ORIGINAL RESEARCH

Evaluation of Neonatal Infections in the NICU over a 10-year Period

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Abstract

Background: Bacterial infections are a leading cause of morbidity and mortality in premature and critically ill neonates. In this quality-improvement (QI) study, we sought to characterize the bacterial infections in our neonatal intensive care unit (NICU).

Aim: Our aim was to determine whether the spectrum of bacteria causing neonatal sepsis and their antibiotic susceptibility was changing over time. This information is essential for optimizing the empirical antibiotic treatment protocols needed for treating suspected sepsis prior to identification of the bacterial isolates.

Materials and methods: We retrospectively reviewed the medical records of all infants treated for culture-positive sepsis in our NICU over the last 10 years.

Results: We identified 151 culture-positive bacterial sepsis events in 125 infants. The organisms isolated each year largely remained similar throughout the study. Early-onset sepsis (EOS) was caused most frequently by *Escherichia coli* (*E. coli*) and group B *Streptococcus*, whereas the leading causes of late-onset sepsis (LOS) were coagulase-negative *Staphylococcus* (CoNS) and methicillin-sensitive *Staphylococcus aureus*. We are also seeing a trend for increasing *Klebsiella* isolates since 2015.

Conclusion: There was no significant shift in organisms causing neonatal infections during the last 10-years. We need to carefully follow the number of *Klebsiella* spp. isolates and also record the antibiotic sensitivity profiles of *E. coli* over time.

Clinical significance: In our NICU, the bacterial isolates and antibiotic susceptibility patterns have not shown major changes in recent years. Hence, the empirical antibiotic protocols for suspected sepsis do not need to be revised right now. We do need to monitor the number and antibiotic sensitivity of certain Gram-negative bacterial isolates. Our antibiotic protocols will need fine adjustment to cover the most frequently isolated bacteria for good outcomes, but also to avoid overuse and secondary resistance.

Keywords: Antibiotic use practices, Infection, Neonate, Neonatal intensive care unit, Newborn, Organism susceptibility.

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Key Points

- Neonatal sepsis continues to be a leading cause of neonatal morbidity and mortality.
- This study was a retrospective review of 151 bacterial infections in neonates admitted to the neonatal intensive care unit (NICU) over a 10-year study period.
- The most common organisms causing sepsis in premature and critically ill newborn infants remained similar throughout the study period. In early-onset sepsis (EOS), *Escherichia coli* and group B *Streptococcus* were the leading agents. Late-onset sepsis (LOS) was caused most often by coagulase-negative Staphylococci and methicillin-sensitive *Staphylococcus aureus*. There has been a recent rise in the number of *Klebsiella* isolates that has not reached statistical significance yet.
- Close surveillance of bacterial isolates and antibiotic sensitivity profiles is needed in all NICUs; these data can help optimize the empirical therapy of suspected neonatal sepsis before the diagnosis is confirmed and the isolated bacteria are fully characterized.

Introduction

Infections can become a life-threatening emergency in premature and critically ill neonates in NICUs. Despite major advancements in the management of neonatal sepsis, infections still continue to be

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a leading cause of neonatal morbidity and mortality. The Global Burden of Disease study in 2016–2017 identified a worldwide annual incidence of 1.3 million cases of neonatal sepsis.[1]

Neonatal sepsis is divided into early-onset infections occurring within the first 3 days after birth, and the late-onset infections that are seen there after.[2,3] Early diagnosis and appropriate empiric antibiotic treatment can minimize morbidity and mortality resulting from these infections. Early onset sepsis is most commonly caused by group B *Streptococcus* (GBS) and *Escherichia coli* (*E. coli*) and recommended empiric antimicrobial therapy is typically ampicillin and gentamicin.[3] Late-onset sepsis organisms vary based on patient-specific risk factors and differ between NICUs; however, coagulase-negative *Staphylococcus* (CoNS), *Staphylococcus aureus*, and Gram-negative bacteria are still the leading causes.[4] Monitoring the epidemiology and resistance patterns in neonatal sepsis over time are important as it would determine the choice and efficacy of empirical antibiotic therapy. For instance, GBS has been viewed as the most frequently-seen organism for EOS. Maternal antibiotic prophylaxis was introduced in 1996 in the United States to minimize GBS vertical transmission, and the incidence of early-onset GBS sepsis decreased from 1.3 to 1.7 per 1000 in the early 1990's to 0.3–0.6 per 1000, even though there has been some increase in the rates of *E. coli* sepsis during this period.[2,5] Intravenous penicillin is the agent of choice for intrapartum prophylaxis, with intravenous ampicillin as an acceptable alternative. First-generation cephalosporins and clindamycin are considered in women with a risk of allergy.[6] There are some regional differences in the organisms responsible for neonatal sepsis; further studies are needed to design prophylactic strategies to reduce neonatal sepsis.[7]

