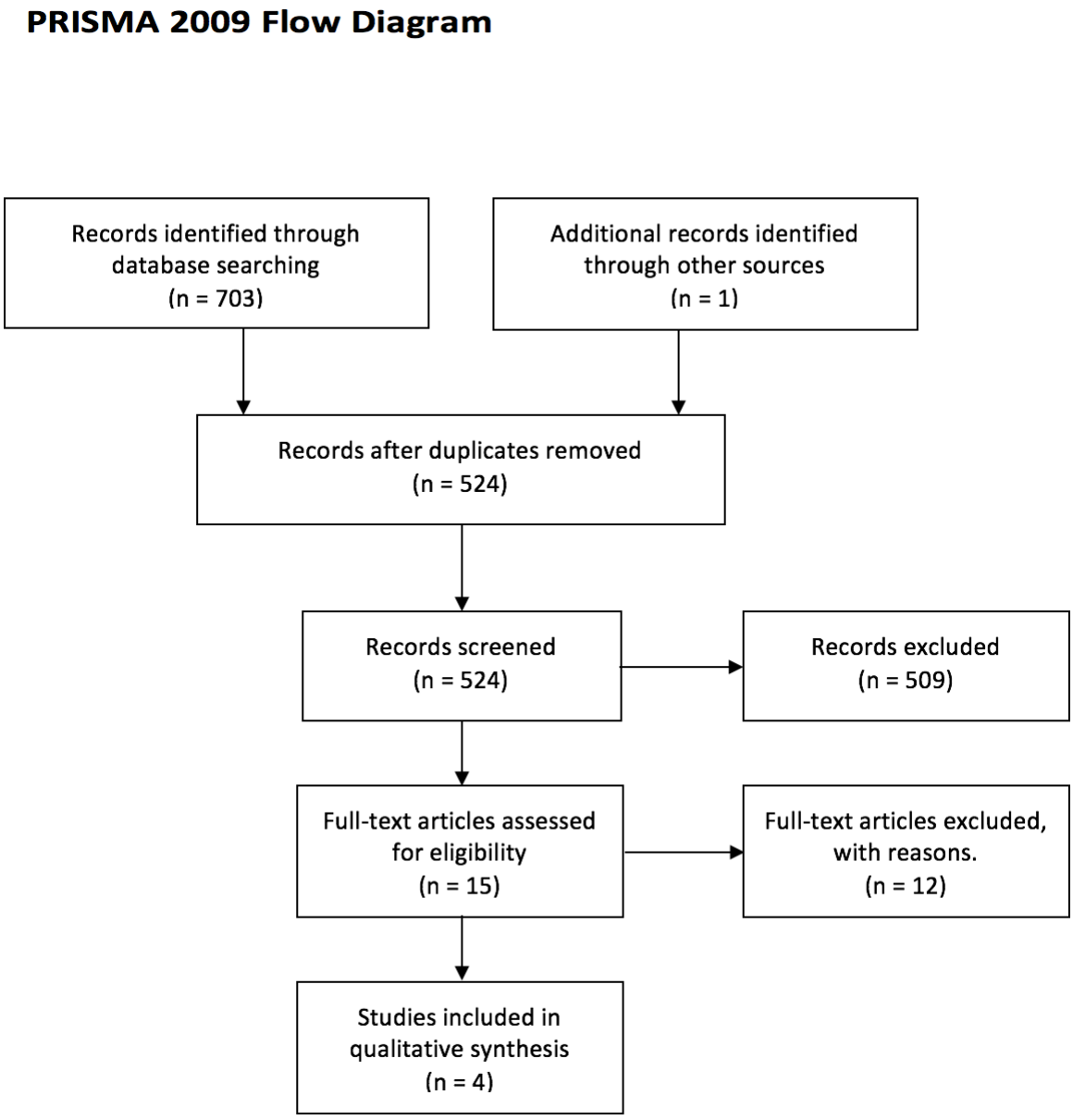

Table 1 Methods of detecting metabolites

	PREPARATION OF SAMPLE	SENSITIVITY	QUANTIFICATION	ADVANTAGES	DISADVANTAGE
NMR	No sample preparation or extraction required	Micromolar (μM) to millimolar (mM)	No standard required, linear response	Non-destructive detection of metabolites, possible to replicate, information about the metabolite structure	Low sensitivity, peak overlap can occur
GC-MS	Extraction, derivatization	Picomolar (pM) to micromolar (μM)	Must have standard, matrix and ionization dependent response	Standard library available for identification, high sensitivity	Challenging sample preparation, destructive detection, not suitable for heat-labile, use of high boiling point
LC-MS	Extraction, desalting, filtration	Picomolar (pM) to micromolar (μM)	Must have isotope labelled standard, matrix and ionization dependent response	High sensitivity, can detect a high number of metabolites	Ion depression effect, no information about the metabolite structure, destructive detection

Table 2 Summary of included studies using metabolomics.

Study	Method	Study population	Material	Main results
Mickiewicz et al. (2013)	NMR	• Septic shock, neonates (n = 5) • SIRS/ICU, neonates (n = 2) • Septic shock, infants (n = 21) • SIRS/ICU, infants (n = 13) • Healthy controls, infants (n = 13, outlier removed n = 1)	Serum	• Decrease in the metabolites 2-Aminobutyrate, acetate, adipate and threonine in sepsis • Increase in 2-Hydroxybutyrate, 2-Hydroxyisovalerate, 2-Oxoisocaproate, creatinine, glucose and lactate in sepsis
Desi et al. (2014)	GC-MS	• Fungal sepsis (n = 1) • Healthy control (n = 13)	Urine	• Decrease of citric acid, hexadecanoic acid and octadecanoic acid in sepsis • Increase of D-glucose, L-threonine, maltose, N-glycine and N-serine in sepsis
Fanos et al. (2014)	GC-MS and ^{1}H NMR	• Sepsis, neonates (n = 9) • Healthy controls (n = 16)	Urine	• Decrease of THBA, ribitol, ribnic acid and citrate in sepsis • Increase of glucose, lactate and acetate
Sarafidis et al. (2017)	H-NMR and LC-MS/MS	• Confirmed sepsis, neonates (n = 9) • Possible sepsis, neonates (n = 7) • Healthy controls, neonates (n = 16)	Urine	• 10 metabolites altered discovered by H-NMR at day 0 (onset of symptoms) • 17 metabolites altered discovered by LC-MS/MS at day 0. • Metabolic alteration become less significant at timepoint day 3 and day 10.

Table 3 Trend of significant metabolites in the included studies.

	Mickiewicz et al. 2013	Sarafidis et al.2017	Sarafidis et al.2017	Fanos et al. 2014	Dessi et al. 2014
	Septic vs Healthy (Infants)	Confirmed sepsis vs Healthy (Day 0)	Possible sepsis vs Healthy (Day 0)	Septic vs Healthy	Septic (fungal) vs Healthy
2-Aminobutyrate	↓				
2-Hydroxybutyrate	↑				
2-Hydroxyisovalerate	↑				
2-Ketogluconic acid				↓	
2-Oxoisocaproate	↑				
2,3,4-Trihydroxybutyric acid				↓	
3,4-dihydroxybutanoic acid				↓	
3,4,5-trihydroxypentanoic acid				↓	
Acetate	↓			↑	
Acetone				↑	
Adipate	↓				
Biotin		↑	↑		
Citrate				↓	
Citric acid					↓
Creatine		↑	↑		
Creatinine	↑				
D-Glucose		↑	↑		↑
Fumaric acid		↓	↓*		
G-aminobutyric acid		↑*	↑		
Glucose	↑	↑	↑	↑	
Glutamic acid		↑*	↑		
Glycine				↑	
Hexadecanoic acid					↓
Hippuric acid		↓*	↓		
Hypotaurine		↑*	↑		
Inosine		↑	↑		
Isoleucine		↑	↑		
Lactate	↑			↑	
Lactic acid		↑	↑		
Lysine				↑	
L-Threonine					↑
Maltose		↑	↑	↑	↑
Methylamine		↑	↑		
Methylguanidine		↑	↑		
Myo-Inositol		↑	↑*		
Nicotinamide		↓	↓		
N-Glycine					↑
N-Serine					↑
Octadecanoic acid					↓
Pseudo uridine				↑	
Phenylalanine		↑	↑		
Pyruvic acid		↑*	↑		
Quinolinic acid		↑	↑*		
Ribitol				↓	
Riboflavine		↓*	↓		
Ribonic acid				↓	
Taurine		↑	↑		
Thiamine		↓	↓*		
Threonine	↓				
Trimethylamine-N-oxide		↓	↓		
Valine		↑	↑		

*P value = 0.05

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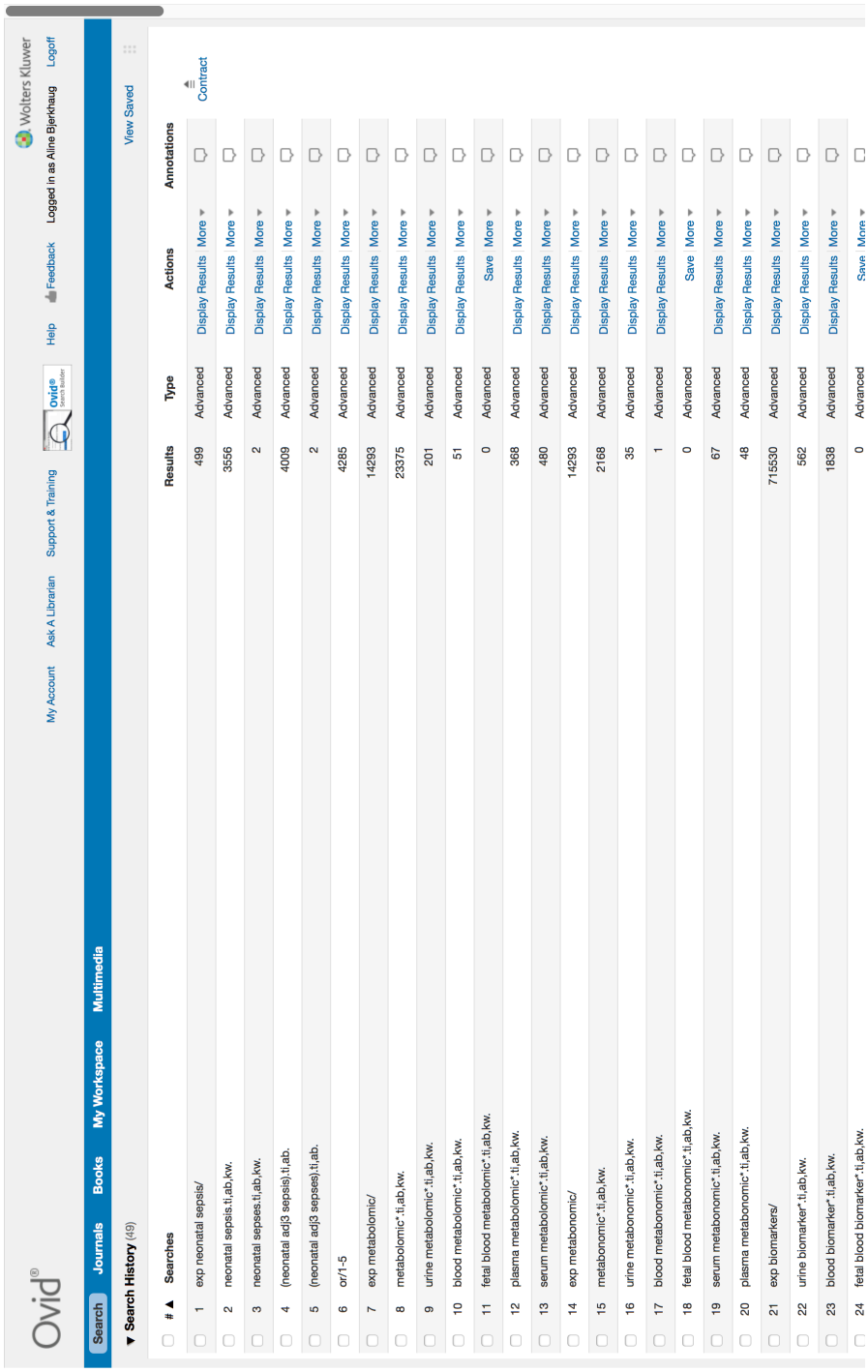
APPENDIX 1

MEDLINE



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APPENDIX 2

EMBASE

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APPENDIX 3

Screening form for source

Animal research study?	**Yes**: not included **No/unclear:** continue	
Neonatal period or preterm neonates upto 44 weeks postmenstrual age	**No:** not included **Yes/unclear:** continue	
Research addresses: - Metabolomics in urine - Metabolomics in plasma - Metabolomics in serum - Metabolomics in blood	**None of the mentioned:** not included **Yes/Unclear:** any or all of the mentioned are considered	
Research methods Nuclear magnetic resonance (NMR) or mass spectrometry (MS) or screening for multiple metabolites.	**No: not included** **Yes/Unclear:** any or all of the mentioned are considered	
Research study design: - Randomized control trial, clinical control trial, other research that has been randomized - Observational study: Cohort, case-control or case-series - Systematic review or meta-analysis - Narrative or descriptive review - Case study	**Narrative or descriptive review:** not included **Single Case study:** not included **Unclear or not mentioned:** full-text assessment	

