Accepted: 9 April 2021

DOI: 10.1111/apa.15874

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REVIEW ARTICLE

Metabolic responses in neonatal sepsis—A systematic review of human metabolomic studies

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Funding information
No specific funding was secured for this systematic review.

Abstract

Aim: To systematically review human metabolomic studies investigating metabolic responses in septic neonates.

Methods: A systematic literature search was performed in the databases MEDLINE, EMBASE and Cochrane library up to the 1st of January 2021. We included studies that assessed neonatal sepsis and the following outcomes; (1) change in the metabolism compared 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. PROSPERO ID: CRD42020164454.

Results: The search identified in total 762 articles. Fifteen articles were assessed for eligibility. Four studies were included, with totally 78 neonates. The studies used different diagnostic criteria and had between 1 and 16 sepsis cases. All studies with bacterial sepsis found alterations in the glucose and lactate metabolism, reflecting possible redistribution of glucose consumption from mitochondrial oxidative phosphorylation to the lactate and pentose phosphate pathway. We also found signs of increased oxidative stress and fatty acid oxidation in sepsis cases.

Conclusion: We found signs of metabolomic signatures in neonatal sepsis. This may lead to better understanding of sepsis pathophysiology and detection of new candidate biomarkers. Results should be validated in large-scale multicentre studies.

KEYWORDS
newborn infant, metabolomics, neonatal sepsis

Key notes

- This is a systematic review of human metabolomic studies investigating metabolic responses in neonates with sepsis compared with healthy control infants.
- Publications up to January 2021 were reviewed and four case-control studies with 78 neonates were included.
- Sepsis cases showed alterations in the glucose and lactate metabolism, and signs of increased oxidative stress and fatty acid oxidation. Larger studies are needed to validate the metabolomic signatures in neonatal sepsis.

Abbreviations: 1D ^{1}H NMR, one-dimensional (1D) ^{1}H nuclear magnetic resonance; ^{1}H-NMR, proton nuclear magnetic resonance; BW, birth weight; GA, gestational age; GC-MS, gas chromatography mass spectrometry; LB, live-born; LC-MS/MS, liquid chromatography tandem mass spectrometry; LOS, late-onset sepsis; MeSH, medical subject headings; MS, mass spectrometry; NMR, nuclear magnetic resonance; SIRS, systemic inflammatory response syndrome; VLBW, very low birth weight.

1 | INTRODUCTION

Neonatal sepsis is a serious and potentially fatal condition. Globally, around 2% of all live-born infants develop sepsis within 28 days of life, with an estimated sepsis-attributable case mortality of 11%–19%.[1] In high-income countries, neonatal sepsis is also a serious threat, in particular to preterm infants.[2] However, unlike in adults[3] there is no undisputable uniform definition for neonatal sepsis.[4] This hampers comparison of studies and limit our pathophysiological understanding. Isolation of a pathogen in a microbiological culture of blood or cerebrospinal fluid is by many considered the diagnostic 'gold standard'. Adjunctive, but imperfect biomarkers supporting a sepsis diagnosis include C-reactive protein (CRP), procalcitonin (PCT) and haematological indices. There has also been extensive research in other biomarkers, but currently there is no single biomarker or panel of markers to specifically diagnose neonatal sepsis.[5–10]

Immunometabolism is an emerging field recognising the complex interactions between the metabolism and the immune system both in infections and other diseases. Recent studies suggest that sepsis simultaneously induces both hyper- and hypo-inflammatory responses.[11] Moreover, some studies report a correlation between early deaths and an acute hyper-inflammatory phase, whereas late deaths are associated with a prolonged immunosuppression and recurrent infection.[12,13] Sepsis causes a dysregulation of the metabolome by inducing hypoxia, oxidative stress and high energy demand. Metabolomics can characterise the normal state of neonates and the metabolic state during sepsis, also in the hopes of identifying novel biomarkers/biomarker panels.[14,15]

We have performed a systematic review of publications evaluating the metabolomic response in neonates with sepsis. Our aim was to characterise metabolome patterns during infection, and how this can be used to better understand sepsis pathophysiology and possibly increase diagnostic accuracy of neonatal sepsis.

