Official Journal of the Irish Medical Organisation

Ir Med J; April 2025; Vol 118; No. 4; P60
April 23rd, 2025

The Burden of Neonatal Late-Onset Sepsis: A Retrospective Review

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Abstract

Aim

Neonatal late-onset sepsis (LOS) causes significant morbidity and mortality, particularly amongst preterm infants. Clinical signs often mimic normal preterm physiology. The aims of this review were to describe predisposing risk factors, presenting signs and clinical course of affected infants within a tertiary neonatal unit.

Methods

This was a retrospective review of 37 infants with confirmed bloodstream or cerebrospinal infection (excluding coagulase-negative staphylococci) over a 46-month period.

Results

Sepsis resulted in mortality in 18 infants (49%), highest under 29 weeks' gestation. Gram-negative bacilli accounted for 24 (70.4%) cases, with 25 (73.6%) pathogens demonstrating antimicrobial resistance.

Desaturations and/or bradycardia were the most common presenting signs (11 cases, 29.7%). Fevers, tachycardia and hypotension occurred infrequently. Further deterioration occurred in 26 (70.3%) infants; 14 (53.8%) developed new respiratory signs, 10 (77%) with a new inotropic requirement died.

Chorioamnionitis did not appear to increase the likelihood of LOS, however pathogenic growth on placental or maternal swabs may predict LOS.

There was an increased need for mechanical ventilation and inotropic support following sepsis, and additionally higher incidence of meningitis, grade IV intraventricular haemorrhage and necrotising enterocolitis.

Discussion

The burden of LOS is high among infants in a neonatal unit. Awareness of the common presenting and deteriorating signs and risk factors may aid diagnosis.

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Introduction

Neonatal late-onset sepsis (LOS) is defined as the onset of infection after 72 hours of life.[1] There is significant morbidity and mortality associated with LOS, particularly amongst the preterm population, with increasing risk of poor outcomes amongst lower gestation and lower birth weight infants.[2] The clinical signs of LOS are varied and can mimic normal preterm physiology or non-infective pathologies, thus identifying and treating LOS in a timely manner poses a challenge to clinicians.[3,4] The aim of this study is to improve clinician recognition and treatment of suspected LOS by describing the predisposing risk factors, presenting signs and clinical course of affected infants within a large tertiary neonatal unit.

Methods

This was a retrospective single-centre review of infants diagnosed with invasive bacterial or fungal LOS in a Level 3 Neonatal Intensive Care Unit (NICU), excluding infants admitted from home, over a 46-month period, from January 2020 to October 2023. Inclusion criteria were infants with a confirmed bloodstream or cerebrospinal fluid (CSF) infection from 73 hours of life until discharge from the neonatal unit. Infection was defined a patient with clinical signs of infection, in addition the presence of bacterial or fungal organisms within a blood or CSF sample (via culture or molecular testing methods), or an elevated white cell count in CSF. Exclusion criteria were infants with detection of coagulase-negative staphylococci (CoNS) in blood culture or CSF, as these are typically due to a contaminant or catheter-associated infection., or viral infection detected through blood or CSF culture or molecular testing.

The aims of this study were four-fold; firstly, to describe the clinical signs that prompted a septic work-up, and any additional clinical signs that suggested the infant was deteriorating as a result of sepsis; secondly to identify antenatal or maternal risk factors that may have predisposed the infant to LOS; thirdly to evaluate the choice and timing of antimicrobial therapy and finally, to describe the subsequent morbidity and mortality of LOS within our cohort.

Laboratory records were reviewed to identify patients for inclusion. During the 46-month period, 593 blood cultures were collected; 120 of these were positive, including multiple repeat samples for a single patient. After repeat samples had been removed, 52 first positive cultures remained. Of these, 19 had a growth of CoNS and were excluded, leaving 33 first positive blood cultures for analysis. A total of 143 CSF samples were collected during the same time period, of these 9 had a positive growth on culture. Five of these samples had a growth of CoNS, with subsequent repeat CSF samples that demonstrated no growth, and were thus

excluded as this likely represented contamination with normal skin flora. Four positive samples remained for 3 patients. Two of these patients also had a positive blood culture so had been included for analysis already, thus 1 additional patient based on CSF culture was included. Finally, 3 additional patients with a high CSF white cell count, defined as 'greater than 30 white blood cells per $mm^{3'}$ and a 'white blood cell:red blood cell ratio of more than 1:500', without growth on CSF culture or detection on molecular testing, were identified for inclusion. Molecular testing was performed externally in reference laboratories.

Results

The electronic charts for a total of 37 infants were reviewed. Figure 1 summarises the recruitment process.