APPENDIX 4

Reference: **Metabolomics as a Novel Approach for Early Diagnosis of Pediatric Septic Shock and Its Mortality.** Mickiewicz et al. 2013			**Design: prospective case-control** GRADE ⊕
Purpose	**Material and method**	**Results**	**Discuscion/comments**
Developing new diagnostic tool for early recognition of septic shock. Using a metab-olomics approach for the diagnosis and prognosis of pediatric septic shock. **Conclusion** Septic shock leads to significant disruption in biochemical homeostasis that strongly contributes to changes in body metabolites. **Country** **Canada** **Year data collection**	**Location:** Intensive Care Unit (NICU) of the University of Cagliari **Participants = 140 (7 neonates)** Case = 60 patients with septic shock Control 1 = 40 systemic inflammatory response syn- drome (not suspected of having an infection) Control 2 = 40 healthy children **Total of 140 children.** *7 neonates (5 septic shock, 2 SIRS, 0 controls) *47 infants *54 toddlers *32 schoolchildren Included if: Admitted to PICU/NICU in addition to clinical signs of sepsis/septic shock and < 11years of age. Controles recruited from outpatient clinics **Sample:** serum Samples collected from arterial or venous lines within 24 hours after admitted to PICU/diagnose septic shock. Controls: Samples collected at the same time as other pre-planed test in the outpatient clinic. **Method:** Proton nuclear magnetic resonance spectroscopy spectra **Statistical analysis:** multivariate analysis	*Neonates and infants have a similar metabolic profile during septic shock * The metabolic profile is a good tool differentiate between the groups *Promising results when used to predict mortality of septic shock in the pediatric population	**GRADE:** **Initial GRADE = Low** **Downgrade: Imprecision (No criteria listed for case definitions), Small sample size with no power analysis conducted, Identified biomarkers not yet validated in large-scale multicenter studies** **Upgrade: -** **Final GRADE = Very low**

APPENDIX 5

Reference: **Dessi et al. (2014) Monitoring neonatal fungal infection with metabolomics**			**Design: prospective case-control** GRADE ⊕
Purpose	**Material and method**	**Results**	**Discussion/comments**
Evaluate the capability of the metabolomics approach to identify the variations of urine metabolites over time related to the neonatal fungal septic condition. **Concluscion** ***Unique urine metabolic profile in septic patient. Possible to evaluate the efficacy of therapy in improving patient health.*** **Country** **Italy** **Year data collection** _____	**Setting:** Neonatal intensive care unit (Singelsenter) **Location:** • NICU of the University of Palermo **Participants:** 14 neonates, Case = fungal sepsis (n=1), (VLBW, 1100 g) male infant born by cesarean delivery at 32 weeks of gestation Control = Healthy (n=13); males, 34+6 weeks mean gestation, not diagnosed with sepsis and considered healthy **Sampling:** Five urine samples from one neonate with fungal sepsis. Collected at 36 hours, 7, 14, 21 and 28 days of life. Controls: samples taken at different timepoints, **at least two controls were coupled with a urine sample of septic patient based on time.** **Method:** • Gas chromatography–mass spectrometry (GC-MS) **Analysis:** • Multivariate statistical analysis	• **A significant different metabolic profile in the urinary sample from the neonate with fungal sepsis compared to the control group.** • **Once the infection resolved the metabolic profile became more similar to the control group**	**GRADE:** **Initial GRADE = Low** **Downgrade: Imprecision (No criteria listed for case definitions), Small sample size with no power analysis conducted, Identified biomarkers not yet validated in large-scale multicenter studies** **Upgrade: -** **Final GRADE = Very low** **OBS! Only one case. Difference in gestation age, difference in sampling timepoint (at least two were coupled with the sepsis case sampling timepoint).**

APPENDIX 6

Reference: **Urinary (1)H-NMR and GC-MS metabolomics predicts early and late onset neonatal sepsis** **Fanos et al. 2014**			**Design: Case-control** GRADE ⊕
Purpose	**Material and method**	**Results**	**Discussion/comments**
Metabolomic analysis to assess variations of metabolites preceding the onset of early and late sepsis in neonates for the purpose of identifying a metabolic state leading to the onset of infection **Concluscion** ***Unique metabolic profile of the patients affected by sepsis compared to non-affected ones with a statistically significant difference between the two groups (p = 0.05).*** **Country** **Italy** **Year data collection** _____	**Location:** • The Neonatal Intensive Care Unit (NICU) of the University of Cagliari • The NICU of the San Matteo General Hospital (Pavia) • The NICU of the University of Palermo and Department of Maternal • Fetal and Neonatal Health in the C. Arrigo Children's Hospital (Alessandria) **Participants:** 25 neonates <35 weeks mean gestation. Case = Sepsis (n=9); Received diagnosis of sepsis Control = Healthy (n=16); Not diagnosed with sepsis and considered healthy **Sampling:** urine **Method:** • Gas chromatography–mass spectrometry (GC-MS) and Nuclear Magnetic Resonance (NMR) **Analysis:** • GC-MS: Orthogonal partial least square discriminant analysis (OPLS- DA) • NMR: SIMCA software package (version 13.0, Umetrics, Umea, Sweden).	**Identified increased concentrations of glucose, lactate and acetate in sepsis group.** **Identified decreased ribitol, ribonic acid, pseudouridine, 2,3,4-trihydroxybutanoic acid and 3,4,5-trihydroxypentanoic acid in sepsis group.** **Samples from EOS neonates were separated from those of LOS.**	**GRADE:** **Initial GRADE = Low** **Downgrade: Imprecision (No criteria listed for case definitions), Small sample size with no power analysis conducted, Identified biomarkers not yet validated in large-scale multicenter studies** **Upgrade: -** **Final GRADE = Very low** **OBS! The samples were too few to arrive at a final assessment of difference between EOS and LOS.**

APPENDIX 7

Reference: Sarafidis et al. 2017 Urine metabolomics in neonates with late-onset sepsis in a case-control study			Design: Case-control GRADE ⊕(⊕)
Purpose	**Material and method**	**Results**	**Discussion/comments**
Investigate metabolic changes related to LOS, employing two analytical platforms: proton nuclear magnetic resonance (1H-NMR) spectroscopy and liquid chromatography-tandem mass spectrometry (LC-MS/MS). **Conclusion** Neonates with confirmed and possible sepsis at the onset of clinical manifestations showed a different metabolic profile compared to those without sepsis allowing their clear discrimination with the use of 1H-NMR and LC-MS/MS-based urine analysis. **Country** **Year data collection** September 2013-August 2015	Participants = 32 neonates Sample = Urine samples were collected from cases and controls at the day of the initial evaluation for LOS and enrollment in the study, respectively, representing day 0 (D0) and on the 3rd (D3) and 10th day (D10), thereafter, using plastic bags or through a bladder catheter placed for clinical reasons. Sepsis group (n=16); confirmed sepsis (n=9) and possible LOS (n=7). Control group (n=16); negative workup for sepsis The two groups were comparable regarding demographic-perinatal characteristics One neonate with confirmed and one with possible LOS died; all controls were discharged home. **Power analysis:** MetSizeR R-package (results = 15 subjects per group). **Method:** (1) 1H-NMR spectroscopy (untargeted metabolomics) (2) LC-MS/MS (targeted metabolomics) **Statistical analysis**: MedCalc software (patient characteristics), Multivariate statistical analysis and MetaboAnalyst 3.0	**Organisms iso- lated in blood cultures were mainly gram (−) microbes [Klebsiella pneumonia (n = 4), Klebsiella oxytoca (n = 1), Enterobacter cloace (n = 2)]; Group B Streptococcus and Candida famata were isolated in two cases.** **H-NMR spectroscopic data:** 110 peaks were selected, and their signals were integrated. Septic infants (confirmed and possible) could be discriminated from non-septic ones (controls) at the time point of sepsis suspicion (D0). This trend was also observed on D3 although differentiation was less clear, whereas on D10, when the LOS infants no longer show symptoms, samples from both patients and controls show no difference. 17 metabolites altered discovered by LC-MS/MS at day 0. Metabolic alteration become less significant at timepoint day 3 and day 10.	**Initial GRADE = Low** **Downgrade: Small sample size (power analysis?), results not validated in a large-scale multicenter** **Upgrade: large magnitude of effect? (Differences on D0).** **Final GRADE = Low/Very low**

APPENDIX 8

A	B	C	D	E	F
Code	Author(s)	Year	Title	Exclusion critera	Date
362	Abdel-Aleem,	2018	Diagnostic Role of CD64 on Different Immune Cells in Early Diagnosis of Neonatal Sepsis	Research methods (flow cytometry)	05.02.2020
547	Abdel-Hady, I	2012	Myocardial dysfunction in neonatal sepsis: a tissue Doppler imaging study	Research addresses, research methods	05.02.2020
49	Abo-ElMagd,	2018	The Role of Serum Interleukin-27 As A Diagnostic Biomarker For Diagnosis of Neonatal Sepsis	Research methods (ELISA)	05.02.2020
255	Adib, M.-//-Ba	2012	Procalcitonin: A reliable marker for the diagnosis of Neonatal sepsis	Research methods (ELISA)	12.02.2020
595	Adib, M.-//-Os	2007	Evaluation of CD11b expression on peripheral blood neutrophils for early detection of neonatal sepsis	Research methods (flow cytometry)	05.02.2020
508	Adly, A. A.-//	2014	Circulating soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) as diagnostic and prognostic marker in neonatal sepsis	Research methods	05.02.2020
372	Agrawal, S.-/,	2018	Effect of probiotics on C-reactive protein levels in preterm infants: Secondary analysis of a randomized controlled trial	Research methods	05.02.2020
188	Aguin, E.-//-V	2014	Cerclage retention versus removal following preterm premature rupture of membranes and association with amniotic fluid markers	Not neonatal period, research methods	05.02.2020
607	Ahmed, Z.-//-	2005	Diagnostic value of C- reactive protein and haematological parameters in neonatal sepsis	Research addresses	05.02.2020
575	Al-Zwaini, E. .	2009	C-reactive protein: a useful marker for guiding duration of antibiotic therapy in suspected neonatal septicaemia?	Research methods	05.02.2020
584	Ali, A. M.-//-M	2008	Reliability of serum procalcitonin concentrations for the diagnosis of sepsis in neonates	Research methods	12.02.2020
512	Aliefendioglu,	2014	Can resistin be a new indicator of neonatal sepsis?	Research methods	05.02.2020
85	Alkan Ozdem	2018	Can neutrophil to lymphocyte ratio predict late-onset sepsis in preterm infants?	Research methods	05.02.2020
550	Altunhan, H.-	2011	Procalcitonin measurement at 24 hours of age may be helpful in the prompt diagnosis of early-onset neonatal sepsis	Research methods	12.02.2020
438	Anandi, V. S.-	2017	Evaluation of factors associated with elevated newborn 17-hydroxyprogesterone levels	congenital adrenal hyperplasia (CAH)	05.02.2020
487	Andres, O.-//-	2015	Platelets in neonates: central mediators in haemostasis, antimicrobial defence and inflammation	Research study design (review)	05.02.2020
178	Annagur, A.-/	2015	Total antioxidant and total oxidant states, and serum paraoxonase-1 in neonatal sepsis	Research methods	05.02.2020
289	Anonymous	2011	23rd National Biochemistry Congress. [Turkish, English]	Research study design (procedings)	05.02.2020
291	Anonymous	2011	12th International Congress of Pediatric Laboratory Medicine, ICPLM 2011	Research study design (procedings)	05.02.2020
640	Anonymous	2019	2019 Congress of the Italian Society of Neonatology	Research study design (procedings)	05.02.2020
64	Anwar, Z.	2018	Pakistan pediatric journal	No information or title	05.02.2020
235	Aranke, M.-//	2013	A Biomarker-Based Approach to Infectious Disease in the Pediatric Emergency Department	Research study design (review)	05.02.2020
65	Arayici, S.-//-	2019	Can base excess be used for prediction to early diagnosis of neonatal sepsis in preterm newborns?	Research methods	05.02.2020
22	Arcagok, B. C	2019	Platelet to lymphocyte ratio in neonates: A predictor of early onset neonatal sepsis	Research methods	05.02.2020
104	Archabald, K.	2017	Limiting the Exposure of Select Fetuses to Intrauterine Infection/Inflammation Improves Short-Term Neonatal Outcomes in Preterm Premature Rupture of Membranes	Research methods (ELISA)	05.02.2020
624	Arnon, S.-//-Li	2002	Serum amyloid A protein in the early detection of late-onset bacterial sepsis in preterm infants	Research methods	05.02.2020
596	Arnon, S.-//-Li	2007	Serum amyloid A: an early and accurate marker of neonatal early-onset sepsis	Research methods	05.02.2020
591	Arnon, S.-//-Li	2008	Diagnostic tests in neonatal sepsis	Research study design (review)	05.02.2020
478	Asci, A.-//-Sur	2015	Oxidant and antioxidant status in neonatal proven and clinical sepsis according to selenium status		05.02.2020
627	Athhan, F.-//-	2002	Procalcitonin: a marker of neonatal sepsis	Research methods	12.02.2020
400	Ayazi, P.-//-M	2014	Comparison of serum IL-1beta and C reactive protein levels in early diagnosis and management of neonatal sepsis	Research methods	05.02.2020
355	Aydemir, C.-/,	2018	The cut-off levels of procalcitonin and C-reactive protein and the kinetics of mean platelet volume in preterm neonates with sepsis	Research methods	12.02.2020
489	Aydemir, O.-/	2015	Asymmetric dimethylarginine and L-arginine levels in neonatal sepsis and septic shock		05.02.2020
494	Aydin, I.-//-Ag	2014	Cord blood and serum hepcidin levels in neonatal sepsis: A biochemical evaluation	Research methods	17.02.2020
105	Aydin, M.-//-E	2017	Application of flow cytometry in the early diagnosis of neonatal sepsis	Research methods	05.02.2020
428	Badr, H. S.-//-	2018	Serum stromal-derived-factor-1 (CXCL12) and its alpha chemokine receptor (CXCR4) as biomarkers in neonatal sepsis	Research methods	05.02.2020
619	Baek, Y. W.-//	2003	Inter-alpha inhibitor proteins in infants and decreased levels in neonatal sepsis	Research methods	05.02.2020
151	Baizat, M.-//-	2016	The analysis of the adjuvant biomarkers in the diagnosis of neonatal sepsis	Research methods	05.02.2020
610	Ballot, D. E.-/,	2004	Serum procalcitonin as an early marker of neonatal sepsis	Research methods	12.02.2020
454	Banupriya, N.	2017	Efficacy of zinc supplementation on serum calprotectin, inflammatory cytokines and outcome in neonatal sepsis - a randomized controlled trial	Research addresses	05.02.2020
292	Bastek, J. A.-/	2011	sRAGE: A biomarker of prematurity and neonatal sepsis	Research methods (ELISA)	05.02.2020
540	Bastek, J. A.-/	2012	The soluble receptor for advanced glycation end products can prospectively identify patients at greatest risk for preterm birth	Research methods (ELISA)	05.02.2020
543	Basu, S.-//-De	2012	Cerebral blood flow velocity in early-onset neonatal sepsis and its clinical significance	Research methods	05.02.2020
15	Battal, F.-//-B	2019	Serum Pentraxin 3 Concentration in Neonatal Sepsis	Research methods	05.02.2020
403	Baud, O.-//-Er	1999	Amniotic fluid concentrations of interleukin-1beta, interleukin-6 and TNF-alpha in chorioamnionitis before 32 weeks of gestation: histological associations and neonatal outcome	Research methods	05.02.2020
472	Bekhof, J.-//-K	2015	Glucosuria as an early marker of late-onset sepsis in preterms: a prospective cohort study	Research methods	05.02.2020
431	Bell, S. G.	2017	Procalcitonin and Neonatal Sepsis: Is This the Biomarker We Are Looking For?	Research study design (review)	05.02.2020
418	Bellos, I.-//-Fi	2018	Soluble TREM-1 as a predictive factor of neonatal sepsis: a meta-analysis	Research methods	05.02.2020
423	Bellos, I.-//-Fi	2018	The diagnostic accuracy of presepsin in neonatal sepsis: a meta-analysis	Research methods	05.02.2020
424	Beltempo, M.	2018	C-reactive protein for late-onset sepsis diagnosis in very low birth weight infants	Research methods	05.02.2020
585	Bender, L.-//-	2008	Early and late markers for the detection of early-onset neonatal sepsis	Research methods	05.02.2020
198	Benito-Fernar	2014	Reply to correspondence letter: Is pro-adrenomedullin more useful marker in hospitalized infants with sepsis?	Research study design (correspondance)	05.02.2020
416	Berkhout, D. .	2017	Detection of Sepsis in Preterm Infants by Fecal Volatile Organic Compounds Analysis: A Proof of Principle Study	Research addresses	05.02.2020
422	Berkhout, D. .	2018	The potential of gut microbiota and fecal volatile organic compounds analysis as early diagnostic biomarker for necrotizing enterocolitis and sepsis in preterm infants	Research study design (review)	05.02.2020
408	Berner, R.-//-E	2002	Elevated levels of lipopolysaccharide-binding protein and soluble CD14 in plasma in neonatal early-onset sepsis	Research methods	05.02.2020
401	Berner, R.-//-	2000	Elevated gene expression of interleukin-8 in cord blood is a sensitive marker for neonatal infection	Research methods	05.02.2020