2 | METHODS

This systematic review is registered in the international prospective register of systematic reviews; PROSPERO ID: CRD42020164454.

2.1 | Search strategy

We developed our search strategy in consultation with a librarian. The search for articles was performed in the high-quality databases MEDLINE, EMBASE and the Cochrane library up to 1 January 2021. The first search was conducted by combining the MeSH terms 'Neonatal sepsis' and 'Metabolomics', with additional appropriate free text search words (Figure S1). 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. We examined reference lists of included studies and relevant reviews to identify additional eligible studies. Identified studies were collated and duplicates/triplicates were manually removed. We did not perform searches in the 'grey literature', that is unpublished studies, non-peer reviewed studies and abstracts and studies not indexed in high-quality databases.

2.2 | Study selection and eligibility criteria

Inclusion criteria were term born neonates (age 0–28 days) or preterm neonates up to 44 weeks postmenstrual age with a systemic infection and evaluated with metabolomic profiling using one of the following techniques: nuclear magnetic resonance spectrometry (^{1}H-NMR), gas chromatography mass spectrometry or liquid chromatography tandem mass spectrometry. In the registered research protocol, we intended to compare metabolomic response between infected neonates and healthy controls, and also to compare metabolomic response with traditional diagnostic tools.

All clinical trials (randomised and non-randomised), 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 reviews were not included. Full-text was read for studies eligible for inclusion to verify its suitability for the study.

2.3 | Screening, data extraction and management

The screened titles and abstracts were independently considered for eligibility by two researchers (A.U.B. and H.N.G.) according to predetermined inclusion and exclusion criteria, while a third author (C.K.) had the decisive vote. We extracted the following information from included studies: study name/article, authors, year of publication, journal and full reference details, country, study design, participants, setting, investigations including metabolomics and traditional diagnostic tools, main results, risk of bias and statistical methods.

2.4 | Assessment of methodological quality

The Newcastle-Ottawa Scale (NOS) was viewed appropriate to assess quality of the included studies. The NOS for case-control studies uses a 'star system' to judge articles on three broad perspectives: the selection of the study groups (maximum four stars), the comparability of the groups (maximum two stars) and the exposure (maximum three stars); highest quality score being nine stars.[16] Two authors (A.U.B and H.N.G) undertook this assessment independently and compared the findings. Disagreements were discussed with C.K.

3 | RESULTS

3.1 | Overview of included studies

The systematic search in this review (Figure 1) resulted in the inclusion of four peer-reviewed publications,[17–20] summarised in Table 1. The results were not possible to meta-analyse, therefore a narrative (descriptive) synthesis was conducted. Seventy-eight neonates were included in this systematic review; 33 with confirmed or possible infection and 45 healthy controls.[17–20]

Three publications reported only data from neonates.[18–20] Mickiewicz et al.[17] included seven neonates with sepsis, but also infants and older children with sepsis. In this publication, neonates and infants were analysed together and the authors found, by using partial least squares discriminant analysis that the ^{1}H-NMR metabolomic profile could discriminate between septic and healthy control patients. However, data on specific metabolites were only reported for the infant group. We decided to include the 'infant group' (age 1 month up to 1 year) in our qualitative analysis, because neonates in this study shared similar characteristics to infants in their metabolomic profile during sepsis. This was supported by the main study finding, reporting specific differences in metabolomic profile during sepsis mainly between school age children and those younger. The overall findings among children, including neonates, in this study was very clear separation between sepsis and healthy controls. Different metabolomic investigational tools were applied across all four studies (Table 1). Sarafidis et al.[20] used a combination of targeted and untargeted metabolomics (Figure 2) for the purpose of internally validating the metabolomic results. This was not done in the other included studies.