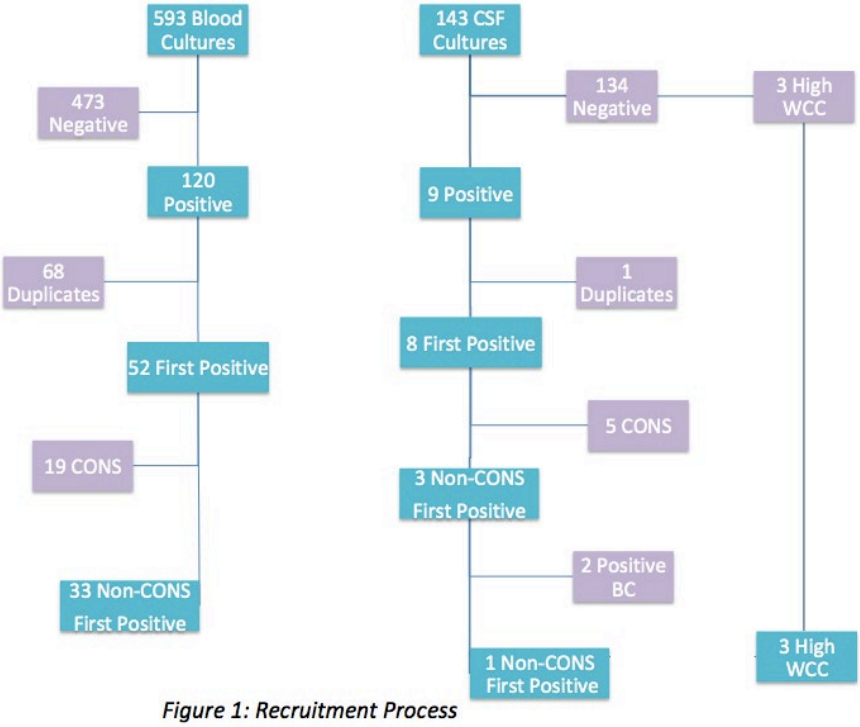

Figure 1: Recruitment Process

The median gestational age was 26.1 weeks (range 23.1 – 38.4 weeks) and median birth weight was 715g (range 450g – 4260g). The median age at onset of sepsis was day 8 of life (range day 4 – day 74). Eighteen babies died as a result, representing nearly half (49%) of the cohort. Of the fatal cases, 15 (83%) occurred in infants less than 29 weeks gestation. The majority of cultured pathogens (n=34) were gram-negative bacilli (24 cases, 70.4%), with *Escherichia coli* (*E. coli*) accounting for 10 cases (29.4%) of all infections. This incidence of gram-negative bacilli sepsis was even higher amongst the cohort of infants that died, accounting for 14 (77.7%) cases, 6 (33.3%) resulting from *E. coli.* Gram-positive bacteria

accounted for 9 (26.5%) cases and there was only one fungal (*Candida albicans*) infection identified. Figure 2 summarises the organisms identified.

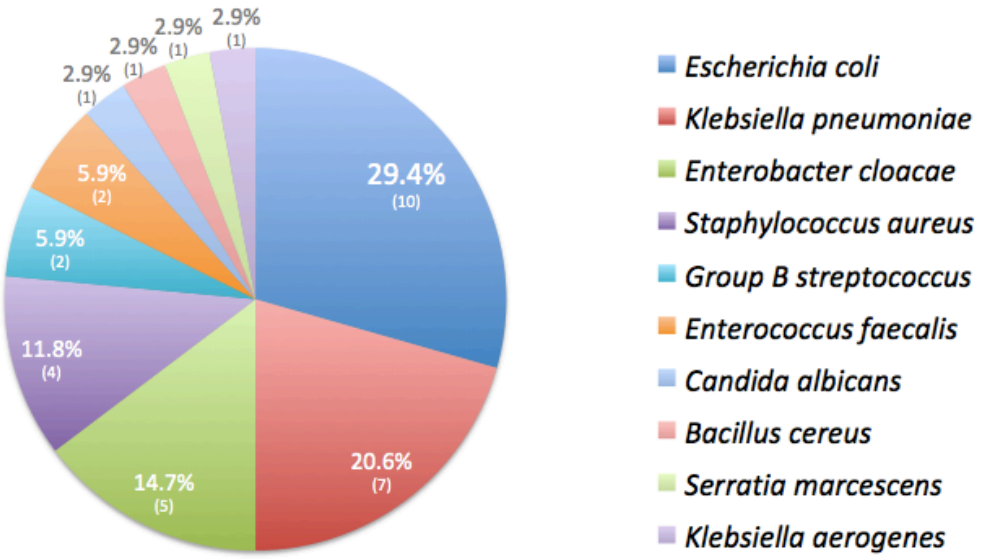

Figure 2: Causative Organisms (n=34)