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628	Berner, R.-//-V	2002	Cytokine expression of cord and adult blood mononuclear cells in response to Streptococcus agalactiae	Research methods	05.02.2020
177	Bersani, I.-//-A	2015	Use of early biomarkers in neonatal brain damage and sepsis: State of the art and future perspectives	Research study design (review)	05.02.2020
207	Bhandari, V.	2014	Effective biomarkers for diagnosis of neonatal sepsis	Research study design (review)	05.02.2020
558	Bhandari, V.-/	2011	Cord blood erythropoietin and interleukin-6 for prediction of intraventricular hemorrhage in the preterm neonate	Research addresses	05.02.2020
594	Bhandari, V.-/	2008	Hematologic profile of sepsis in neonates: neutrophil CD64 as a diagnostic marker	Research methods	05.02.2020
394	Blommendahl	2002	Comparison of procalcitonin with CRP and differential white blood cell count for diagnosis of culture-proven neonatal sepsis	Research methods	05.02.2020
521	Boonkasidech	2013	An optimal cut-off point of serum C-reactive protein in prediction of neonatal sepsis	Research methods	05.02.2020
217	Borghesi, A.-/	2014	Neonatal sepsis, new preventive strategies	Research study design (review)	05.02.2020
55	Borghesi, A.-/	2018	Novel Approaches to the Study of Neonatal Infections	Research study design (review)	05.02.2020
367	Boskabadi, H.	2018	Evaluate the diagnosis of neonatal sepsis by measuring interleukins: A systematic review	Research methods	05.02.2020
164	Brownell, A. [	2015	Human Parechovirus-3 encephalitis in two neonates: Acute and follow-up magnetic resonance imaging and evaluation of central nervous system markers of inflammation	Research study design (case study)	05.02.2020
282	Brugge, D.-//-	2011	Association of environment and place of birth with asthma in Chinese immigrant children	Research methods	05.02.2020
538	Buchegger, P.	2012	Miniaturized protein microarray with internal calibration as point-of-care device for diagnosis of neonatal sepsis	Research methods	05.02.2020
310	Buhimschi, C.-	2009	Significance of early haptoglobin (HP) switching-on, levels and phenotypes in preterm newborns with early onset neonatal sepsis (EONS)	Research methods	05.02.2020
323	Buhimschi, C.	2007	Proteomic biomarkers of intra-amniotic inflammation: Relationship with funisitis and early-onset sepsis in the premature neonate	Research addresses (Amniotic Fluid)	05.02.2020
599	Buhimschi, C.	2007	Proteomic profiling of the amniotic fluid to detect inflammation, infection, and neonatal sepsis	Research addresses (Amniotic Fluid)	05.02.2020
576	Buhimschi, C.	2009	Using proteomics in perinatal and neonatal sepsis: hopes and challenges for the future		05.02.2020
582	Buhimschi, C.	2009	Fetal inflammatory response in women with proteomic biomarkers characteristic of intra-amniotic inflammation and preterm birth	Research addresses (Amniotic Fluid)	05.02.2020
549	Buhimschi, C.	2011	Proteomics mapping of cord blood identifies haptoglobin "switch-on" pattern as biomarker of early-onset neonatal sepsis in preterm newborns		05.02.2020
318	Buhimschi, I. A	2008	Proteomics of the Amniotic Fluid in Assessment of the Placenta. Relevance for Preterm Birth	Research addresses (Amniotic Fluid)	05.02.2020
563	Buhimschi, I. A	2010	The role of proteomics in the diagnosis of chorioamnionitis and early-onset neonatal sepsis		05.02.2020
270	Buhimschi, I. A	2012	Proteomics/diagnosis of chorioamnionitis and of relationships with the fetal exposome	Research study design (review)	05.02.2020
6	Burchfield, D.	2019	RE: Management of neonates born at 34 6/7 weeks' gestation with suspected or proven early-onset bacterial sepsis	Research study design (correspondance)	12.02.2020
61	Buyuktiryaki,	2019	Can Endocan Predict Late-Onset Neonatal Sepsis?	Research methods	12.02.2020
620	Caksen, H.-//-	2003	The relationship between scoring systems and cytokine levels in neonatal sepsis	Research methods (ELISA)	12.02.2020
414	Caldas, J. P.-/,	2008	Accuracy of white blood cell count, C-reactive protein, interleukin-6 and tumor necrosis factor alpha for diagnosing late neonatal sepsis	Research methods (ELISA)	12.02.2020
524	Camacho-Gon	2013	Neonatal infectious diseases: evaluation of neonatal sepsis	Research study design (review)	12.02.2020
579	Cancelier, A. (	2009	Inflammatory and oxidative parameters in cord blood as diagnostic of early-onset neonatal sepsis: a case-control study	Research methods	12.02.2020
221	Cannon, D. C.-	2014	Focused proteomic profiling for rapid detection of late-onset neonatal sepsis in preterm infants		12.02.2020
201	Cao, Z.-//-Rob	2014	The role of proteomics in understanding biological mechanisms of sepsis		12.02.2020
515	Carvalho, J. K	2013	Prediction of sepsis-related outcomes in neonates through systematic genotyping of polymorphisms in genes for innate immunity and inflammation: a narrative review and critical perspective	Research study design (review)	12.02.2020
233	Cekmez, Y.-//-	2013	Proadrenomedullin and serum Amyloid a as a predictor of Subclinical Chorioamnionitis in preterm premature rupture of membranes	Not neonatal period	12.02.2020
434	Cekmez, Y.-//-	2017	The utility of maternal mean platelet volume levels for early onset neonatal sepsis prediction of term infants	Research methods	12.02.2020
525	Celik, I. H.-//-	2013	Inflammatory responses to hepatitis B virus vaccine in healthy term infants	Research methods	12.02.2020
460	Cernada, M.-/	2016	Sepsis in preterm infants causes alterations in mucosal gene expression and microbiota profiles compared to non-septic twins	Research addresses (fecal)	12.02.2020
210	Cernada, M.-/	2014	Genome-wide expression profiles in very low birth weight infants with neonatal sepsis	Research methods	12.02.2020
116	Cetin, O.-//-A	2017	Is Maternal Blood Procalcitonin Level a Reliable Predictor for Early Onset Neonatal Sepsis in Preterm Premature Rupture of Membranes?	Not neonatal period	12.02.2020
495	Cetin, O.-//-D	2014	Serial ultrasonographic examination of the fetal thymus in the prediction of early neonatal sepsis in preterm premature rupture of membranes	Research methods (ultrasound)	12.02.2020
581	Cetinkaya, M	2009	Comparison of serum amyloid A concentrations with those of C-reactive protein and procalcitonin in diagnosis and follow-up of neonatal sepsis in premature infants	Research methods	12.02.2020
388	Chang, B. A.-/	2011	Early inflammation in the absence of overt infection in preterm neonates exposed to intensive care	Research methods (ELISA)	12.02.2020
439	Chauhan, N.-/	2017	Potential biomarkers for effective screening of neonatal sepsis infections: An overview	Research study design (review)	12.02.2020
556	Chavez-Buenc	2011	'Haptoglobin concentrations in preterm and term newborns'	Research methods (flow cytometry)	12.02.2020
466	Chen, C. N.-//-	2016	Urinary Neutrophil Gelatinase-Associated Lipocalin Levels in Neonates	Research methods (flow cytometry)	12.02.2020
499	Chen, Q.-//-Xu	2014	High serum trypsin levels and the -409 T/T genotype of PRSS1 gene are susceptible to neonatal sepsis	Research methods	12.02.2020
240	Chiabi, A.-//-N	2013	Diagnosis of neonatal sepsis in low resource settings: C-reactive protein or procalcitonin?	Research methods	12.02.2020
383	Chiesa, C.-//-P	2003	C-reactive protein, interleukin-6, and procalcitonin in the immediate postnatal period: influence of illness severity, risk status, antenatal and perinatal complications, and infection	Research methods	12.02.2020
402	Chiesa, C.-//-P	2004	Diagnosis of neonatal sepsis: a clinical and laboratory challenge	Research study design (review)	12.02.2020
477	Chiesa, C.-//-P	2015	Early-Onset Neonatal Sepsis: Still Room for Improvement in Procalcitonin Diagnostic Accuracy Studies	Research methods	12.02.2020
380	Chirico, G.-//-	2007	Bacterial sepsis	Research study design (review)	12.02.2020
283	Chirico, G.-//-	2011	Laboratory aid to the diagnosis and therapy of infection in the neonate	Research study design (review)	12.02.2020
63	Choe, M.-//-Z	2019	Red blood cell distribution width (RDW) as marker for neonatal sepsis	Research methods	12.02.2020
577	Chaaban, H.-/	2009	The role of inter-alpha inhibitor proteins in the diagnosis of neonatal sepsis	Research methods	12.02.2020
505	Cizmeci, M. N	2014	Detection of cord blood hepcidin levels as a biomarker for early-onset neonatal sepsis	Research methods	12.02.2020
238	Clerico, A.-//-	2013	Biomarkers for sepsis: An unfinished journey	Research study design (review)	12.02.2020
392	Clyne, B.-//-Ol	1999	The C-reactive protein	Research methods	12.02.2020
639	Conti, M. G.-/	2020	Immunometabolic approaches to prevent, detect, and treat neonatal sepsis	Research study design (review)	12.02.2020