This is a retrospective observational study of all neonates with culture-positive sepsis in a single NICU cohort to identify any major shifts in organisms over a 10-year-period (2011–2020). We listed the most frequently-identified organisms to determine whether currently-accepted treatment guidelines and our unit protocols for EOS and LOS will likely be effective.[8,9] We also sought to identify the host and or clinical factors that would increase the risk of infections with certain organisms or more resistant pathogens. The risk of infection can increase, particularly in preterm infants, due to an immature immune system, prolonged hospitalization and frequent use of invasive devices.[10] Identification of these risk factors could help develop/improve the treatment regimens currently used to treat neonates with suspected infections.

Materials and Methods

This retrospective cohort study included neonates admitted to a single regional perinatal center level IIIB NICU with 40 licensed beds located in New Jersey, US between January 1, 2011, to December 31, 2020. We have an average of 896 admissions per year and approximately 5% of patients are out born. The cohort has a high case mix index.[11] The study was approved by the institutional review board and informed consent was waived.

During the study period, we did not have a formalized antimicrobial stewardship program in the NICU. We retrieved patient information from a central, electronic data repository. Demographic data included gestational and postnatal age at time of infection, birth-weight, and sex. Patient specific risk factors for infection included mode of delivery, need for mechanical ventilation and presence of a central line. Comorbid conditions present at the time of infection, such as necrotizing enterocolitis (NEC) and bacterial meningitis were also included.

Information about positive cultures [blood, urine, respiratory or cerebrospinal fluid (CSF)] over the 10-year time period was evaluated. If a neonate had more than 1 infection at different times during the hospitalization, those were recorded as separate events as these were not always caused by the same organism. Neonates whose cultures were identified as contaminants by the treatment team and not treated for infection, and those who had only positive respiratory cultures were excluded from the study. Fungal cultures were not included.

The primary endpoint in this study was to identify the prevalence of organisms causing neonatal infections and evaluate the susceptibility patterns of the most common organisms throughout the study period. For EOS, our primary empiric protocol included ampicillin and gentamicin. Late-onset sepsis was typically treated with vancomycin and gentamicin.

Secondary endpoints included evaluating potential risk factors for resistant organisms including time onset of sepsis (early vs late), gestational age (very preterm (≤30 weeks), preterm (31–36 weeks), and term infants (≥37 weeks), mode of delivery, presence of central line or mechanical ventilation and diseases including meningitis or NEC . Resistant organisms for our study were defined as strains of *E. coli* resistant to gentamicin, any organisms with detectable AmpC beta-lactamase production or extended spectrum beta-lactamases or *Staphylococcus aureus* strains resistant to methicillin. Results were categorized by EOS (onset within the first 3 days of life) or LOS (occurring after 3 days of life). In addition, we evaluated the correlation of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screens with systemic infection MRSA.

Summary statistics were used for descriptive purposes. Depending on variable type and underlying distribution, these included mean with standard deviation, median with interquartile range, or counts with associated percentages. Longitudinal plots, heat maps and bar charts were used to visualize relationships between infection, antibiotic usage and time. Generalized linear regression models were used to explore significant associations between infection type and central line or mechanical ventilation, with a significance threshold of 0.05. Only primary infections were considered to preserve the independent assumption of the model for patients that had more than 1 infection for secondary endpoints. All statistical analyses were performed using JMP®, Version 17.2. SAS Institute Inc., Cary, NC, 1989–2023.

Results

During the 10-year study period, we had an average of 896 admissions per year, where about 5% were out born. There were 151 recorded bacterial infection events in 125 infants. As mentioned above, we have a high case mix index.[12] During the study period, we did not have a formalized antimicrobial stewardship program in our NICU.[13]

There were 131 cases of isolated bacteremia, 7 cases of meningitis, 9 isolated urinary tract infections (UTI), and 4 cases of bacteremia with UTI. Four cases had positive cultures for two separate organisms. Complete baseline demographics are provided in Table 1. In our cohort, 69 (55%) were male. The gestational age was median (range) 26.6 (24.9–32.3) weeks and the birth weight was 0.9 (0.7–1.5) kg. Most [92 (72%)] were delivered via cesarean sections and singletons (87.2%).

We did not find any significant changes in the occurrence of infections over time. The rate of infections ranged from 0.4 to 1.7% during the 10-year study period, but there were no obvious trends.