3.2 | Quality assessment

All four included case-control studies were small. The number of neonates with sepsis evaluated with metabolomics varied from one to 16 and the number of controls varied from 13 to 16 for each study. Methodological quality assessment evaluated using the Newcastle-Ottawa scale is presented in Table 2. We considered gestational age (main confounder), postnatal age and the Apgar scores (proxy for perinatal asphyxia) and mode of feeding as the most important potential confounding factors when assessing the comparability between cases and controls. All studies used non-infected infants recruited in the hospital as the healthy controls. We rewarded with one star if the controls were collected from a well-described healthy population from a hospital setting.

3.3 | The metabolomic profiling in the four included studies

All four studies showed alterations in glucose metabolism, and three studies showed alterations in lactate and maltose metabolism, when comparing sepsis cases with healthy controls (Table 1). Overall, we did not find any other distinct metabolomic patterns reported

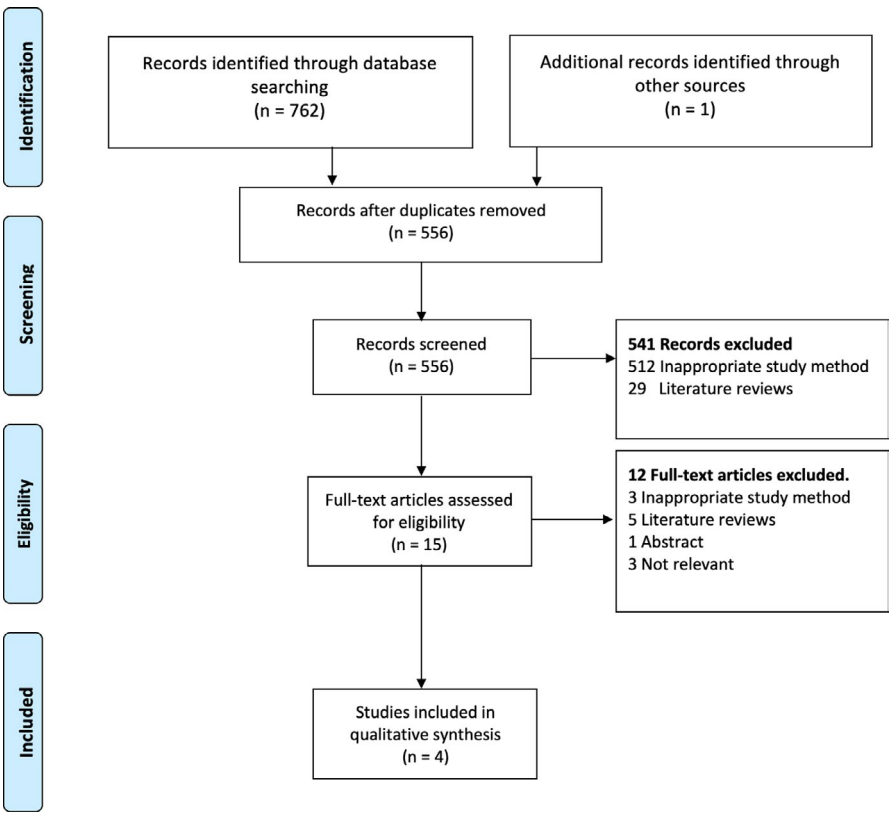

FIGURE 1 Prisma flow diagram of selected articles

TABLE 1 Summary of included studies using metabolomics, and main results in sepsis cases