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464	Cordeiro, C. N	2016	Mathematical Modeling of the Biomarker Milieu to Characterize Preterm Birth and Predict Adverse Neonatal Outcomes	Research methods	12.02.2020
462	Coufal, S.-//-K	2016	Urinary Intestinal Fatty Acid-Binding Protein Can Distinguish Necrotizing Enterocolitis from Sepsis in Early Stage of the Disease	Research addresses (gut)	12.02.2020
411	Coutinho, F. C	2018	Assessment of oxidative damage and enzymatic antioxidant system activity on the umbilical cord blood and saliva from preterm newborns with risk factors for early-onset neonatal sepsis		12.02.2020
350	Cuestas, E.-//	2019	Sustained Neonatal Inflammation Is Associated with Poor Growth in Infants Born Very Preterm during the First Year of Life	Not neonatal period, research methods	12.02.2020
433	Dai, J.-//-Jian	2017	Neutrophil CD64 as a diagnostic marker for neonatal sepsis: Meta-analysis	Research methods	12.02.2020
29	Dani, C.-//-Mc	2019	Role of Oxidative Stress in Maternal and Neonatal Diseases.	Research study design (review)	12.02.2020
473	Decembrino,	2015	Serum Calprotectin: A Potential Biomarker for Neonatal Sepsis	Research methods (ELISA)	12.02.2020
348	Degirmenciog	2019	Presepsin and fetuin-A dyad for the diagnosis of proven sepsis in preterm neonates	Research methods	12.02.2020
568	Degraeuwe, F	2010	The diagnostic value of inter-alpha inhibitor proteins for neonatal sepsis	Research study design (correspondance)	12.02.2020
481	Delanghe, J. F	2015	Translational research and biomarkers in neonatal sepsis	Research study design (review)	12.02.2020
502	Dessi, A.-//-Co	2014	New diagnostic possibilities in systemic neonatal infections: metabolomics	Research study design (review)	12.02.2020
205	Dessi, A.-//-Li	2014	Monitoring neonatal fungal infection with metabolomics		12.02.2020
290	Devrim, E.	2011	Biomarkers for neonatal sepsis. [Turkish, English]	Research study design (conferance abstract	12.02.2020
2	DeWitt, J. C.-	2016	Associating Changes in the Immune System with Clinical Diseases for Interpretation in Risk Assessment	Research study design (review)	12.02.2020
486	Dhas, B. B.-//	2015	Global DNA methylation in neonatal sepsis	Research methods	12.02.2020
163	Dhas, D. B. B.	2015	Comparison of genomic DNA methylation pattern among septic and non-septic newborns - An epigenome wide association study	Research methods	12.02.2020
234	Dhlamini, M.	2013	Neutrophil CD64 has a high negative predictive value for exclusion of neonatal sepsis	Research methods (ELISA)	12.02.2020
377	Dilli, D.-//-Ogu	2010	Predictive values of neutrophil CD64 expression compared with interleukin-6 and C-reactive protein in early diagnosis of neonatal sepsis	Research methods	12.02.2020
118	Dima, M.-//-Ia	2017	New emerging biological markers of neonatal sepsis	Research study design (correspondance)	12.02.2020
638	Dimitriou, G.	2019	Antimicrobial stewardship in the NICU	Research methods	12.02.2020
5	Dincgez Cakm	2019	Assessment of relationship between serum vascular adhesion protein-1 (VAP-1) and gestational diabetes mellitus	Research methods	12.02.2020
393	Dollner, H.-//	2001	Early diagnostic markers for neonatal sepsis: comparing C-reactive protein, interleukin-6, soluble tumour necrosis factor receptors and soluble adhesion molecules	Research methods	12.02.2020
641	Donadel, E.-//	2019	Metabolomics for early detection of preterm newborns with early onset sepsis	Research study design (conferance abstract	12.02.2020
155	Dorfeuille, N.	2016	Vaginal fluid inflammatory biomarkers and the risk of adverse neonatal outcomes in women with PPROM	Research methods	12.02.2020
190	Du, J.-//-Li, L.	2014	Diagnostic utility of neutrophil CD64 as a marker for early-onset sepsis in preterm neonates	Research methods	12.02.2020
456	Du, W. X.-//-H	2016	Interleukin 35: A novel candidate biomarker to diagnose early onset sepsis in neonates	Research methods	12.02.2020
219	Dujic-Bilusic, S	2014	Can CD15s (sialyl Lewis x) be used as a potential marker for neonatal sepsis? Control study. Split, Croatia	Research methods (flow cytometry)	12.02.2020
66	Eggimann, P.-	2019	Measurement of pancreatic stone protein in the identification and management of sepsis	Research study design (review)	12.02.2020
304	El Beshlawy, A	2010	Study of protein C, protein S, and antithrombin III in newborns with sepsis	Research methods	12.02.2020
452	El Shimi, M. S	2017	Significance of neutrophilic CD64 as an early marker for detection of neonatal sepsis and prediction of disease outcome	Research methods	14.02.2020
351	El Shimy, M. S	2018	Cerebral blood flow and serum neuron-specific enolase in early-onset neonatal sepsis	Research methods	14.02.2020
89	El-Kader, M. A	2018	Relation between vitamin D level and some inflammatory cytokines in full-term newborns with early onset sepsis	Research methods	14.02.2020
62	El-Madbouly,	2019	Utility of presepsin, soluble triggering receptor expressed on myeloid cells-1, and neutrophil CD64 for early detection of neonatal sepsis	Research methods	14.02.2020
467	El-Mashad, A.	2016	Can melatonin be used as a marker for neonatal sepsis?	Research methods	14.02.2020
609	el-Sameea, E.	2004	Evaluation of natural killer cells as diagnostic markers of early onset neonatal sepsis: comparison with C-reactive protein and interleukin-8	Research methods	14.02.2020
127	El-Sonbaty, M	2016	Diagnostic utility of biomarkers in diagnosis of early stages of neonatal sepsis in neonatal intensive care unit in Egypt	Research methods	14.02.2020
504	Elawady, S.-/	2014	Neutrophil CD64 as a diagnostic marker of sepsis in neonates	Research methods	14.02.2020
391	Eliakim, A.-//	2003	The effect of neonatal sepsis on bone turnover in very-low birth weight premature infants	Research methods	14.02.2020
143	Elmazahi, M.	2016	Intercellular adhesion molecule-1 in early diagnosis of neonatal infection	Research methods	14.02.2020
146	Emami, S.-//-H	2016	Diagnostic role of serum haptoglobin level in early onset neonatal sepsis	Research methods	14.02.2020
631	Ergenekon, E.	2000	Urinary nitric oxide in newborns with infections	Research methods	14.02.2020
225	Ertugrul, S.-//	2013	Comparison of urinary neutrophil gelatinase-associated lipocalin, C-reactive protein and procalcitonin in the diagnosis of late onset sepsis in preterm newborns.	Research methods	14.02.2020
41	Eschborn, S.-/	2019	Procalcitonin versus C-reactive protein: review of kinetics and performance for diagnosis of neonatal sepsis	Research study design (review)	14.02.2020
88	Fahmey, S. S.	2018	Diagnostic and prognostic value of proadrenomedullin in neonatal sepsis	Research methods	14.02.2020
32	Fahmey, S. S.	2019	Pentraxin 3 as a novel diagnostic marker in neonatal sepsis	Research methods	14.02.2020
535	Fan, Y.-//-Yu,	2012	Umbilical blood biomarkers for predicting early-onset neonatal sepsis	Research methods	14.02.2020
480	Fang, D. H.-//	2015	Ratios of CD64 expressed on neutrophils, monocytes, and lymphocytes may be a novel method for diagnosis of neonatal sepsis	Research methods	14.02.2020
204	Fanos, V.-//-B	2014	Neonatomics and childomics: The right route to the future	Research study design (review)	14.02.2020
500	Fanos, V.-//-C	2014	Urinary (1)H-NMR and GC-MS metabolomics predicts early and late onset neonatal sepsis		
634	Fanos, V.-//-M	2019	Neonatal sepsis: From a reductionist to an holistic approach design	Research study design (review)	14.02.2020
218	Fanos, V.-//-S	2014	Metabolomics in the diagnosis of sepsis		
345	Frerot, A.-//-E	2019	Cord blood procalcitonin level and early-onset sepsis in extremely preterm infants	Research methods	14.02.2020
215	Fusch, C.-//-Sa	2014	Promoting healthy growth and nutrition in preterm infants: A challenge for clinicians and researchers	Research methods	14.02.2020
493	Gad, G. I.-//-Is	2014	Serum apelin in early-onset neonatal sepsis: is it diagnostic?	Research methods	14.02.2020
485	Gad, G. I.-//-A	2015	Diagnostic value of anti-microbial peptide, cathelicidin in congenital pneumonia	Research methods	14.02.2020
387	Garland, S. M	2002	Mechanisms, organisms and markers of infection in pregnancy	Research methods	14.02.2020

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390	Garland, S. M	2003	Reappraisal of C-reactive protein as a screening tool for neonatal sepsis	Research methods	14.02.2020
444	Gilfillan, M.-/	2017	Biomarkers for the diagnosis of neonatal sepsis and necrotizing enterocolitis: Clinical practice guidelines	Research methods, study design (review)	14.02.2020
546	Gille, C.-//-Dr	2012	Differential modulation of cord blood and peripheral blood monocytes by intravenous immunoglobulin	Research methods	14.02.2020
398	Gille, C.-//-Lei	2008	Diminished phagocytosis-induced cell death (PICD) in neonatal monocytes upon infection with Escherichia coli	Research methods	14.02.2020
622	Gonzalez, B. E	2003	Early markers of late-onset sepsis in premature neonates: clinical, hematological and cytokine profile	Research methods	14.02.2020
608	Greenwood, C	2005	Why is there a modifying effect of gestational age on risk factors for cerebral palsy?	Research methods	14.02.2020
326	Griffin, M. P.-	2005	Heart rate characteristics: Novel physiomarkers to predict neonatal infection and death	Research methods	14.02.2020
626	Guibourdench	2002	Biochemical markers of neonatal sepsis: value of procalcitonin in the emergency setting	Research methods	14.02.2020
251	Gulati, S.-//-A	2012	Maternal serum interleukin-6 and its association with clinicopathological infectious morbidity in preterm premature rupture of membranes: A prospective cohort study	Research methods	14.02.2020
208	Gveric-Ahmet	2014	Procalcitonin vs C-reactive protein in early detection of intrauterine infection in premature rupture of membranes and neonatal infections	Research methods	14.02.2020
4	Hackler, J.-//-	2020	Copper and selenium status as biomarkers of neonatal infections	Research methods	14.02.2020
430	Hahn, W. H.-/	2018	Is procalcitonin to C-reactive protein ratio useful for the detection of late onset neonatal sepsis?	Research methods	14.02.2020
356	Halil, H.-//-Ta	2018	Serum Interleukin-33 as a Biomarker in Predicting Neonatal Sepsis in Premature Infants	Research methods	14.02.2020
216	Halis, H.-//-Gu	2014	Preliminary study: Is gelsolin possible an early diagnostic biomarker for neonatal sepsis?	Research methods	14.02.2020
457	Halis, H.-//-Gu	2016	In the diagnosis of neonatal sepsis importance of gelsolin and relationship with mortality and morbidity	Research methods	14.02.2020
441	Hashem, R. H.	2017	Doppler ultrasound assessment of the splanchnic circulation in preterms with neonatal sepsis at risk for necrotizing enterocolitis	Research methods	14.02.2020
605	Hatzidaki, E.-	2005	Interleukin-6 in preterm premature rupture of membranes as an indicator of neonatal outcome	Research methods	14.02.2020
592	Hawk, M.	2008	C-reactive protein in neonatal sepsis	Research methods	14.02.2020
34	He, Y.-//-Cher	2019	Efficacy and safety of applying a neonatal early-onset sepsis risk calculator in China	Research methods	14.02.2020
108	He, Y.-//-Xia D	2017	Multiplex cytokine profiling identifies interleukin-27 as a novel biomarker for neonatal early onset sepsis	Research methods	14.02.2020
483	Hedegaard, S	2015	Diagnostic utility of biomarkers for neonatal sepsis--a systematic review	Research methods	14.02.2020
448	Heinemann, A	2017	In neonates S100A8/S100A9 alarmins prevent the expansion of a specific inflammatory monocyte population promoting septic shock	Research methods	14.02.2020
117	Hekimoglu, B.	2017	Predictive values of Ischemia modified albumin in neonatal sepsis	Research methods	14.02.2020
74	Henderson, R.	2018	Use of melatonin as adjunctive therapy in neonatal sepsis: A systematic review and meta-analysis	Research methods	14.02.2020
23	Hendrix, M. L	2019	Maternal vascular malformation in the placenta is an indicator for fetal growth restriction irrespective of neonatal birthweight	Research methods	14.02.2020
220	Hernando Hol	2014	Value of lipopolysaccharide binding protein for diagnosing late-onset neonatal sepsis in very low birth weight newborns	Research methods	14.02.2020
187	Hernando Hol	2015	Lipopolysaccharide binding protein in very low birth weight newborns: Preliminary reference interval	Research methods	14.02.2020
453	Hilgendorff, A	2017	Gene expression profiling at birth characterizing the preterm infant with early onset infection	Research methods	14.02.2020
106	Ho, J.-//-Zhan	2017	Pathological Role and Diagnostic Value of Endogenous Host Defense Peptides in Adult and Neonatal Sepsis: A Systematic Review	Research methods	14.02.2020
407	Hodge, G.-//-H	2004	Multiple leucocyte activation markers to detect neonatal infection	Research methods	14.02.2020
615	Hodge, G.-//-H	2004	Rapid simultaneous measurement of multiple cytokines using 100 microl sample volumes--association with neonatal sepsis	Research methods	14.02.2020
536	Hofer, N.-//-Z	2012	An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks	Research methods	14.02.2020
281	Hoffmann, J. J	2011	Neutrophil CD64 as a sepsis biomarker	Research methods	14.02.2020
385	Horns, K. M.	2000	Neoteric physiologic and immunologic methods for assessing early-onset neonatal sepsis	Research methods	14.02.2020
544	Hotoura, E.-//	2012	Pre-inflammatory mediators and lymphocyte subpopulations in preterm neonates with sepsis	Research methods	14.02.2020
130	Hou, J. W.	2016	Maple Syrup Urine Disease Complicated with Kyphoscoliosis and Myelopathy	Research methods	14.02.2020
25	Hu, S.-//-Zhor	2019	Rapid and visual detection of Group B streptococcus using recombinase polymerase amplification combined with lateral flow strips	Research methods	14.02.2020
137	Huang, F. K.-/	2016	Bird's Eye View of a Neonatologist: Clinical Approach to Emergency Neonatal Infection	Research methods	14.02.2020
160	Huang, Y.-//-H	2015	Glycated albumin is an optimal biomarker for gestational diabetes mellitus	Research methods	14.02.2020
202	Iacovidou, N.-	2014	Metabolomics applied in neonatology	Research study design (review)	14.02.2020
623	Icagasioglu, D	2002	Serum C-reactive protein and interleukin6 levels in neonatal sepsis	Research methods	14.02.2020
498	Ince, Z.	2014	Diagnosis of neonatal sepsis: what the clinician expects, what the laboratory tells	Research methods, study design (review)	14.02.2020
437	Iroh Tam, P. Y	2017	Diagnostics for neonatal sepsis: current approaches and future directions	Research methods	14.02.2020
370	Ishii, M.-//-Hc	2018	The Physiological Variation in Plasma Presepsin Levels During the Early Neonatal Period	Research methods	14.02.2020
24	Iskandar, A.-/	2019	Comparison between presepsin and procalcitonin in early diagnosis of neonatal sepsis	Research methods	14.02.2020
491	Ismail, A. Q.-/	2015	Using CRP in neonatal practice	Research methods	14.02.2020
520	Ivarsson, M.-/	2013	Staphylococcus epidermidis and Staphylococcus aureus trigger different interleukin-8 and intercellular adhesion molecule-1 in lung cells: implications for inflammatory complications following neonatal sepsis	Research methods	14.02.2020
257	Jacqz-Aigrain,	2012	How to Optimize the Evaluation and Use of Antibiotics in Neonates	Research methods	14.02.2020
248	Jalali, S. Z.-//-	2013	Diagnostic and prognostic value of Procalcitonin in the management of sepsis in the NICU department	Research methods	14.02.2020
98	Jefferies, A. L	2017	Management of term infants at increased risk for early-onset bacterial sepsis	Research methods	14.02.2020
637	Jekova, N.-//-	2019	Challenges in defining early onset neonatal sepsis diagnosis	Research methods	14.02.2020
11	Karabulut, B.-	2019	New Diagnostic Possibilities for Early Onset Neonatal Sepsis: Red Cell Distribution Width to Platelet Ratio	Research methods	14.02.2020
523	Kasper, D. C.-	2013	Molecular detection of late-onset neonatal sepsis in premature infants using small blood volumes: proof-of-concept	Research methods	14.02.2020
139	Kasztelewicz,	2016	Assessment of interleukin-17A, C5a and RANTES for early diagnosis of neonatal sepsis - a preliminary study	Research methods	14.02.2020
545	Khalil, S.-//-Sh	2012	Prevalence and outcome of hepatobiliary dysfunction in neonatal septicaemia	Research methods	14.02.2020
7	Khan, F.	2019	C-reactive protein as a screening biomarker in neonatal sepsis	Research methods	14.02.2020

