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# Acute kidney injury in late-onset neonatal bacteraemia: The role of the neonatal sequential organ failure assessment tool in predicting kidney injury

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## ABSTRACT

**Introduction** Neonatal sepsis remains a leading cause of morbidity and mortality across all healthcare systems. Acute kidney injury (AKI) is common in neonates and is associated with poor clinical outcomes. We sought to profile the incidence of AKI in infants with culture-positive bacteraemia and to assess the utility of the neonatal sequential organ failure (nSOFA) tool in AKI prediction.

**Methods** A single-centre retrospective review of infants with culture-positive bacteraemia was performed at the Rotunda Hospital, Dublin, Ireland. Clinical, demographic and biochemical data were collated, with the modified neonatal Kidney Disease: Improving Global Outcomes (KDIGO) criteria and nSOFA scoring applied to each included patient.

**Results** Our cohort of n=35 patients with culture-positive bacteraemia had an AKI incidence of 48.6%. There was no statistically significant association between peak nSOFA and the development of AKI.

**Conclusion** The incidence of AKI in late-onset neonatal clinically significant bacteraemia is high. nSOFA within 24 hours of culture has poor utility in predicting acute kidney injury in neonatal patients with culture-positive bacteraemia.

### WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Neonatal bacteraemia remains a leading cause of morbidity and mortality, often leading to vital organ dysfunction. Prognostication of neonates with bacteraemia/sepsis has become an area of increasing interest in literature, with the advent of the neonatal sequential organ failure (nSOFA) assessment tool in 2019, showing prognostic potential to predict mortality.

### WHAT THIS STUDY ADDS?

⇒ This study presents a retrospective cohort of neonates with late-onset clinically significant bacteraemia, investigating the relationship between late onset bacteraemia and acute kidney injury (AKI), as well as the role of the nSOFA tool in AKI prediction.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

⇒ Broadening the scope of parameters included in nSOFA may lead to a scoring system that more accurately reflects kidney dysfunction in neonatal cohorts.

## INTRODUCTION

Neonatal bacteraemia remains a leading cause of morbidity and mortality, with premature infants comprising a significantly high-risk cohort due to immature immune regulation, poor epithelialisation and iatrogenic factors. Acute kidney injury is common in critically ill neonates and is associated with poor clinical outcomes.[1] Premature infants and infants who have a very low birth weight (VLBW) are particularly predisposed to episodes of AKI for a multitude of other reasons including: High insensible losses, low nephron endowment and patent ductus arteriosus, among others. Survivors of neonatal AKI are at risk of developing chronic kidney disease.[2]

Late-onset bacteraemia has been shown to affect 10%–30% of VLBW infants, with a mortality rate of up to 15%.[3–5] Consequential neonatal sepsis has deleterious effects on an infant's predisposition to AKI, owing to inflammation, nephrotoxic antimicrobial use, inotropic use and end-organ hypoperfusion.[4 6 7] Prognostication of neonates with bacteraemia/sepsis has become an area of increasing interest in literature, with the advent of the neonatal sequential organ failure (nSOFA) assessment tool in 2019, showing validated prognostic potential in infants under 33 weeks' gestation.[8 9] nSOFA incorporates haematological, cardiac and respiratory parameters to profile an infant's risk of subsequent organ failure. The markers

used are the need for mechanical ventilation, fraction of inspired oxygen, steroid exposure, presence of thrombocytopaenia and the use of vasoactive medications. There have been limited studies addressing the role of nSOFA in the prognostication of AKI in this patient population.

We hypothesised that the nSOFA assessment tool could predict AKI in neonates with clinically significant bacteraemia. Secondary outcomes were to assess the relationship between AKI in late-onset bacteraemia and death by discharge. We also aimed to test whether gram-negative bacteraemia was associated with AKI, moreso than Gram-positive bacteraemia.

## METHODS

We sought to ascertain whether an elevated nSOFA score was associated with AKI in infants with clinically significant late-onset bacteraemia. A retrospective cohort study was conducted at a tertiary neonatal intensive care unit, the Rotunda Hospital, Dublin, Ireland. All positive blood cultures taken from neonatal patients between 23 and 42 weeks' gestation over a 5-year period spanning quarter four (Q4) 2018 and Q4 2023 were reviewed.