The highest number of neonatal infections were noted in the years 2012, 2015, and 2019 (n = 16 each year), and the lowest number of infections (n = 4) was seen in 2013 (Fig. 1). Of the total 151 infection events, 32 were EOS and 119 were LOS. The most common organisms responsible for EOS were *E. coli* (n = 14) and GBS (n = 6). In infants with LOS, CoNS (n = 42) and methicillin-sensitive *Staphylococcus aureus* (MSSA; n = 22; Table 2). Figure 2 shows the yearly frequencies of *gram-positive* and *gram-negative* pathogens over the study period.

Table 1: Demographics

	Total (n = 125)			
Characteristics	*Count*	*Percentage (%)*	*Median*	*IQR*
Repeated infections				
Yes	16	12.8		
Delivery				
C-section	90	72.0		
Gestation				
Multiple	16	12.8		
Gender				
Male	69	55.2		
Race*				
African American	13	15.3		
Asian	16	18.8		
White	55	64.7		
Ethnicity**				
Hispanic	32	34.8		
Nonhispanic	60	65.2		
Gestational age (weeks)			26.6	24.9–32.3
Birthweight (kg)			0.9	0.7–1.5

Table 1 depicts the demographics for all the patients who had an infection in the NICU. Summary statistics include the count, percentage, median and interquartile range (IQR); *Total number of patients is 84; **Total number of patients is 92

Gram-positive Infections

The majority of the infections were caused by gram-positive organisms (99, 65.5%) with CoNS as the most common cause (n = 45). Coagulase-negative *Staphylococcus* infections were noted in the entire study period; the largest number was seen in 2015 (n = 11). Eleven percent of the CoNS isolates were susceptible to

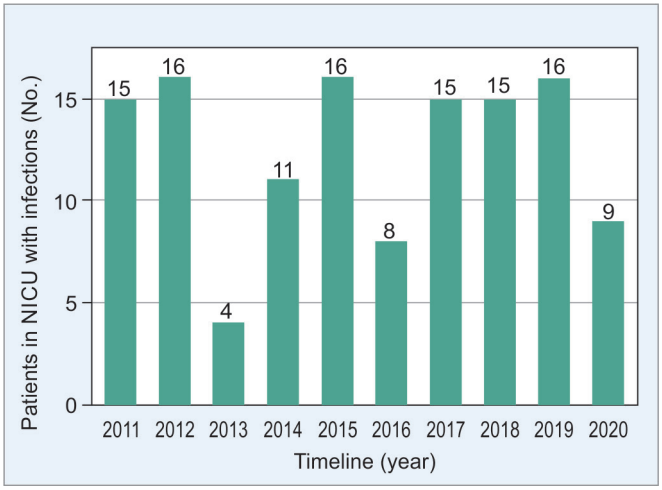
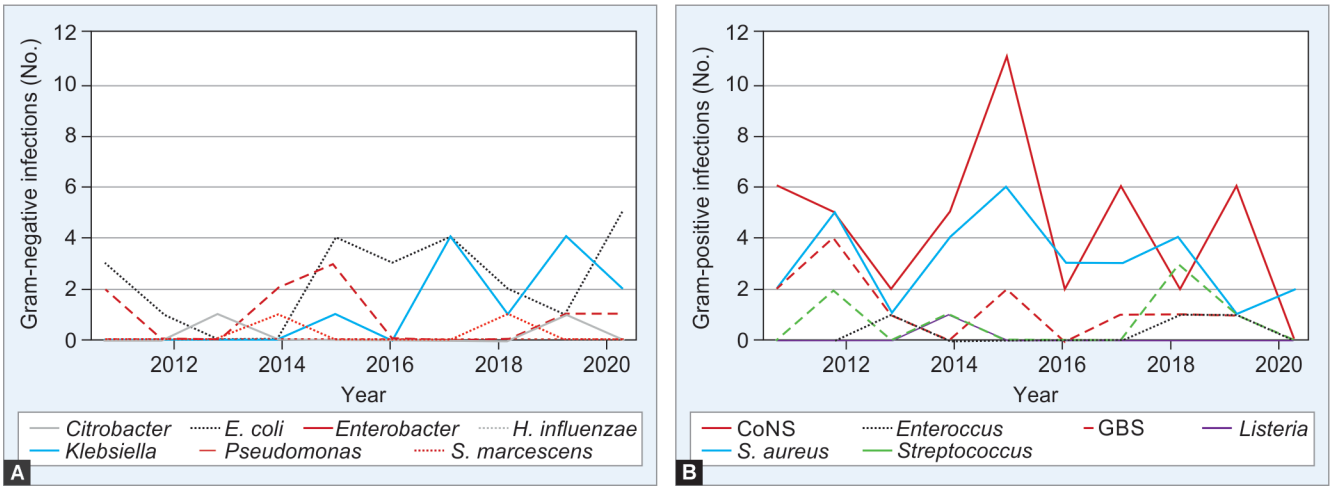


Fig. 1: Patients in the NICU with infections from 2011 to 2020
Bar chart depicts the number of patients admitted to the NICU with infections over a 10-year span. Counts are displayed for each year.