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463	Khashana, A.-	2016	Ischemia modified albumin in early neonatal sepsis	Research methods	14.02.2020
598	Khassawneh,	2007	Diagnostic markers for neonatal sepsis: comparing C-reactive protein, interleukin-6 and immunoglobulin M	Research methods	14.02.2020
368	Khattab, A. A	2018	Utility of serum resistin in the diagnosis of neonatal sepsis and prediction of disease severity in term and late preterm infants	Research methods	14.02.2020
184	Kholoussi Ism	2015	Value of presepsin in the diagnosis of neonatal sepsis	Research methods	14.02.2020
321	Kingsmore, S.	2008	Identification of diagnostic biomarkers for infection in premature neonates	Research methods	14.02.2020
551	Kinjo, Y.-//-Ill	2011	Invariant natural killer T cells recognize glycolipids from pathogenic Gram-positive bacteria	Research methods	14.02.2020
375	Kordek, A.-//-	2014	Usefulness of estimation of blood procalcitonin concentration versus C-reactive protein concentration and white blood cell count for therapeutic monitoring of sepsis in neonates	Research methods	14.02.2020
381	Kourtis, A. P.-	2003	Soluble L-selectin, a marker of immune activation, in neonatal infection	Research methods	14.02.2020
361	Kumar, J.-//-S	2019	A Comparative Evaluation of Presepsin with Procalcitonin and CRP in Diagnosing Neonatal Sepsis: Correspondence	Research methods	14.02.2020
621	Kurtogglu, S.-	2003	Serum tumor necrosis factor-alpha and interleukin-6 levels in neonatal sepsis	Research methods	14.02.2020
617	Laborada, G.-	2003	Diagnostic value of cytokines and C-reactive protein in the first 24 hours of neonatal sepsis	Research methods	14.02.2020
322	Lam, H. S.-//-	2007	Diagnostic markers in neonatal sepsis	Research methods	14.02.2020
593	Lam, H. S.-//-	2008	Biochemical markers of neonatal sepsis	Research methods	14.02.2020
337	Layseca-Espin	2002	Expression of CD64 as a potential marker of neonatal sepsis	Research methods	14.02.2020
1	Leal, Y. A.-//-	2019	Cytokine profile as diagnostic and prognostic factor in neonatal sepsis	Research methods	14.02.2020
86	Lee, I. S.-//-Pa	2018	Usefulness of the procalcitonin test in young febrile infants between 1 and 3 months of age	Research methods	14.02.2020
636	Lee, J. H.	2019	Eosinophil count and neutrophil-to-lymphocyte count ratio as biomarkers for predicting early-onset neonatal sepsis	Research methods	14.02.2020
534	Lee, S. Y.-//-P	2012	Relationship between maternal serum C-reactive protein, funisitis and early-onset neonatal sepsis	Research methods	14.02.2020
93	Leroy, S.-//-Ca	2018	A Time-Based Analysis of Inflammation in Infants at Risk of Bronchopulmonary Dysplasia	Research methods	14.02.2020
236	Levesque, B. M	2013	Low urine vascular endothelial growth factor levels are associated with mechanical ventilation, bronchopulmonary dysplasia and retinopathy of prematurity	Research methods	14.02.2020
629	Lewis, D. F.-//	2001	Detection of interleukin-6 in maternal plasma predicts neonatal and infectious complications in preterm premature rupture of membranes	Research methods	14.02.2020
369	Li, S.-//-Ma, F	2018	Marked elevation of circulating CD19⁺CD38^{hi}CD24^{hi} transitional B cells give protection against neonatal sepsis	Research methods	14.02.2020
300	Lione, V. O. F.	2010	Fever temperature enhances mechanisms of survival of Streptococcus agalactiae within human endothelial cells	Research methods	14.02.2020
272	Liong, S.-//-Di	2012	Biomarkers of impending preterm pre-labor rupture of fetal membranes	Research methods	14.02.2020
578	Lippi, G.	2009	Lipoprotein(a) in late onset neonatal sepsis	Research study design (corespondance)	14.02.2020
165	Liu, X.-//-Wan	2015	miR-15a/16 are upreuglated in the serum of neonatal sepsis patients and inhibit the LPS-induced inflammatory pathway	Research methods	14.02.2020
601	Lopez Sastre,	2006	Procalcitonin is not sufficiently reliable to be the sole marker of neonatal sepsis of nosocomial origin	Research methods	14.02.2020
597	Lopez Sastre,	2007	Evaluation of procalcitonin for diagnosis of neonatal sepsis of vertical transmission	Research methods	14.02.2020
382	Lott, J. W.	2003	Neonatal bacterial sepsis	Research methods	14.02.2020
373	Lu, Q.-//-Duar	2016	Are Global Coagulation and Platelet Parameters Useful Markers for Predicting Late-Onset Neonatal Sepsis?	Research methods	14.02.2020
154	Lucas, C.-//-Rc	2016	Non-infective influences on a continuous predictor of infection (hero score)	Research methods	14.02.2020
443	Ludwig, K. R.-	2017	Mass spectrometry for the discovery of biomarkers of sepsis		14.02.2020
503	Lv, B.-//-Huan	2014	Tumor necrosis factor-alpha as a diagnostic marker for neonatal sepsis: a meta-analysis	Research methods	14.02.2020
488	Lynema, S.-//	2015	Neutrophil CD64 as a diagnostic marker of sepsis: impact on neonatal care	Research methods	14.02.2020
399	Machado, J. F	2014	Neonatal sepsis and inflammatory mediators	Research methods	14.02.2020
630	Magudumana	2000	Serial interleukin 6 measurements in the early diagnosis of neonatal sepsis	Research methods	14.02.2020
42	Mahendiran,	2018	Procalcitonin as Predictor of Bacterial Infection in Meconium Aspiration Syndrome	Research methods	14.02.2020
572	Mahmoud, S.-	2009	Soluble intercellular adhesion molecule-1 (sICAM-1) for early diagnosis of neonatal infections	Research methods	14.02.2020
97	Majors, C. E.-	2017	Point-of-care diagnostics to improve maternal and neonatal health in low-resource settings	Research methods	14.02.2020
417	Mani, S.-//-Ca	2017	Protein biomarker druggability profiling		14.02.2020
564	Mannan, M. A	2010	Utility of C-reactive protein and hematological parameters in the detection of neonatal sepsis	Research methods	14.02.2020
179	Markic, J.	2015	Biomarkers of sepsis in neonates and children	Research methods	14.02.2020
405	Martin, H.-//-	2001	Reactive hyperemia and interleukin 6, interleukin 8, and tumor necrosis factor-alpha in the diagnosis of early-onset neonatal sepsis	Research methods	14.02.2020
237	Mazzucchelli,	2013	Diagnostic performance of triggering receptor expressed on myeloid cells-1 and CD64 index as markers of sepsis in preterm newborns	Research methods	14.02.2020
274	McAllister, K.	2012	Clinical utility of using C-reactive protein and procalcitonin as biomarkers for a novel neonatal sepsis diagnostic platform (ASCMicroPlat)	Research methods	14.02.2020
138	McArdle, A. J	2016	Determinants of Carboxyhemoglobin levels and relationship with sepsis in a retrospective cohort of preterm neonates	Research methods	14.02.2020
565	McWilliam, S.	2010	How to use: C-reactive protein	Research methods	14.02.2020
632	Mehr, S.-//-De	1999	Interleukin-6 concentrations in neonatal sepsis	Research methods	14.02.2020
412	Memar, M. Y.	2019	Immunologic biomarkers for diagnostic of early-onset neonatal sepsis	Research methods	14.02.2020
71	Meng, Y.-//-Ca	2018	Potential Genes and Pathways of Neonatal Sepsis Based on Functional Gene Set Enrichment Analyses	Research methods	14.02.2020
557	Miguel, D.-//-	2011	Cord blood plasma reference intervals for potential sepsis markers: pro-adrenomedullin, pro-endothelin, and pro-atrial natriuretic peptide	Research methods	14.02.2020
87	Mishra, N. R.-	2018	Role of CSF C-reactive protein for rapid diagnosis and differentiation of different forms of meningitis in children	Research methods	14.02.2020
602	Mishra, U. K.-	2006	Newer approaches to the diagnosis of early onset neonatal sepsis	Research methods, research study (review)	14.02.2020
446	Mithal, L. B.-/	2017	Cord Blood Acute Phase Reactants Predict Early Onset Neonatal Sepsis in Preterm Infants	Research methods	14.02.2020
413	Mithal, L. B.-/	2018	Vital signs analysis algorithm detects inflammatory response in premature infants with late onset sepsis and necrotizing enterocolitis	Research methods	14.02.2020
461	Miyake, F.-//	2016	Analysis of the Physiological Variation in Neutrophil CD64 Expression during the Early Neonatal Period	Research methods	14.02.2020