Clinically significant late-onset bacteraemia was defined by the following criteria:

- Blood culture taken after 72 hours of life.
- Subjective clinical concern for serious infection (demonstrated by the taking of said culture and commencement of empiric antimicrobial agents).
- Clinically significant organism isolated from blood culture.

Coagulase-negative staphylococcus isolates were included if they were identified on serial cultures, or if antimicrobial therapy was continued for at least 5 days due to clinician concern for bacteraemia.

To avoid confounders which may contribute to impaired kidney function or accuracy of the dataset, the following exclusion criteria were applied:

- Congenital heart disease (excluding patent ductus arteriosus or patent foramen ovale).
- Congenital anomalies of the kidney or urinary tract (CAKUT).
- Hydrops fetalis.
- Chromosomal abnormality on genetic screening.
- Incomplete data due to transfer to alternate hospitals (repatriation to secondary units or transfer for specialist input in a national quaternary centre).

### Acute kidney Injury

AKI was defined in accordance with the modified neonatal Kidney Disease: Improving Global Outcomes (KDIGO) working group definition.[10] All serum creatinine values prior to and following an episode of culture-positive bacteraemia were reviewed, with each measurement compared with the lowest prior measurement to assess for an absolute rise from baseline. This methodology is increasingly accepted as the gold standard of neonatal AKI definitions and has been used in multiple high-impact studies on this topic.[1 11–13] The rationale for the comparison to the lowest prior serum creatinine is required due to the constantly evolving 'baseline' creatinine, with the normal physiological decline over the first months of life.

AKI definition by urinary output was also assessed, in keeping with the modified KDIGO standard. Urinary output was reported in 24-hour increments, with an average in millilitres per kilogram per hour used to measure for the presence of AKI. Details of AKI definition criteria by stage are outlined below (table 1).

If an infant did not have at least two serum creatinine measurements, or at least one day with quantifiable urine output, they were deemed to have insufficient data for diagnosis.

### Severity of illness

The nSOFA score was used to assess for severity of illness in infants included in this cohort. This is a tool which collates variables at multiple time points to characterise progressive organ dysfunction resulting in mortality.[8] nSOFA employs a categorical score with a range of 0–15 to describe changes in ventilatory support and fraction of inspired oxygen, the need for inotropic support and the presence/degree of thrombocytopaenia.

### Statistical analysis

All statistical analyses were performed on R statistical software (R-foundation for statistical computing). Base R package 'glm' was used to generate a binomial logistic regression

**Table 1** Modified neonatal KDIGO criteria for acute kidney injury diagnosis

| Stage | Serum creatinine | Urine output |
|---|---|---|
| 0 | No change or rise <0.3 mg/dL (26.5 micromol/L) | >1 mL/kg/hour |
| 1 | Rise greater than or equal to 0.3 mg/dL within 48 hours or 1.5–1.9× prior lowest creatinine value within 7 days | >0·5 and ≤ 1 mL/kg/hour |
| 2 | Rise greater than or equal to 2–2.9× prior lowest creatinine | >0·3 and ≤0·5 mL/kg/hour |
| 3 | Rise in creatinine greater than or equal to 3× reference or greater than or equal to 2.5 mg/dL or receipt of kidney replacement therapy | ≤ 0·3 mL/kg/hour |

KDIGO, Kidney Disease: Improving Global Outcomes.

Table 2 Cohort details

| Demographic | Value |
|---|---|
| Birth weight (g) | 887.5 (690–1272.25) |
| Gestation (weeks) | 27.07 (25.5–33.75) |
| Male | 18 (51.4%) |
| LSCS (Lower segment caesarean section) | 22 (62.8%) |
| Intrauterine growth restriction (<10$^{th}$ centile for gestational age) | 9 (25.7%) |
| Pre-eclampsia | 4 (11.4%) |
| Acute kidney injury (AKI) | 17 (48.6%) |
| Peak nSOFA | 2 (0–5) |
| Gestation at positive culture (weeks) | 30 (27.3–33.9) |
| Time of onset of AKI from onset of positive culture (days) | 2 (1–4) |
| Time to culture positivity from incubation (hours) | 12.5 (9.9–16.1) |
| Death by discharge | 11 (31.4%) |

Values listed with median (IQR), or count (%).
Gestational age and birth weight presented as median (IQR), rather than mean (standard deviation) following distribution testing.
nSOFA, neonatal sequential organ failure.