Study/Country	Material and methods	Study population	Comment	Main results in sepsis cases
Mickiewicz, 2013 Canada	Serum ^{1}H NMR	• Septic shock, neonates (*n* = 5) • SIRS/ICU, neonates (*n* = 2) • Septic shock, infants (*n* = 21) • SIRS/ICU, infants (*n* = 13) • Healthy control infants (*n* = 13)	Samples were collected within 24 h of admission to the PICU, or within 24 h of diagnosis for septic shock patients	• **Increased**: 2-hydroxybutyrate, 2-hydroxy- isovalerate, 2-oxoisocaproate, creatinine, glucose and lactate • **Decreased**: 2-Aminobutyrate, acetate, adipate and threonine
Dessì, 2014 Italy	Urine GC-MS	• Fungal sepsis (*n* = 1) • Healthy control (*n* = 13)	Urine samples were collected at 36 h, day 7-14-21-28	• **Increased**: D-glucose, L-threonine, maltose, N-glycine and D-serine • **Decreased**: Citric acid, hexadecanoic acid and octadecanoic acid
Fanos, 2014 Italy	Urine GC-MS and ^{1}H NMR	• Sepsis, neonates (*n* = 9) • Healthy controls (*n* = 16)	Sepsis cases were both EOS (*n* = 5) and LOS (*n* = 4). Samples collected at birth and at regular intervals during the first month of life	• **Increased GC-MS**: Glucose, lactate and maltose • **Decreased GC-MS**: Ribitol, ribonic acid, pseudo uridine, 2,3,4-trihydroxybutyric acid, 2-ketogluconic acid, 3,4-dihydroxybutanoic acid and 3,4,5-trihydroxypentanoic acid • **Increased ^{1}H-NMR**: Acetate, acetone, glycine, lactate and glucose • **Decreased ^{1}H-NMR**: Citrate and creatinine
Sarafidis, 2017 Greece	Urine ^{1}H NMR and LC-MS/MS	• Confirmed LOS, neonates (*n* = 9) • Possible sepsis, neonates (*n* = 7) • Healthy control neonates (*n* = 16)	All sepsis cases (*n* = 16) were serially evaluated on day 0, day 3 and day 10, thus covering both the acute phase and the recovery phase of sepsis Samples from healthy controls were collected at the same time intervals after enrolment in the study	• **Increased (^{1}H-NMR) day 0**: Glucose, maltose, biotin, methylamine, inosine, methylguanine, creatine, myoinositol and quinolinic acid • **Decreased (^{1}H-NMR) day 0**: None reported. • **Increased (LC-MS/MS) day 0:** Valine, phenylalanine, taurine, aminobutyric acid, isoleucine, glutamic acid, hypotaurine, pyruvic acid, lactic acid, glucose and insosine • **Decreased (LC-MS/MS) day 0**: Trimethylamine-N-oxide, fumaric acid, hippuric acid, nicotinamide, riboflavin and thiamine Underlined metabolites significantly increased/decreased also on day 3, but the overall trend for ^{1}H-NMR and LC-MS/MS was that metabolic alterations in sepsis vs. controls were less different on day 3 and 10

Abbreviations: ^{1}H NMR, proton nuclear magnetic resonance; EOS, early-onset sepsis; GC-MS, gas chromatography mass spectrometry; ICU, intensive care unit; LC-MS/MS, liquid chromatography tandem mass spectrometry; LOS, late-onset sepsis; SIRS, systemic inflammatory response syndrome.

across all four studies (Table 3). However, clearly some of the metabolites that were increased or decreased during sepsis in all studies were connected to the same metabolomic pathways, such as the mitochondrial oxidative phosphorylation, the pentose phosphate pathway and the glycolysis or involved in oxidative stress and fatty acid oxidation.[17–21] None of the four studies evaluated the diagnostic value of metabolomics compared to traditional diagnostic tools like CRP, PCT or cytokine responses.

4 | DISCUSSION

4.1 | Key findings

Metabolomic studies allow an exact evaluation of individual metabolic responses to pathophysiological stimuli, potentially useful for early diagnosis and management of many neonatal conditions.[22] Characterising the ontogeny of immunometabolism has recently been put forward as promising opportunity to prevent, diagnose and treat neonatal sepsis.[21] In our systematic review, we identified four case-control studies with a total of 78 neonates characterising the metabolic responses in sepsis. The most salient findings were alterations in glucose, lactate, 2-hydroxybutyrate and acetate metabolism during neonatal sepsis. Moreover, the different studies detected alterations in an array of metabolites that could be connected to similar metabolomic pathways. A large study assessing analytes (MS/MS) in dried blood spots (DBS) in a newborn screening programme and linking these data to neonatal sepsis cases was not included as timing of onset of sepsis was not documented, and sepsis may have occurred prior to or weeks after the DBS was obtained.[23]