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425	Miyosawa, Y.	2018	Presepsin as a predictor of positive blood culture in suspected neonatal sepsis	Research methods	14.02.2020
492	Mkony, M. F.	2014	Management of neonatal sepsis at Muhimbili National Hospital in Dar es Salaam: diagnostic accuracy of C-reactive protein and newborn scale of sepsis and antimicrobial resistance pattern of etiological bac	Research methods	14.02.2020
70	Montaldo, P.-	2019	Whole blood gene expression reveals specific transcriptome changes in neonatal encephalopathy.	Research methods	14.02.2020
112	Montaldo, P.-	2017	Presepsin for the detection of early-onset sepsis in preterm newborns	Research methods	14.02.2020
247	Moraes-Barbo	2013	Procalcitonin and c-reactive protein in umbilical cord blood as markers for early suspicion of infection in newborns of women with urinary tract infection	Research methods	14.02.2020
583	Morsy, A. A.-/	2008	CD64 cell surface expression on neutrophils for diagnosis of neonatal sepsis	Research methods	14.02.2020
269	Murphy, K.-//	2012	Reply: Use of Immature-to-total-neutrophil ratio in early neonatal sepsis	Research study design (correspondance)	14.02.2020
531	Mussap, M.	2012	Laboratory medicine in neonatal sepsis and inflammation	Research methods	14.02.2020
516	Mussap, M.-/	2013	In search of biomarkers for diagnosing and managing neonatal sepsis: the role of angiopoietins	Research methods	14.02.2020
379	Mussap, M.-/	2007	Biochemical markers for the early assessment of neonatal sepsis: the role of procalcitonin	Research methods	14.02.2020
553	Mussap, M.-/	2011	Soluble CD14 subtype presepsin (sCD14-ST) and lipopolysaccharide binding protein (LBP) in neonatal sepsis: new clinical and analytical perspectives for two old biomarkers	Research methods	14.02.2020
249	Mussap, M.-/	2012	Emerging biomarkers in neonatal sepsis	Research methods	14.02.2020
226	Mussap, M.-/	2013	The importance of biomarkers in neonatology	Research methods	14.02.2020
625	Mussap, M.-/	2002	Laboratory management of neonatal sepsis and urinary tract infections: new perspectives	Research methods	14.02.2020
253	Mussap, M.-/	2012	Soluble CD14 subtype (sCD14-ST) presepsin in critically ill preterm newborns: Preliminary reference ranges	Research methods	14.02.2020
476	Mussap, M.-/	2015	Soluble CD14 subtype (sCD14-ST) presepsin in premature and full term critically ill newborns with sepsis and SIRS	Research methods	14.02.2020
532	Nabulsi, M.-/	2012	Impact of C-reactive protein test results on evidence-based decision-making in cases of bacterial infection	Research methods	14.02.2020
378	Naher, B. S.-/	2011	Role of serum procalcitonin and C-reactive protein in the diagnosis of neonatal sepsis	Research methods	14.02.2020
91	Nakstad, B.	2018	The diagnostic utility of procalcitonin, interleukin-6 and interleukin-8, and hyaluronic acid in the Norwegian consensus definition for early-onset neonatal sepsis (EONS)	Research methods	14.02.2020
147	Nakstad, B.-/	2016	Early detection of neonatal group B streptococcus sepsis and the possible diagnostic utility of IL-6, IL-8, and CD11b in a human umbilical cord blood in vitro model	Research methods	14.02.2020
159	Nasir, I. A.-//	2015	Serum Procalcitonin Assay for Investigations and Clinical Management of Neonatal Sepsis: A Review	Research methods	14.02.2020
471	Neunhoeffer,	2016	Serum Concentrations of Interleukin-6, Procalcitonin, and C-Reactive Protein: Discrimination of Septical Complications and Systemic Inflammatory Response Syndrome after Pediatric Surgery	Research methods	14.02.2020
409	Ng, P. C.	2004	Diagnostic markers of infection in neonates	Research methods	14.02.2020
242	Ng, P. C.	2013	Biomarkers of neonatal infection and necrotising enterocolitis-the state of the art approach	Research methods	14.02.2020
614	Ng, P. C.-//-Li,	2004	Neutrophil CD64 is a sensitive diagnostic marker for early-onset neonatal infection	Research methods	14.02.2020
603	Ng, P. C.-//-La	2006	Diagnostic markers for neonatal sepsis	Research methods	14.02.2020
562	Ng, P. C.-//-La	2010	Biomarkers for late-onset neonatal sepsis: cytokines and beyond	Research methods	14.02.2020
264	Ng, P. C.-//-La	2012	Biomarkers in neonatology: The next generation of tests	Research methods	14.02.2020
239	Ng, P. C.-//-Ch	2013	Biomarkers for Prediction and Diagnosis of Necrotizing Enterocolitis	Research methods	14.02.2020
167	Ng, P. C.-//-M	2015	The use of laboratory biomarkers for surveillance, diagnosis and prediction of clinical outcomes in neonatal sepsis and necrotising enterocolitis	Research methods	14.02.2020
349	Ng, P. C.-//-Ch	2019	Plasma miR-1290 Is a Novel and Specific Biomarker for Early Diagnosis of Necrotizing Enterocolitis-Biomarker Discovery with Prospective Cohort Evaluation	Research methods	14.02.2020
435	Nguyen, D. N.	2017	Elevated levels of circulating cell-free DNA and neutrophil proteins are associated with neonatal sepsis and necrotizing enterocolitis in immature mice, pigs and infants	Research methods	14.02.2020
346	Niemarkt, H.	2019	Necrotizing Enterocolitis, Gut Microbiota, and Brain Development: Role of the Brain-Gut Axis	Research methods	14.02.2020
141	Nillsen, A.-//-	2016	Sepsis and Neonatal Acute Kidney Injury	Research methods	14.02.2020
432	Nishizaki, N.-/	2017	Evaluation of urinary IL-6 in neonates with septic shock treated with polymyxin B-immobilized fiber column	Research methods	14.02.2020
587	Noor, M. K.-/	2008	Comparison between CRP and IL-6 as early markers of neonatal sepsis	Research methods	14.02.2020
271	Noto, A.-//-Fa	2012	Soluble CD14-subtype (SCD14-ST) presepsin in critically ill preterm and term newborns for the early assessment of neonatal sepsis: Preliminary results.	Research methods	14.02.2020
510	Noto, A.-//-M	2014	Is 1H NMR metabolomics becoming the promising early biomarker for neonatal sepsis and for monitoring the antibiotic toxicity?	Research study design (review)	14.02.2020
406	Nupponen, I.-	2001	Neutrophil CD11b expression and circulating interleukin-8 as diagnostic markers for early-onset neonatal sepsis	Research methods	14.02.2020
129	O'Gorman, N.	2016	Study protocol for the randomised controlled trial: Combined multimarker screening and randomised patient treatment with ASpirin for evidence-based PREeclampsia prevention (ASPRE)	Research methods	14.02.2020
172	Offringa, M.-/	2015	Applying regulatory science to develop safe and effective medicines for neonates: Report of the US food and drug administration first annual neonatal scientific workshop, october 28-29, 2014	Research methods	14.02.2020
559	Oguz, S. S.-//	2011	C-reactive protein and interleukin-6 responses for differentiating fungal and bacterial aetiology in late-onset neonatal sepsis	Research methods	14.02.2020
158	Okulu, E.-//-A	2015	Serum Levels of Soluble Urokinase Plasminogen Activator Receptor in Infants with Late-onset Sepsis	Research methods	14.02.2020
14	Okur, N.-//-Bu	2019	Role of N-Terminal Pro-brain Natriuretic Peptide in the Early Diagnosis of Neonatal Sepsis	Research methods	14.02.2020
12	Omar, J.-//-Isa	2019	Procalcitonin as an early laboratory marker of sepsis in neonates: Variation in diagnostic performance and discrimination value	Research methods	14.02.2020
426	Omran, A.-//-	2018	Salivary C-reactive protein, mean platelet volume and neutrophil lymphocyte ratio as diagnostic markers for neonatal sepsis	Research methods	14.02.2020
633	Onal, E. E.-//-	1999	Interleukin-6 concentrations in neonatal sepsis	Research methods	14.02.2020
376	Oncel, M. Y.-/	2012	Mean platelet volume in neonatal sepsis	Research methods	14.02.2020
533	Oncel, M. Y.-/	2012	Proadrenomedullin as a prognostic marker in neonatal sepsis	Research methods	14.02.2020
539	Osterholt, H.	2012	The impact of hyaluronan on monocyte Toll-like receptor expression in term infant cord blood	Research methods	14.02.2020
527	Oswari, H.-//-	2013	Prognostic value of biochemical liver parameters in neonatal sepsis-associated cholestasis	Research methods	14.02.2020
449	Ozdemir, A. A	2017	Diagnostic Value of Presepsin in Detection of Early-Onset Neonatal Sepsis	Research methods	14.02.2020
366	Ozlu, F.-//-Ak	2019	New biomarkers for antenatal infection: MICA and MICB gene expression in preterm babies	Research methods	14.02.2020
157	Pai, S.-//-Enoc	2015	Bacteremia in children: Epidemiology, clinical diagnosis and antibiotic treatment	Research methods	14.02.2020
246	Pak, C. Ng	2013	Biomarkers of Neonatal Infection and Necrotising Enterocolitis-The State of the Art Approach	Research methods	14.02.2020
95	Palchaudhuri,	2018	Diagnosis of sepsis at the point of care	Research methods	14.02.2020

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613	Palmer, A.-//-	2004	The use of CRP for diagnosing infections in young infants < 3 months of age in developing countries	Research methods	14.02.2020
404	Pan, X.-//-Ji, Z	2016	Percentage of Peripheral CD19+CD24hiCD38hi Regulatory B Cells in Neonatal Sepsis Patients and Its Functional Implication	Research methods	14.02.2020
199	Park, I. H.-//-L	2014	Serum procalcitonin as a diagnostic marker of neonatal sepsis	Research methods	14.02.2020
616	Park, K. H.-//-	2004	Amniotic fluid tumor necrosis factor-alpha is a marker for the prediction of early-onset neonatal sepsis in preterm labor	Research methods	14.02.2020
299	Parravicini, E.	2010	The clinical utility of urinary neutrophil gelatinase-associated lipocalin in the neonatal ICU	Research methods	14.02.2020
305	Parravicini, E.	2010	Urinary neutrophil gelatinase-associated lipocalin is a promising biomarker for late onset culture-positive sepsis in very low birth weight infants	Research methods	14.02.2020
57	Parri, N.-//-Tr	2019	Accuracy of presepsin in neonatal sepsis: systematic review and meta-analysis	Research methods	14.02.2020
353	Patoulias, D.-,	2018	Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1) and its soluble in the plasma form (sTREM-1) as a diagnostic biomarker in neonatal sepsis	Research methods	14.02.2020
197	Pavcnik-Arnol	2014	Lipopolysaccharide-binding protein as marker of fetal inflammatory response syndrome after preterm premature rupture of membranes	Research methods	14.02.2020
386	Perenyi, A.-//	1999	Assessment of cord blood IL-6 levels as an indicator of neonatal sepsis	Research methods	14.02.2020
27	Perrone, S.-//	2017	Creactive protein in healthy term newborns during the first 48 hours of life	Research methods	14.02.2020
501	Picone, S.-//-A	2014	Infection in late preterm infants	Research methods	14.02.2020
206	Pierce, R.-//-B	2014	Use of procalcitonin for the prediction and treatment of acute bacterial infection in children	Research methods	14.02.2020
19	Pietrasanta, C	2019	Vascular Endothelium in Neonatal Sepsis: Basic Mechanisms and Translational Opportunities	Research methods	14.02.2020
554	Piva, J. P.-//-G	2011	Development of an accurate score to predict early-onset neonatal sepsis	Research methods	14.02.2020
161	Poggi, C.-//-Bi	2015	Presepsin for the detection of late-onset sepsis in preterm newborns	Research methods	14.02.2020
72	Poggi, C.-//-Di	2018	Sepsis and Oxidative Stress in the Newborn: From Pathogenesis to Novel Therapeutic Targets	Research methods	14.02.2020
263	Polin, R. A.	2012	Strategies to improve the outcomes of neonatal intensive care: The search for a magic bullet	Research methods	14.02.2020
303	Polin, R. A.-//-	2010	Biomarkers for late-onset neonatal sepsis	Research methods	14.02.2020
109	Pontrelli, G.-/	2017	Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: A meta-analysis	Research methods	14.02.2020
470	Pradhan, R.-//	2016	Ratio of neutrophilic CD64 and monocytic HLA-DR: A novel parameter in diagnosis and prognostication of neonatal sepsis	Research methods	14.02.2020
519	Prashant, A.-/	2013	Comparative assessment of cytokines and other inflammatory markers for the early diagnosis of neonatal sepsis-a case control study	Research methods	14.02.2020
419	Pravin Charle	2018	Evaluation of procalcitonin as a diagnostic marker in neonatal sepsis	Research methods	14.02.2020
224	Prieto, C. L.-//	2013	Prognostic factors of mortality in very low-birth-weight infants with neonatal sepsis of nosocomial origin	Research methods	14.02.2020
13	Prince, K.-//-C	2019	A Comparison of Point of Care C-Reactive Protein Test to Standard C-Reactive Protein Laboratory Measurement in a Neonatal Intensive Care Unit Setting	Research methods	14.02.2020
589	Prinsen, J. H.-	2008	Interleukin-6 as diagnostic marker for neonatal sepsis: determination of Access IL-6 cutoff for newborns	Research methods	14.02.2020
611	Procianoy, R.	2004	The role of sample collection timing on interleukin-6 levels in early-onset neonatal sepsis	Research methods	14.02.2020
173	Pugni, L.-//-Pi	2015	Presepsin (soluble CD14 subtype): Reference ranges of a new sepsis marker in term and preterm neonates	Research methods	14.02.2020
52	Qiu, X.-//-Li, J.	2019	Is neutrophil CD11b a special marker for the early diagnosis of sepsis in neonates A systematic review and meta-analysis	Research methods	14.02.2020
410	Qiu, X.-//-Zhai	2018	Interleukin-6 for early diagnosis of neonatal sepsis with premature rupture of the membranes: A meta-analysis	Research methods	14.02.2020
352	Quadir, A. F.-,	2018	Procalcitonin and C-reactive protein as biomarkers for neonatal bacterial infection	Research methods	14.02.2020
451	Raimondi, F.-/	2017	Bilirubin exposure is associated with neonatal sepsis in the eight days preceding symptoms: a retrospective study	Research methods	14.02.2020
635	Rao, L.-//-Son	2020	Progranulin as a novel biomarker in diagnosis of early-onset neonatal sepsis	Research methods	14.02.2020
38	Rashwan, N. I	2019	Validity of biomarkers in screening for neonatal sepsis - A single center -hospital based study	Research methods	14.02.2020
465	Rasid, O.-//-Ca	2016	Recent developments in severe sepsis research: from bench to bedside and back	Research methods	14.02.2020
541	Raynor, L. L.-/	2012	Cytokine screening identifies NICU patients with Gram-negative bacteremia	Research methods	14.02.2020
307	Reinhart, K.-/,	2010	Biomarkers as a guide for antimicrobial therapy	Research methods	14.02.2020
183	Rodriguez Rev	2015	Infectious epidemiology of early and late-onset sepsis at a neonatal intensive care unit: An eleven-year surveillance study	Research methods	14.02.2020
134	Romero, R.-//-	2016	Clinical chorioamnionitis at term V: Umbilical cord plasma cytokine profile in the context of a systemic maternal inflammatory response	Research methods	14.02.2020
39	Ronzoni, S.-//-	2019	Maternal blood endotoxin activity in pregnancies complicated by preterm premature rupture of membranes	Research methods	14.02.2020
8	Rosenfeld, C. I	2019	Screening and Serial Neutrophil Counts Do Not Contribute to the Recognition or Diagnosis of Late-Onset Neonatal Sepsis.	Research methods	14.02.2020
511	Rotshenker-O	2014	Comparison of hematologic indices and markers of infection in umbilical cord and neonatal blood	Research methods	14.02.2020
360	Ruan, L.-//-Ch	2018	The combination of procalcitonin and C-reactive protein or presepsin alone improves the accuracy of diagnosis of neonatal sepsis: a meta-analysis and systematic review	Research methods	14.02.2020
604	Sa de Sao Jos	2006	Intracellular viability in human non-polarized respiratory epithelial 16 HBE 14o- cells by group B Streptococcus serotype III clinical isolates presenting 162-kb and 183-kb virulence markers	Research methods	14.02.2020
3	Saeed, K.-//-G	2019	Hot topics on procalcitonin use in clinical practice, can it help antibiotic stewardship?	Research methods	14.02.2020
142	Sakr, M. A.-//	2016	Evaluation of serum leptin level as early marker in early onset neonatal sepsis	Research methods	14.02.2020
101	Salava, A.-//-,	2017	Loss of cutaneous microbial diversity during first 3 weeks of life in very low birthweight infants	Research methods	14.02.2020
474	Saldir, M.-//-T	2015	Endocan and Soluble Triggering Receptor Expressed on Myeloid Cells-1 as Novel Markers for Neonatal Sepsis	Research methods	14.02.2020
33	Samra, N.-//-A	2019	Serum Level of Antithrombin III (ATIII) Could Serve as a Prognostic Biomarker in Neonatal Sepsis	Research methods	14.02.2020
288	Sancho-Rodrig	2011	Cord blood levels of biomarkers in early neonatal sepsis	Research methods	14.02.2020
245	Sancho-Rodrig	2013	Early-onset neonatal sepsis: Cord blood levels biomarkers	Research methods	14.02.2020
600	Sanodze, N.-/,	2006	Parameters of oxidative metabolism in neonates suffering from sepsis and anemia	Research methods	14.02.2020
395	Santana, C.-//	2001	Cord blood levels of cytokines as predictors of early neonatal sepsis	Research methods	14.02.2020
440	Sarafidis, K.-/,	2017	Urine metabolomics in neonates with late-onset sepsis in a case-control study		14.02.2020
298	Sarafidis, K.-/,	2010	Diagnostic utility of elevated serum soluble triggering receptor expressed on myeloid cells (sTREM)-1 in infected neonates	Research methods	14.02.2020
275	Schlapbach, L	2012	Pancreatic stone protein as a novel marker for neonatal sepsis	Research methods	14.02.2020