In 25 cases, (73.6%) some form of antimicrobial resistance was identified, with 6 (17.6%) demonstrating multi-drug resistance, defined as resistance to one or more agents in three or more antimicrobial classes.[5, 6] Antimicrobial resistance included Extended-spectrum beta-lactamases (ESBLs) in 2 cases, and one case each of methicillin-resistant *Staphylococcus aureus (*MRSA*)*, Carbapenemase-producing *Enterobacteriaceae (*CPE*)*, gentamicin-resistant Gram-negative bacilli and AmpC beta-lactamases.

Choice of antimicrobial therapy varied, with 13 (35%) clinicians prescribing first-line antibiotics in accordance with local hospital policy, which recommends flucloxacillin and gentamicin as empiric management for NICU-acquired LOS with unknown source of infection. Cefotaxime, recommended in local antimicrobial guidelines for meningitis and ventilator associated pneumonia, used alone or in combination with other antimicrobials, was commenced first line in 20 (54%) cases, and meropenem, recommended in local antimicrobial guidelines for severe sepsis, was used alone or in combination in a further 3 (8%) cases. The majority (94%) of babies received their first dose of antibiotics within 1 hour after obtaining a blood culture. Antimicrobial therapy was escalated in 29 patients (78%), with the majority of prescription changes (21.6%) occurring 6-12 hours after the initial septic work-up.

Looking at the signs documented in the clinical notes as the indication for septic work-up, desaturations and/or bradycardias resulted in a work-up in 11 (29.7%) patients, whilst rising

oxygen requirements accounted for a further 9 (21.6%) cases. Five patients with apnoeas and a further 5 with pallor (13.5% each) had a work-up, with feed intolerance or seizures accounting for 4 (10.8%) cases respectively. Notably, classical signs of sepsis including fevers, tachycardia and hypotension were seen infrequently in our cohort.
Figure 3 summarises the signs at presentation.

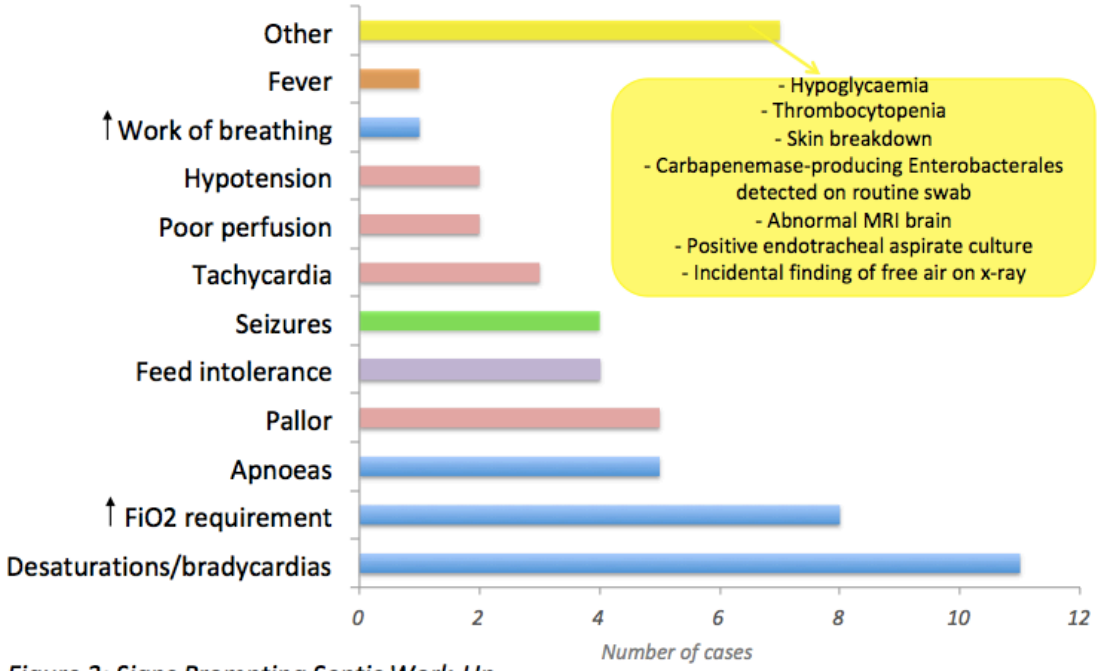

Figure 3: Signs Prompting Septic Work-Up

The frequency of the more common signs prompting septic work-up were similar amongst infants less than 29 weeks gestations compared to the overall cohort, however the majority (6 out of 7 cases, 85%) of the more unusual signs (recorded as 'other') occurred in those less than 29 completed weeks gestation.