Neonates with sepsis often display disturbances in glucose metabolism, both hypo- and hyperglycaemia, the latter observed in all studies in our review.[17–20] In particular, hyperglycaemia may be an important early sign of late onset sepsis in preterm infants,[17,20] reflecting both the redistribution of glucose consumption from mitochondrial oxidative phosphorylation to the lactate and pentose phosphate pathway, and due to upregulated glycolysis in hyperinflammatory cells.[18] Repeated blood glucose measurements for sepsis evaluation are, however, not feasible due to disadvantages of discomfort and stress for the neonate. Moreover, the association between a single finding of hyperglycaemia or glucosuria is too weak to be of diagnostic value.[24] Still, our findings support the concept that level of glucosuria or hyperglycaemia are relevant components in a future (urine or blood) panel of metabolites suggestive of sepsis. Continuous glucose monitoring, with algorithms detecting, for example mean amplitude of glycaemic excursions, may in the future also become adjunctive tools for improved sepsis detection.[25,26]

In adults, a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation is used to identify septic shock.[3,27] In children and neonates, lactate is neither sensitive nor specific for diagnosing sepsis, but mainly used to determine sepsis severity and as an indicator of organ dysfunction in patients with septic shock. Additionally, serial measurements may be useful in monitoring treatment, but lactate concentrations often do not increase until late in the sepsis continuum.[28] In our systematic review, lactate was increased in the sepsis group in three studies,[17,18,20] but not in the single fungal sepsis case, described by Dessì et al.[19] Our finding is in line with reports showing that aerobic glycolysis sustains the energy requirements for the activated immune cells.[29,30] Recently, this process has also been shown to alter the metabolism in a way that promotes changes in the immune cell's phenotype.[31–35] Even though a single lactate value is of limited prognostic value, greater lactate production than clearance ('lactate kinetics') may be significant despite an initial normal value.[36] Overall, our findings support that measures of lactate metabolism should be incorporated in metabolic panels for sepsis. Indeed, the neonatal sepsis criteria suggested by a working group in the European Medicine Agency,[37] and later also evaluated in the study on late-onset sepsis,[38] includes metabolic alterations in glucose and lactate values. However, the sensitivity for sepsis when only using the suggested cut-off values is low.[38]

We observed in two studies[17,20] elevated levels of 2-oxoisocaproate, creatine, creatinine and phenylalanine; metabolites associated with decreased energy supply and organ failure during the hypo-inflammatory phase of sepsis.[39–41] There is a likelihood that the two studies illustrate the same metabolomic process, but have identified different metabolites. We also observed increased levels of the organic acid 2-hydroxybutyrate[17] and alterations in threonine metabolism.[17,19] These metabolites are parts of hepatic metabolomic pathways associated with increased lipid oxidation and oxidative stress. The metabolite 2-hydroxybutyrate is also an early marker for insulin resistance,[19,42] which often occurs during sepsis. Alterations in acetate levels may reflect increased fatty acid oxidation.[43] Through beta-oxidation, fatty acid chains are broken down to acetate molecules, which combined with CoA, form acetyl-CoA and enters the Krebs-cycle as energy substrates. Lipolysis is known to provide fuel for endotoxin-tolerant hypo-inflammatory immune cells.[43] The 'acetate switch' hypothesis may explain diverging results regarding increased[18] or decreased[17] acetate levels during phases of sepsis.[44] Finally, increased levels of branched-chain 2-oxo acids (eg 2-oxoisocaproate) as observed by Mickiewicz et al.[17] have been associated with dysmyelinating changes in the central nervous system after prolonged exposure.[45]

4.2 | Strengths and limitations

The primary strength of this study is our rigorous and sensitive search strategy based on a previously registered search protocol. Additionally, characterising the metabolic responses in neonatal sepsis is of great clinical and scientific interest in our urge to delineate pathophysiology and harmonise diagnostic criteria. The dynamic metabolic process during sepsis and the ambiguous clinical presentation of neonatal sepsis, makes it challenging to standardise key variables, but three studies in our systematic review provided adequate information about the diagnostic criteria for culture proven and culture negative neonatal sepsis.[17,19,20] All four studies used biological material (urine or blood/serum) that is well-established and often preferred for metabolomic studies.[46] Urine sampling is less invasive and thus an advantage given reliable and reproducible analytical results. However, urine also contains numerous metabolites originating from metabolised nutrients and drugs, while metabolites in blood derives from metabolism of endogenous substances.[47] Thus, sampling both body fluids would have provided complementary data. Sampling of saliva is also simple and non-invasive, and may in neonates become a promising matrix in future studies.[48]