Code	Author(s)	Year	Title	Exclusion critera	Date
280	Schlapbach, L	2011	Copeptin concentration in cord blood in infants with early-onset sepsis, chorioamnionitis and perinatal asphyxia	Research methods	14.02.2020
243	Schlapbach, L	2013	The combination of pancreatic stone protein and procalcitonin improves diagnosis of early-onset neonatal sepsis	Research methods	14.02.2020
526	Schlapbach, L	2013	Pancreatic stone protein as a novel marker for neonatal sepsis	Research methods	14.02.2020
396	Schollin, J.	2001	Interleukin-8 in neonatal sepsis	Research methods	14.02.2020
442	Schuller, S. S.	2017	Pentoxifylline modulates LPS-induced hyperinflammation in monocytes of preterm infants in vitro	Research methods	14.02.2020
421	Seliem, W.-//	2018	Presepsin as a predictor of early onset neonatal sepsis in the umbilical cord blood of premature infants with premature rupture of membranes	Research methods	14.02.2020
365	Shabuj, K. H.-	2017	C-reactive Protein (CRP) as a Single Biomarker for Diagnosis of Neonatal Sepsis: A Comprehensive Meta-analysis	Research methods	14.02.2020
359	Shabaan, A. E	2018	Role of serum (1,3)-beta-d-glucan assay in early diagnosis of invasive fungal infections in a neonatal intensive care unit	Research methods	14.02.2020
509	Shah, B. A.-//	2014	Neonatal sepsis: an old problem with new insights	Research methods	14.02.2020
429	Sharma, D.-//	2018	Biomarkers for diagnosis of neonatal sepsis: a literature review	Research study design (review)	14.02.2020
363	Sheneef, A.-//	2017	Neutrophil CD11b, CD64 and Lipocalin-2: Early Diagnostic Markers of Neonatal Sepsis	Research methods	14.02.2020
588	Sherwin, C.-//	2008	Utility of interleukin-12 and interleukin-10 in comparison with other cytokines and acute-phase reactants in the diagnosis of neonatal sepsis	Research methods	14.02.2020
458	Shi, J.-//-Tang	2016	Meta-analysis of diagnostic accuracy of neutrophil CD64 for neonatal sepsis	Research methods	14.02.2020
570	Shouman, B.-/	2010	Regulated on activation, normal T cell expressed and secreted and tumor necrosis factor-alpha in septic neonates	Research methods	14.02.2020
192	Siahanidou, T	2014	Clinical value of plasma soluble Urokinase-type plasminogen activator receptor levels in term neonates with infection or sepsis: A prospective study	Research methods	14.02.2020
344	Siahanidou, T	2019	Association of fibroblast growth factor 21 plasma levels with neonatal sepsis: preliminary results	Research methods	14.02.2020
252	Silva-Bravo, F	2012	Color of meconium and interleukin-6	Research methods	14.02.2020
186	Sison, R. C.-//	2015	An evaluation of procalcitonin in the clinical management of sepsis among filipino pediatrics in a tertiary hospital in Quezon City, Philippines	Research methods	14.02.2020
496	Smith, C. L.-//	2014	Identification of a human neonatal immune-metabolic network associated with bacterial infection	Research methods	14.02.2020
124	Solberg, R.-//	2017	Intrauterine transfer of campylobacter jejuni causing fetal sepsis and neonatal death	Research methods	14.02.2020
529	Soni, S.-//-Wa	2013	Evaluation of CD64 expression on neutrophils as an early indicator of neonatal sepsis	Research methods	14.02.2020
566	Sorokin, Y.-//	2010	Maternal serum interleukin-6, C-reactive protein, and matrix metalloproteinase-9 concentrations as risk factors for preterm birth <32 weeks and adverse neonatal outcomes	Research methods	14.02.2020
573	Spada, S.-//-C	2009	Reliability of procalcitonin in neonatology. Experience in 59 preterm newborns	Research methods	14.02.2020
276	Speer, C. P.	2012	Chorioamnionitis: the good or the evil for neonatal pulmonary outcome	Research methods	14.02.2020
185	Speer, C. P.	2015	Fetal inflammatory response and possible consequences for the very immature preterm infant	Research methods	14.02.2020
445	Speer, E. M.-/	2017	Pentoxifylline inhibits TLR- and inflammasome-mediated in vitro inflammatory cytokine production in human blood with greater efficacy and potency in newborns	Research methods	14.02.2020
320	Spitzer, A. R.-	2008	Proteomics- and Metabolomics-Based Neonatal Diagnostics in Assessing and Managing the Critically Ill Neonate	Review	14.02.2020
277	Srinivas, S. K.	2012	Maternal IL6 levels: A failed biomarker for preterm birth	Research methods	14.02.2020
542	Srinivasan, L.	2012	New technologies for the rapid diagnosis of neonatal sepsis	Research methods	14.02.2020
436	Stewart, C. J.	2017	Longitudinal development of the gut microbiome and metabolome in preterm neonates with late onset sepsis and healthy controls	Research methods	14.02.2020
244	Stocker, M.	2013	Interest and limitations of procalcitonin in children and newborn with sepsis	Research methods	14.02.2020
571	Stocker, M.-/	2010	Use of procalcitonin-guided decision-making to shorten antibiotic therapy in suspected neonatal early-onset sepsis: prospective randomized intervention trial	Research methods	14.02.2020
560	Stocker, M.-/	2010	Neonatal Procalcitonin Intervention Study (NeoPInS): Effect of Procalcitonin-guided decision making on duration of antibiotic therapy in suspected neonatal early-onset sepsis: A multi-centre randomized sup	Research methods	14.02.2020
152	Stojewska, M	2016	Presepsin (soluble CD14-ST) as a new marker for the diagnosis of sepsis in newborns	Research methods	14.02.2020
420	Stolz, M.-//-Z	2018	An sFlt-1:PlGF ratio of 655 is not a reliable cut-off value for predicting perinatal outcomes in women with preeclampsia	Research methods	14.02.2020
99	Straub, J.-//-F	2017	Diagnostic accuracy of the ROCHE Septifast PCR system for the rapid detection of blood pathogens in neonatal sepsis - A prospective clinical trial	Research methods	14.02.2020
537	Streimish, I.-/	2012	Neutrophil CD64 as a diagnostic marker in neonatal sepsis	Research methods	14.02.2020
513	Streimish, I.-/	2014	Neutrophil CD64 with hematologic criteria for diagnosis of neonatal sepsis	Research methods	14.02.2020
341	Su, P. H.-//-Ch	2000	Interleukin-6 (IL-6), Tumor Necrosis Factor alpha (TNF alpha), and C-reactive Protein (CRP) serum levels in new-borns with sepsis	Research methods	14.02.2020
268	Sucilathangar	2012	Early diagnostic markers for neonatal sepsis: Comparing procalcitonin (PCT) and C-reactive protein (CRP)	Research methods	14.02.2020
497	Sugitharini, V	2014	TLR-mediated inflammatory response to neonatal pathogens and co-infection in neonatal immune cells	Research methods	14.02.2020
522	Suguna Naras	2013	Usefulness of urinary immune biomarkers in the evaluation of neonatal sepsis: a pilot project	Research methods	14.02.2020
357	Sun, B.-//-Lian	2019	A meta-analysis of interleukin-6 as a valid and accurate index in diagnosing early neonatal sepsis	Research methods	14.02.2020
145	Suresh, S.-//-T	2016	Recurrent sepsis and neuroinvasive disease in a neonate culture-positive for a group B streptococcus CPS III serotype, hvgA+ strain	Research methods	14.02.2020
228	Swarnkar, K.-	2013	Sepsis biomarkers in early onset neonatal infections: A review	Research study design	14.02.2020
191	Sylvester, K.	2014	Urine protein biomarkers for the diagnosis and prognosis of necrotizing enterocolitis in infants	Research methods	14.02.2020
148	Tabl, H. A. E.	2016	Diagnostic Value of Presepsin in Neonatal Sepsis	Research methods	14.02.2020
475	Tao, G. Z.-//-L	2015	Impaired Activity of Blood Coagulant Factor XIII in Patients with Necrotizing Enterocolitis	Research methods	14.02.2020
567	Tapisiz, A.-//-	2010	C1 inhibitor level on neonatal sepsis and its relations with clinical findings	Research methods	14.02.2020
102	Tarko, A.-//-S	2017	Zonulin: A Potential Marker of Intestine Injury in Newborns	Research methods	14.02.2020
84	Tchirikov, M.	2018	Mid-trimester preterm premature rupture of membranes (PPROM): Etiology, diagnosis, classification, international recommendations of treatment options and outcome	Research methods	14.02.2020
552	Terrin, G.-//-F	2011	Serum calprotectin: an antimicrobial peptide as a new marker for the diagnosis of sepsis in very low birth weight newborns	Research methods	14.02.2020
469	Topcuoglu, S.	2016	Role of presepsin in the diagnosis of late-onset neonatal sepsis in preterm infants	Research methods	14.02.2020
26	Tosson, A. M.	2018	Evaluation of the S100 protein A12 as a biomarker of neonatal sepsis	Research methods	14.02.2020
612	Toti, P.-//-De	2004	Spleen depletion in neonatal sepsis and chorioamnionitis	Research methods	14.02.2020
490	Tunc, T.-//-Ce	2015	Diagnostic value of elevated CXCR4 and CXCL12 in neonatal sepsis	Research methods	14.02.2020