### Public and patient involvement

There was no public or patient involvement in the conduct of this study.

## RESULTS

A total of 46 positive cultures from n=44 patients were eligible for data extraction. Following the application of exclusion criteria, the final cohort comprised n=35 patients, with 36 defined late-onset clinically significant bacteraemia episodes. Four patients were excluded due to CAKUT, two for CCHD, one for hydrops fetalis, one for recurrence of GBS bacteraemia and one due to transfer to an alternate centre (incomplete data).

### Cohort demographics

The median gestation of the cohort was 27.1 weeks with an IQR of 25.5–30.1. The median birth weight was 887.5 g with an IQR of 690–1272.3. The median time of onset of AKI postculture positivity was 2 days with an IQR of 1–4). The median gestation at onset of bacteraemia was 30 weeks with an IQR of (27.3–33.9). The median time to culture positivity from incubation was 12.5 hours, with an IQR of 9.9–16.1. Data pertaining to the cohort and their outcomes are displayed in tabular format below (table 2). Ten of the cohort included had a diagnosis of necrotising enterocolitis during their NICU stay.

### Acute kidney injury

A total of 17 AKI episodes occurred across 35 patients with 36 episodes of culture-positive bacteraemia, representing an incidence of 48.5%. Eleven were KDIGO stage I, and six were KDIGO stage II AKI. Two of the AKIs were diagnosed based solely on serum creatinine, ten based solely on urinary output and five based on both urine output and serum creatinine.

### Gram staining

There were 36 cases of clinically significant late-onset bacteraemia events (arising in n=35 patients) in the cohort which underwent data analysis. The following organisms were identified: *Klebsiella pneumoniae* (n=9), *Escherichia coli* (n=8), *Staphylococcus aureus* (n=5), *Candida albicans* (n=3), *Streptococcus agalactiae* (n=3), *Staphylococcus epidermidis* (n=2), *Enterococcus faecium* (n=1), *Staphylococcus warnerii* (n=1) and *Serratia marcescens* (n=1). Two of the *K. pneumoniae*–infected patients were co-infected, one with *P. aeruginosa* and the other with *E. faecalis*. The patient with *E. faecium* bacteraemia also grew *S. liquefaciens*.

A Fisher's exact test was performed to ascertain whether there was an increased incidence of AKI with gram-negative bacteraemia compared with gram-positive bacteraemia. Three had candida, and two had a mixed gram-positive and gram-negative culture. As such, they were excluded from this subsection of analysis due to potential confounding. This left 18 episodes of gram-negative bacteraemia and 13 of gram-positive. There was no statistically significant difference in AKI incidence between the gram-negative and gram-positive cohorts, p=1.0, with an OR of 0.98 and a 95% CI of 0.17 to 5.3.

### Neonatal sequential organ failure assessment tool

There was no statistically significant association between peak nSOFA within the first 24 hours from blood culture and the development of AKI on univariate logistic regression with a p value of 0.3, OR 1.1 and 95% CI of 0.92 to 1.33.

When controlling for confounders (birth weight and gestation) with multivariate logistic regression, there was no significant association between peak nSOFA within the first 24-hours from blood culture and AKI (p value=0.4 with OR of 1.1 and a 95% CI of 0.89 to 1.35).

Those with AKI in the setting of late-onset clinically significant bacteraemia were found to have an association with the clinical outcome of death by discharge. Analysis was performed using binary logistic regression that controlled for birth weight and gestation (p value of 0.018, with an OR of 9.4 and a 95% CI of 1.68 to 77.9).