This systematic review also has several limitations. First and most important, only four relatively small case-control studies were

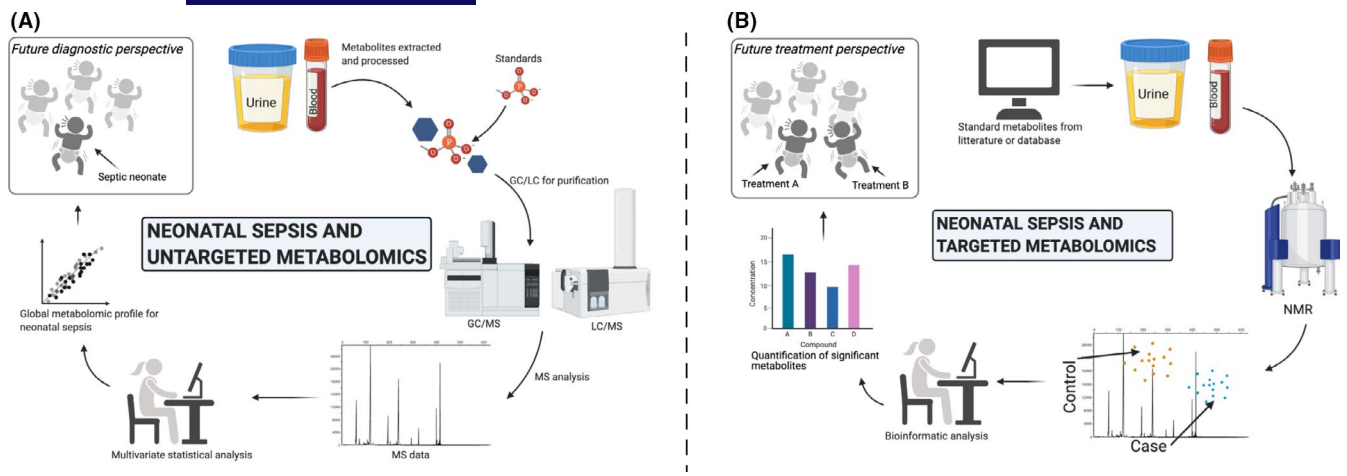

FIGURE 2 (A) Untargeted metabolomics with gas or liquid chromatography (GC/LC-MS); often considered as a 'Hypothesis-generating process'. Global analysis and relative quantification of a broad range of different types of metabolites including low-abundant metabolites and for the detection of lipid and volatile compounds. (B) Targeted metabolomics with ^{1}H-nuclear magnetic resonance (NMR) spectroscopy; often considered as a 'Hypothesis-driven process'. Absolute quantification of predetermined metabolites using commercially available spectral processing and analysis software

TABLE 2 The Newcastle-Ottawa Scale (NOS) for included studies

Perspective	Assessment	Mickewiecz (2013)	Dessì (2014)	Fanos (2014)	Sarafidis (2017)
Selection	Case definition			–	
	Representativeness		–	–	
	Selection of controls				
	Definition of controls		–	–	
Comparability	Cases and controls[a]	–		–	
Exposure	Ascertainment of exposure	–	–	–	–
	Same method cases & controls				
	Non-Response rate				–
Total score		6	5	3	7

[a]For each assessment domain, one star is maximum score, except Comparability where 2 stars is maximum score.