Code	Author(s)	Year	Title	Exclusion critera	Date
16	Tunc, T.-//-Po	2019	Assessment of novel biomarkers: sTREM-1, pentraxin-3 and pro-adrenomedullin in the early diagnosis of neonatal early onset sepsis	Research methods	14.02.2020
36	Turner, M. J.	2019	Maternal sepsis is an evolving challenge	Research methods	14.02.2020
364	Tzialla, C.-//-N	2018	New Diagnostic Possibilities for Neonatal Sepsis	Research study design (review)	14.02.2020
586	Ucar, B.-//-Yil	2008	Serum amyloid A, procalcitonin, tumor necrosis factor-alpha, and interleukin-1beta levels in neonatal late-onset sepsis	Research methods	14.02.2020
518	van der Flier,	2013	Increased CD4(+) T cell co-inhibitory immune receptor CEACAM1 in neonatal sepsis and soluble-CEACAM1 in meningococcal sepsis: a role in sepsis-associated immune suppression?	Research methods	14.02.2020
131	van Herk, W.-	2016	Recognising early onset neonatal sepsis: an essential step in appropriate antimicrobial use	Research methods	14.02.2020
343	van Maldegh	2019	Soluble CD14 subtype (sCD14-ST) as biomarker in neonatal early-onset sepsis and late-onset sepsis: a systematic review and meta-analysis	Research methods	14.02.2020
35	Van Maldegh	2019	Improving antibiotic stewardship in neonates through means of a new biomarker, soluble cd14 subtype (scd14-st): a systematic review and meta-analysis	Research methods	14.02.2020
60	Vasani, A.-//-	2019	Advances in the proteomics of amniotic fluid to detect biomarkers for chromosomal abnormalities and fetomaternal complications during pregnancy.	Research methods	14.02.2020
389	Vasquez-De K	2012	Leukocyte adhesion deficiency syndrome: report on the first case in Chile and South America	Research methods	14.02.2020
267	Vaz Marecos,	2012	Sepsis, meningitis and cerebral abscesses caused by Citrobacter koseri	Research methods	14.02.2020
10	Vazquez Rodr	2019	Multiparameter flow cytometry analysis of leukocyte markers for diagnosis in preterm neonatal sepsis	Research methods	14.02.2020
606	Vazzalwar, R.	2005	Procalcitonin as a screening test for late-onset sepsis in preterm very low birth weight infants	Research methods	14.02.2020
590	Veleminsky, I	2008	Relationship of IL-6, IL-8, TNF and sICAM-1 levels to PROM, pPROM, and the risk of early-onset neonatal sepsis	Research methods	14.02.2020
94	Verma, M. S.	2018	Sliding-strip microfluidic device enables ELISA on paper	Research methods	14.02.2020
555	Vouloumanou	2011	Serum procalcitonin as a diagnostic marker for neonatal sepsis: a systematic review and meta-analysis	Research methods	14.02.2020
254	Wahab Moha	2012	Mannose-binding lectin serum levels in neonatal sepsis and septic shock	Research methods	14.02.2020
48	Walker, O.-//-	2019	Neonatal sepsis	Research methods	14.02.2020
119	Wang, C.-//-Lu	2017	Determination of biomarkers for neonatal sepsis based on differential modules	Research methods	14.02.2020
514	Wang, K.-//-Bi	2013	Which biomarkers reveal neonatal sepsis?	Research methods	14.02.2020
28	Willis, Z.-//-De	2019	Strategies to improve antibiotic use in the neonatal ICU	Research methods	14.02.2020
59	Wisgrill, L.-//-	2019	Interleukin-6 serum levels predict surgical intervention in infants with necrotizing enterocolitis	Research methods	14.02.2020
51	Wright, J.-//-H	2016	Circulating biomarkers of endothelial dysfunction predict mortality in newborn sepsis	Research methods	14.02.2020
371	Wright, J. K.-/	2018	Biomarkers of endothelial dysfunction predict sepsis mortality in young infants: a matched case-control study	Research methods	14.02.2020
96	Wu, R.-//-Zha	2017	The value of pancreatic stone protein in the prediction of infected neonates	Research methods	14.02.2020
530	Wu, T. W.-//-T	2013	The utility of serum hepcidin as a biomarker for late-onset neonatal sepsis	Research methods	14.02.2020
415	Xiao, T.-//-Che	2017	The Analysis of Etiology and Risk Factors for 192 Cases of Neonatal Sepsis	Research methods	14.02.2020
73	Xue, H.-//-Xue	2017	Low serum mannose binding lectin (MBL) levels and -221 yx genotype of MBL2 gene are susceptible to neonatal sepsis in the chinese han population	Research methods	14.02.2020
468	Yang, A. P.-//	2016	Neutrophil CD64 combined with PCT, CRP and WBC improves the sensitivity for the early diagnosis of neonatal sepsis	Research methods	14.02.2020
447	Ye, Q.-//-Du, L	2017	Utility of cytokines to predict neonatal sepsis	Research methods	14.02.2020
506	Yerlikaya, F. I	2014	Serum ischemia-modified albumin levels at diagnosis and during treatment of late-onset neonatal sepsis	Research methods	14.02.2020
580	Yildiz, B.-//-Uc	2009	Diagnostic values of lipid and lipoprotein levels in late onset neonatal sepsis	Research methods	14.02.2020
618	Yoon, B. H.-//	2003	C-reactive protein in umbilical cord blood: a simple and widely available clinical method to assess the risk of amniotic fluid infection and funisitis	Research methods	14.02.2020
90	Younis, F. Q.-/	2018	TLR2 and TLR4 as a biomarker of bacterial sepsis syndrome in adult and children patients in Iraq	Research methods	14.02.2020
342	Youssef, M. A	2019	In neonates with vitamin D deficiency, low lymphocyte activation markers are risk factors for infection	Research methods	14.02.2020
561	Yu, Z.-//-Liu, J	2010	The accuracy of the procalcitonin test for the diagnosis of neonatal sepsis: a meta-analysis	Research methods	14.02.2020
517	Yuan, H.-//-Hu	2013	Diagnosis value of the serum amyloid A test in neonatal sepsis: a meta-analysis	Research methods	14.02.2020
574	Zaki Mel, S.-/	2009	Evaluation of microbiologic and hematologic parameters and E-selectin as early predictors for outcome of neonatal sepsis	Research methods	14.02.2020
40	Zdraveska, N.	2019	Multiple vital signs analysis algorithm detects systemic inflammatory response in premature infants with late-onset sepsis and necrotising enterocolitis	Research methods	14.02.2020
170	Zea-Vera, A.-/	2015	Challenges in the diagnosis and management of neonatal sepsis.	Research methods	14.02.2020
306	Zeitoun, A. A.	2010	Evaluation of neutrophilic CD64, interleukin 10 and procalcitonin as diagnostic markers of early- and late-onset neonatal sepsis	Research methods	14.02.2020
211	Zeng, M.-//-G	2014	Value of serum procalcitonin and interleukin-6 in patients with bullous impetigo and staphylococcal scalded skin syndrome	Research methods	14.02.2020
231	Zhao, Z.-//-Sh	2013	Translational biomedical informatics and computational systems medicine	Research methods	14.02.2020
479	Zhou, M.-//-C	2015	Interleukin-8 for diagnosis of neonatal sepsis: a meta-analysis	Research methods	14.02.2020
354	Zohrer, E.-//-I	2018	Neonatal sepsis leads to early rise of rare serum bile acid tauro-omega-muricholic acid (TOMCA)	Research methods	14.02.2020
140	Zohrer, E.-//-I	2016	Serum bile acids in term and preterm neonates A case-control study determining reference values and the influence of early-onset sepsis		14.02.2020
374	Zolakova, B.-/	2016	Soluble receptor for advanced glycation end products in late-onset neonatal infection	Research methods	14.02.2020
17	Zollkau, J.-//-	2019	PEONS-CAAP48-Evaluation of C-terminal alpha-1 Antitrypsin peptide (CAAP48) as a putative biomarker to assess Early-Onset Neonatal Sepsis (EONS) after maternal Preterm Premature Rupture of membrar	Research methods	14.02.2020
44	Zonda, G. I.-//	2019	Endocan - A potential diagnostic marker for early onset sepsis in neonates	Research methods	14.02.2020
18	Zonneveld, R.	2018	Serum concentrations of endothelial cell adhesion molecules and their shedding enzymes and early onset sepsis in newborns in Suriname	Research methods	14.02.2020

Code	Author(s)	Year	Title	Exclusion critera	Date
659	Barnette, B.-//-Wynn, J. L.-//-Lawrence, S.	2020	Independent evaluation of the neonatal sequential organ failure assessment score with direct comparison to hero technology	Method	01.03.2020
660	Bilg, A.-//-Choi, M.-//-Tewari, S.-//-Chan, B.-//-Anis, S.-//-Luu, J.-//-Afghani, B.	2020	Comparison of procalcitonin and C-reactive protein (CRP) in neonatal bacterial sepsis	Method	01.03.2020
656	Handke, J.-//-Piazza, O.-//-Larmann, J.-//-Tesoro, S.-//-De Robertis, E.	2020	Presepsin as a biomarker in perioperative medicine	Method	01.03.2020
655	He, Y.-//-Chen, J.-//-Liu, Z.-//-Yu, J.	2020	Efficacy and safety of applying a neonatal early-onset sepsis risk calculator in China	Method	01.03.2020
658	Liu, G.-//-Liu, W.-//-Guo, J.	2020	Clinical significance of miR-181a in patients with neonatal sepsis and its regulatory role in the lipopolysaccharide-induced inflammatory response	Method	01.03.2020
653	Saleeh, A.-//-Fouad, M.-//-Mosbah, B. E.-//-Khashana, A.	2020	Activin A is a novel biomarker in early screening of neonatal sepsis	Method	01.03.2020
652	Sharma, A.-//-Thakur, A.-//-Bhardwaj, C.-//-Kler, N.-//-Garg, P.-//-Singh, M.-//-Choudhury, S.	2020	Potential biomarkers for diagnosing neonatal sepsis	Method	01.03.2020
654	Zonda, G. I.-//-Zonda, R.-//-Cernomaz, A. T.-//-Paduraru, L.-//-Grigoriu, B. D.	2019	Endocan serum concentration in uninfected newborn infants	Method	01.03.2020
657	Zonda, G. I.-//-Zonda, R.-//-Cernomaz, A. T.-//-Paduraru, L.-//-Avasiloaiei, A. L.-//-Grigoriu, B. D.	2019	Endocan - A potential diagnostic marker for early onset sepsis in neonates	Method	01.03.2020

Code	Author(s)	Year	Title	Exclusion critera	Date
671	Cantey, J. B.-	2020	C-Reactive Protein Testing in Late-Onset Neonatal Sepsis: Hazardous Waste	Method	01.04.2020
670	Chambers, S	2020	A Solution to Antifolate Resistance in Group B Streptococcus: Untargeted Metabolomics Identifies Human Milk Oligosaccharide-Induced Perturbations That Result in Potentiation of Trimethoprim	Human milk	01.04.2020

Code	Author(s)	Year	Title	Exclusion critera	Date
675	Bourika, V.-/	2020	Clinical Value of Serum Amyloid-A Protein, High-density Lipoprotein Cholesterol and Apolipoprotein-A1 in the Diagnosis and Follow-up of Neonatal Sepsis	Method	01.05.2020
677	Bunduki, G. H	2020	The usefulness of C-reactive protein as a biomarker in predicting neonatal sepsis in a sub-Saharan African region	Method	01.05.2020
680	Fanos, V.-//-	2018	Neonatal sepsis in neonatology: Conventional and emerging biomarkers	Method	01.05.2020
678	Liu, L.-//-Wa	2020	Identification of Potential Biomarkers in Neonatal Sepsis by Establishing of a Competitive Endogenous RNA Network	Method	01.05.2020
679	Majors, C. E.	2017	Point-of-care diagnostics to improve maternal and neonatal health in low-resource settings	Method	01.05.2020
674	Tunc, T.-//-P	2020	Assessment of novel biomarkers: STREM-1, pentraxin-3 and pro-adrenomedullin in the early diagnosis of neonatal early onset sepsis	Method	01.05.2020
676	Bardanzellu,	2020	How could metabolomics change pediatric health?	Review	01.05.2020

Code	Author(s)	Year	Title	Exclusion critera	Date
691	Cortes, J. S.,	2020	Interleukin-6 as a Biomarker of Early-Onset Neonatal Sepsis	No metabolomics, Method	01.07.2020
692	Kacerovsky, M	2020	Antibiotic administration reduces the rate of intraamniotic inflammation in preterm prelabor rupture of the membranes	No metabolomics, Method	01.07.2020

Code	Author(s)	Year	Title	Exclusion critera	Date
694	Yang, K. D., Y	2020	Identification of progranulin as a novel diagnostic biomarker for early-onset sepsis in neonates	Method	01.08.2020
695	Fievet, N., S.	2020	SEPSIS project: a protocol for studying biomarkers of neonatal sepsis and immune responses of infants in a malaria-endemic region	Protocol	01.08.2020
696	Spacova, I., H	2020	Future of Probiotics and Prebiotics and the Implications for Early Career Researchers	Not metabolomics, method	01.08.2020
697	Tosson, A. M	2020	Evaluation of the S100 protein A12 as a biomarker of neonatal sepsis	Method	01.08.2020
698	Molloy, E. J.,	2020	Neonatal sepsis: need for consensus definition, collaboration and core outcomes	Study design	01.08.2020
699	McGovern, M	2020	Challenges in developing a consensus definition of neonatal sepsis	Study design	01.08.2020

APPENDIX 9

FULL-TEXT ARTICLES EXCLUDED

Code	Author	Year	Title	Inclusion	Exclusion	Explaination	GRADE
478	Asci, A.-//-Surmeli-O	2015	Oxidant and antioxidant status in neonatal proven and clinical sepsis according to selenium status	05.02.2020	02.04.2020	Spectometry, looked at oxidant/antioxidant status, selenium and selenoproteins (SePP)	
489	Aydemir, O.-//-Ozcar	2015	Asymmetric dimethylarginine and L-arginine levels in neonatal sepsis and septic shock	05.02.2020	02.04.2020	Serum ADMA and L -arginine levels were measured by ELISA	
576	Buhimschi, C. S.-//-B	2009	Using proteomics in perinatal and neonatal sepsis: hopes and challenges for the future	05.02.2020		Review	
549	Buhimschi, C. S.-//-B	2011	Proteomics mapping of cord blood identifies haptoglobin "switch-on" pattern as biomarker of early-onset neonat	05.02.2020	Included	Mass spectrometry	
563	Buhimschi, I. A.-//-Bu	2010	The role of proteomics in the diagnosis of chorioamnionitis and early-onset neonatal sepsis	05.02.2020		Review	
221	Cannon, D. C.-//-Ohl	2014	Focused proteomic profiling for rapid detection of late-onset neonatal sepsis in preterm infants	12.02.2020	02.04.2020	Abstract	
201	Cao, Z.-//-Robinson,	2014	The role of proteomics in understanding biological mechanisms of sepsis	12.02.2020	02.04.2020	Review	
411	Coutinho, F. G.-//-Di	2018	Assessment of oxidative damage and enzymatic antioxidant system activity on the umbilical cord blood and saliva	12.02.2020		Spectrophotomy	
205	Dessi, A.-//-Liori, B.-/	2014	Monitoring neonatal fungal infection with metabolomics	12.02.2020	Included	Fungal sepsis	Very low
500	Fanos, V.-//-Caboni,	2014	Urinary (1)H-NMR and GC-MS metabolomics predicts early and late onset neonatal sepsis		Included		Very low
218	Fanos, V.-//-Stronati,	2014	Metabolomics in the diagnosis of sepsis	14.02.2020	02.04.2020	Review	
443	Ludwig, K. R.-//-Hum	2017	Mass spectrometry for the discovery of biomarkers of sepsis	14.02.2020	02.04.2020	Review	
417	Mani, S.-//-Cannon, I	2017	Protein biomarker druggability profiling	14.02.2020		Not looking at metabolomics in regards of diagnostic	
440	Sarafidis, K.-//-Chatz	2017	Urine metabolomics in neonates with late-onset sepsis in a case-control study	14.02.2020	Included		Low/very low
140	Zohrer, E.-//-Resch, E	2016	Serum bile acids in term and preterm neonates A case-control study determining reference values and the influen	14.02.2020		Serum bile, not metalobis	
			Included FROM Review				
	Mickiewicz et al	2013	Metabolomics as a Novel Approach for Early Diagnosis of Pediatric Septic Shock and Its Mortality				Very low