## DISCUSSION

This retrospective cohort of neonates with late-onset clinically significant bacteraemia investigates the relationship between late-onset bacteraemia and AKI, as well as the role of the nSOFA tool in AKI prediction. Within this sample, the prevalence of AKI among infants with late-onset bacteraemia was 48.5%. There was no proven association between peak nSOFA score and the occurrence of AKI on both univariate and multivariate regression

analysis controlling for birth weight and gestation. There is a statistically significant association between bacteraemia-induced AKI and death.

Bacteraemia can result in sepsis, which may contribute to organ dysfunction resulting in hypotension. Sepsis management typically includes the use of boluses, antimicrobials and often inotropic infusions to combat its physiological sequelae. Creatinine as a marker of kidney function poses challenges in neonatal physiology. Extremely low gestational age infants are particularly at risk of iatrogenic fluid overload, which can dilute serum creatinine, resulting in under-recognition of kidney injury. Bauer and Young in their work have addressed the concept of total body water and fluid balance in neonatal physiology.[14 15] Starr *et al* have proposed clinicians employ an approach of creatinine interpretation, taking into account the fluid balance of the neonate, with interesting depictions of creatinine trends, corrected for fluid status. They describe correcting serum creatinine with a factor created by measuring a child's % fluid overload (or hypovolaemia).[16] This approach has been taken by adult critical care colleagues for many years and merits consideration in the field of neonatal critical care.[17] Recent efforts have focused on the identification of novel biomarkers to identify kidney injury in the neonate, recognising the limitations of measurement in both urine output and creatinine in the premature infant. Serum Cystatin C has been studied and shows promise as a biomarker for neonatal AKI. It is an endogenously produced cysteine protease inhibitor that is not reabsorbed by the renal tubules. There is no transplacental carriage of maternal Cystatin C, nor is it influenced by age, sex or muscle mass.[18 19] Greater effort to integrate novel markers of neonatal kidney function into clinical practice is needed.

Our study outlines detailed longitudinal data of a cohort of infants with defined late-onset clinically significant bacteraemia. We acknowledge that this study has a number of limitations. Retrospective studies have an inherent risk of bias, which we addressed by employing stringent definitions of both AKI and late-onset bacteraemia. Ten of our cohort had a diagnosis of necrotising enterocolitis, which may act as a confounder as it has a known association with AKI in the neonatal population. nSOFA scores can have inter-centre variability and confounding due to local approaches to care, which may include lower intubation thresholds. Though single-centre studies are usually deemed weaker in the hierarchy of evidence, a strength in this case is the uniform clinical practice and the well-defined approach we took to labelling infants with a diagnosis of late-onset bacteraemia.

nSOFA itself has flaws in its' design, with regard to the prediction of kidney failure. Unlike its' paediatric and adult scoring counterparts, there are no measures of kidney, liver or central nervous system dysfunction included in the parameters used to calculate the score.[20] Broadening the scope of included parameters may lead to a scoring system that more accurately reflects organ dysfunction in this patient cohort. As discussed above, the role of Cystatin C as a potential marker in organ dysfunction modelling warrants exploration in future work. Binary logistic regression in smaller cohort studies poses challenges, and we note that logistic regression does overestimate ORs in smaller sample sizes.

## CONCLUSION

The incidence of AKI in late-onset neonatal clinically significant bacteraemia is high, with our cohort of infants displaying an AKI incidence of 48.6%. There is no difference between the incidence of AKI, comparing neonates with gram-negative bacteraemia to those with gram-positive bacteraemia. Peak nSOFA at 24-hours from culture showed poor utility in predicting AKI in neonatal patients with culture-positive bacteraemia. The inclusion of markers of kidney dysfunction in predictive models of neonatal organ dysfunction warrants further study.

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**Contributors** DW is the lead author and guarantor of this work. DW and DOR conceptualised the study. DW, DOR, EB, RJD, AA and MAB were involved in study design. DW, EB and DOR performed data collection and statistical analysis. All authors critically reviewed the manuscript for important intellectual content.

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**Data availability statement** Data are available upon reasonable request. Data from this cohort may be made available upon reasonable request, subject to the approval of the corresponding author and hospital ethics committee.



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