included and there was a large heterogeneity in study designs, outcomes, techniques and body fluid used for metabolomic profiling and methodological quality. Due to the limited sample size, any subgroup analysis based on causative pathogens was not possible. In one study, neonates and infants were analysed as one common group.[17] Even though this study reported similar metabolomic profiles in the sepsis cases below school age, a distinction between neonates and infants would have allowed an even more detailed assessment of the neonatal response. Observational studies are prone to biases and confounding, and in these small studies few attempts were made to adjust for confounding. Evidence from observational studies is usually considered to be of low quality. Second, the studies did not thoroughly record the time of day when sample were collected, and circadian variations may influence the metabolomic results. Third, the neonate's nutritional status was often not reported but should be carefully considered as, for example formula feeding greatly impacts plasma concentrations of threonine.[19,49] Only one study provided information about medications other than antibiotics.[19] There was also little information about the quality checks for the sampling material and stability of metabolites over time.[50] All this limit the quality of evidence regarding our report on significant alterations in metabolomic profiles during neonatal sepsis. None of the included publications evaluated the diagnostic value of metabolomics compared with traditional diagnostic tools.

4.3 | Implications for future research

Precision medicine led by the fields of the omics is reported to be the future of medicine, but there are still significant challenges to

TABLE 3 Trend of significant metabolites in the included studies

	Mickiewicz 2013	Dessì 2014	Fanos 2014	Sarafidis 2017
	Sepsis[a] vs. Healthy (infants)	Sepsis (fungal) vs Healthy	Sepsis[a] vs Healthy	Sepsis[a] vs Healthy (day 0)
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		↑		↑
D-serine		↑		
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				↑
Nicotiamide				↓
N-glycine		↑		
Octadecanoic acid		↓		
Pseudo uridine			↓	
Phenylalanine				↑
Pyruvic acid				↑
Quinolinic acid				↑

(Continues)

TABLE 3 (Continued)

	Mickiewicz 2013	Dessì 2014	Fanos 2014	Sarafidis 2017
	Sepsis[a] vs. Healthy (infants)	Sepsis (fungal) vs Healthy	Sepsis[a] vs Healthy	Sepsis[a] vs Healthy (day 0)
Ribitol			↓	
Riboflavine				↓
Ribonic acid			↓	
Taurine				↑
Thiamine				↓
Threonine	↓			
Trimethylamine-*N*-oxide				↓
Valine				↑

[a]The sepsis group contains both confirmed and possible sepsis, and the significant metabolites in one or both groups.

overcome. Untargeted metabolomics (Figure 2A) is useful for a hypothesis-free screening in order to discover novel compositions of metabolites in neonatal sepsis. However, by using untargeted metabolomics we cannot be certain of the metabolomic pathways activated during neonatal sepsis.[51–53] In contrast, targeted metabolomics (Figure 2B) can quantify identified metabolites and combined with bioinformatic analyses, activated metabolomic pathways during sepsis can be predicted.[54,55] Only a limited number of studies were identified in this systematic review. Translation of the hitherto identified metabolite biomarker panels for bedside diagnosis of neonatal sepsis thus remains unknown. MS/MS-based technologies are currently widely used in newborn screening of inborn errors of metabolism. The advantages of this technique using very small blood volumes extracted from DBS may pave the way to efficient metabolite-based biomarker diagnostic tests for neonatal sepsis.[56,57] The combined use of metabolomics with other omics techniques may also further enhance sensitivity and specificity for neonatal sepsis,[11,58] but it also requires powerful computer technology to interpret and present data in a meaningful way for clinicians.

5 | CONCLUSION

Alterations in glucose and lactate metabolism, and signs of increased oxidative stress and increased fatty acid oxidation were the most prominent findings. Metabolomic profiling of small volume samples of different body fluids combined with state-of-the-art bioinformatics holds promise to become powerful tools to evaluate and diagnose neonatal sepsis and may in the future lead to identification of potentially new treatment strategies. Candidate metabolomic biomarkers for neonatal sepsis, identified in this systematic review, need to be validated in large-scale multicentre studies.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Eirik Reierth for contributing during the development of our search strategy.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Bjerkhaug AU, Granslo HN, Klingenberg C. Metabolic responses in neonatal sepsis—A systematic review of human metabolomic studies. *Acta Paediatr.* 2021;00:1–10. https://doi.org/10.1111/apa.15874