A documented deterioration was seen in 26 babies (70.3%) following the initial septic work-up. Amongst this group, 14 (53.8%) presented with further respiratory signs (either rising oxygen requirement or need for ventilator support), 9 babies (34.6%) had cardiovascular instability requiring inotropic support, 3 (11.5%) had gastrointestinal features of feed intolerance, whilst a further 3 (11.5%) had seizures suggesting neurological involvement. Renal impairment was seen in one case, whilst hepatic impairment was not noted. Unfortunately, 77% of infants with a new requirement for inotropic support subsequently died.

Looking at the predisposing risk factors for LOS, 11 (29.7%) of cases had confirmed chorioamnionitis on placental histology, although no infant had a positive blood culture growth in the first 72 hours that would indicate early-onset sepsis. Amongst infants diagnosed

with sepsis on day of life 10 or less (n=23), 5 (21.7%) had placental swabs sent, and 10 (43%) mothers had vaginal and rectal swabs sent. In total, 4 swabs (36%) swabs yielded pathogenic growth. *E. coli* was isolated on 3 swabs and subsequently cultured in 2 cases. Group B Streptococcus (GBS) was detected on 1 swab and whilst the affected baby in this case had culture-negative meningitis, their MRI brain showed multiple punctate lesions suspicious for GBS meningitis. Central access was present in 21 babies (56.7%) at the time of septic work-up, with a median duration of 7 days since insertion. Sixteen patients (43%) had a peripheral intravenous cannula in situ with a median duration of 1 day since insertion. One quarter of these infants also had central access.

Finally, we reviewed the clinical condition of infants in the 48 hours before and after the episode of sepsis, the findings of which are summarised in Figure 4.

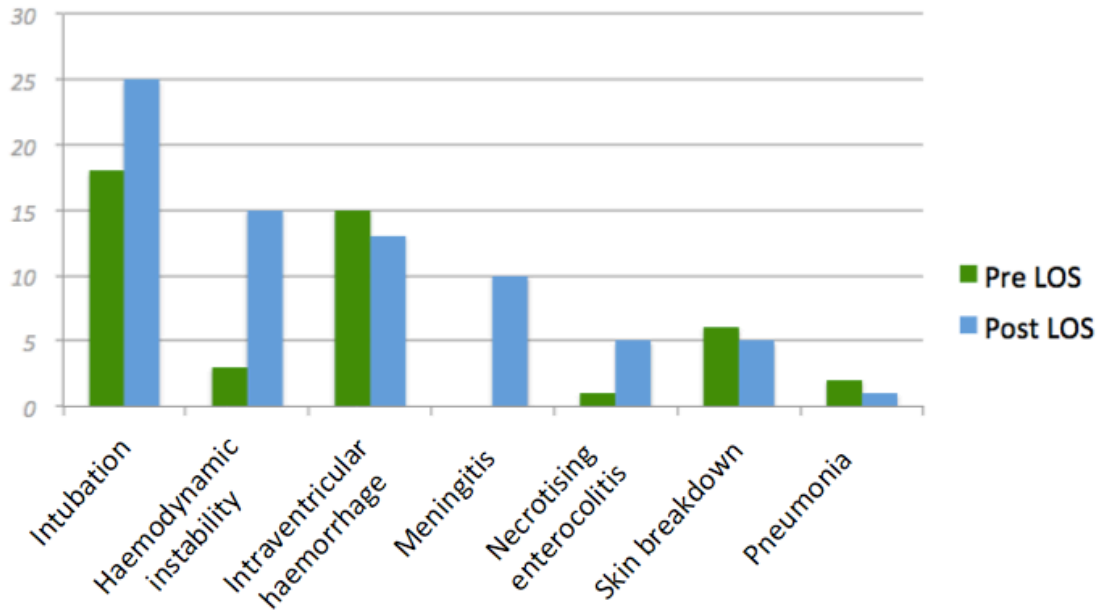

Figure 4: Clinical Status Pre and Post LOS

Notably the number of intubated infants increased by 19%, whilst those requiring inotropic support increased from 8% to 40%. Skin breakdown was documented in the clinical notes of 16% of infants before the onset of sepsis, although only 1 infant had a skin swab taken for analysis. Whilst no infant had been diagnosed with meningitis prior to their episode of sepsis, 6 infants developed confirmed meningitis, with a further 4 probable cases resulting from the sepsis episode. The rate of necrotising enterocolitis also increased in the 48 hours following diagnosis of sepsis, with 4 babies developing the condition. Although the overall incidence of intraventricular haemorrhage (IVH) did not increase, only one baby prior to deterioration had a diagnosis of grade IV IVH; this increased to 3 babies following deterioration. All of these examples highlight the burden of LOS on infants.

IMJ
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Discussion

The goal of this study was to better understand LOS in our NICU cohort with the hope of identifying areas for improvement in clinical practice or clinician education. Echoing previous research,[2] this review demonstrates the significant morbidity and mortality associated with neonatal LOS, in particular preterm and low birth weight infants.

Whilst antibiotic resistance is an ever-growing concern, reassuringly our susceptibility patterns show effective response to our local policy first-line agents of flucloxacillin and gentamicin. Only one pathogen was resistant to flucloxacillin (n=1 MRSA)and one strain of *E. coli* demonstrated resistance to gentamicin. Therefore, our current guidelines are appropriate in empiric treatment of the majority of pathogens.

Interestingly, however, first-line agents were used in only 35% patients, with broader spectrum agents being preferentially selected for the majority. Of the babies that died, only 4 infants (22%) were commenced on flucloxacillin and gentamicin as first line therapy. In contrast, 11 (61%) were commenced on cefotaxime, either monotherapy or in combination with other agents, and 3 infants (16%) received meropenem alone or combined with additional antibiotics. Many infants during their NICU admission will be investigated for LOS and treated with empiric flucloxacillin and gentamicin whilst awaiting blood or CSF results to rule out the diagnosis. However amongst this cohort of confirmed LOS, the early use of broader spectrum antimicrobials may suggest that clinicians are appropriately using their clinical acumen to identify a more unwell patient from the outset, and choosing to start a broader antimicrobial before results become available confirming a sepsis diagnosis.

Whilst timely escalation of antibiotics is crucial in a deteriorating infant, it is important to advocate for early de-escalation of broader spectrum cover after 24 to 48 hours if the baby shows clinical signs of improvement with a sterile blood or CSF culture. The inclusion of a dedicated microbiology ward round in the NICU may be beneficial to promote antimicrobial stewardship.

Staff awareness of the presenting signs of LOS is essential to identify and treat the infection as early as possible. Amongst our cohort, episodes of bradycardia, desaturations and apnoeas were the most common signs of sepsis. Normal preterm physiology also predisposes well infants to these clinical features as a result of their immature respiratory drive, thus presenting a diagnostic challenge for clinicians.[3,7] Our findings align with previous research in this area by Sullivan et al, who investigated the occurrence of these common respiratory

episodes between infants with confirmed sepsis and infants in whom sepsis was ruled out.[3] They found equal incidence between both groups, and cautioned the clinician against dismissing these episodes as normal physiology.

Perhaps surprisingly, tachycardia, hypotension, poor perfusion and fevers were seen infrequently amongst our cohort. Whilst these signs are often considered hallmarks of sepsis, our findings suggest they may occur less commonly than previously cited.[2] As discussed previously, given the importance of good clinical judgement when recognising and initiating treatment for sepsis, these distinctions are important to highlight. Amongst infants less than 29 weeks gestation, a wider variety of less common signs were observed, thus adding to the diagnostic challenge in this particularly vulnerable cohort.

This study sought to describe the burden of LOS amongst our neonatal population, and by reviewing charts over a comprehensive time frame we believe we have achieved this. We hope the results will enhance clinician awareness of the signs of LOS and provide reassurance to those deviating from antimicrobial guidelines in favour of clinical judgment. This study has benefited from interdepartmental collaboration between neonatology and microbiology to strengthen our protocols and recommendations.

Undoubtedly there are limitations to this study. This was a single-centre review; therefore, results may not be applicable to other neonatal units, especially those with different acuity levels and antimicrobial resistance. Despite evaluating a wide time period, the numbers of patients included were small and caution is required when interpreting these numbers and percentages. A larger multi-centre study to strengthen numbers and enable statistical analysis of results would be very beneficial.

Regardless, we hope the findings of this study will be beneficial to clinicians caring for at-risk infants. To summarise our recommendations, firstly we recommend early escalation and importantly de-escalation of antimicrobial therapy and secondly we would advocate for the inclusion of clinical microbiology on the NICU ward rounds. Clinicians must be aware of the varied clinical presentation of neonatal late-onset sepsis, and the significant mortality particularly in infants less than 29 weeks completed gestational age. It is hoped that these measures may reduce the burden of LOS, thus improving outcomes for our neonatal population.

Declarations of Conflicts of Interest:
None declared.

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