Table 2: Organisms isolated in early onset sepsis and late onset sepsis

	EOS (n = 32)		LOS (n = 119)		Total (n = 151)	
Isolated cultures	*Count*	*Percentage (%)*	*Count*	*Percentage (%)*	*Count*	*Percentage (%)*
Gram-negative						
E. coli	14	43.8	9	7.6	23	15.2
Klebsiella	1	3.1	11	9.2	12	7.9
Pseudomonas	0	0.0	9	7.6	9	6.0
Enterobacter	1	3.1	6	5.0	7	4.6
Citrobacter	1	3.1	1	0.8	2	1.3
Haemophilus influenzae	1	3.1	0	0.0	1	0.7
Serratia marcescens	0	0.0	1	0.8	1	0.7
Gram-positive						
CoNS	3	9.4	42	35.3	45	29.8
MSSA	1	3.1	21	17.6	22	14.6
GBS	6	18.8	8	6.7	14	9.3
Nonhemolytic *Streptococcus*	4	12.5	3	2.5	7	4.6
MRSA	0	0.0	8	6.7	8	5.3
Enterococcus	0	0.0	3	2.5	3	2.0
Listeria	1	3.1	0	0.0	1	0.7

The EOS, LOS and totals reflect infection events. Some infections may include co-infections resulting in more organisms than infection events



Figs 2A and B: Number of infections by organism per year
Above figure illustrates the trends of infection over a 10-year timespan (2011–2020). The graph on the left is gram-negative trends and the graph on the right is gram-positive trends. Organisms depicted in grey scale and patterned according to each respective legend.

penicillin and resistance did not show any change over the 10-year study period (Fig. 3). The number of MSSA infections declined over the 10-year period with the highest numbers of yearly cases (4 per year) in 2012 and 2015. We recorded only 0–2 MRSA infections per year. A few GBS cases (1–2 per year) were seen every year and all isolates were susceptible to penicillin. There were no obvious trends of change in the susceptibility patterns of the most-frequently seen Gram-positive organisms throughout the study period (Fig. 3).

Gram-negative Infections

E.coli was the most frequently-seen gram-negative bacterial isolate; isolated in 23 total cases, where the highest number occurred in 2020 ($n = 5$). Table 2 shows the susceptibility patterns of most prevalent *Gram-positive* infections, with no obvious trends over the 10-year study period. Ten of these *E.coli* isolates (43%) were susceptible to ampicillin and gentamicin. One extended spectrum β-lactamase *E. coli* isolate was identified in 2019 and another that was resistant to gentamicin was seen in 2020.[14] The remaining 11 isolates were susceptible to both gentamicin and 1st generation cephalosporins. *Klebsiella* spp. emerged as a pathogen in our NICU with cases occurring almost every year since 2015; all isolates showed susceptibility to gentamicin and 1st generation cephalosporins. All patients with Klebsiella sepsis were premature, with a gestational age >30 weeks. We noted a total of 8 *Pseudomonas aeruginosa* infections during the study period; all were susceptible to cefepime and ceftazidime. There were 7 *Enterobacter* infections, where all isolates were susceptible to carbapenems.

Patient Factors

A total of 23 (15.3%) infection-events occurred in patients with NEC. The most frequently seen organisms in these patients were CoNS ($n = 8$), *E. coli* ($n = 4$), and *S. aureus* ($n = 6$; 3 MSSA, 3 MRSA). A total of 19 (12.6%) infection events were treated for meningitis, although only 7 had documented positive CSF cultures. Group B *Streptococcus* ($n = 5$), *E.coli* ($n = 3$) and MSSA ($n = 3$) were identified most frequently with meningitis.

In preterm infants, the top 3 infections were CoNS ($n = 39$), MSSA ($n = 22$) and *E.coli* ($n = 17$). These babies were also more likely to have drug-resistant infections such as MRSA ($n = 7$), *Pseudomonas* spp. ($n = 5$) and *Enterobacter* spp. ($n = 6$). In patients with central lines ($n = 81$, 58.9%), 60 (39.7%) isolates were gram-positive bacteria. However, the presence of a central line was not a significant factor for having a gram-positive infection ($p = 0.7$). Seventy infection-events (46.4%) occurred in patients who required mechanical ventilation; 46 (65.7%) bacterial isolates were Gram positive. There was no significant difference in the odds of Gram-positive or Gram-negative primary infections between patients on ventilatory support (OR = 0.80, 95% CI: 0.37–1.74) vs those who were not (OR = 1.28, 95% CI: 0.59–2.78). Nasal screens were evaluated for MRSA colonization to determine whether a positive result could predict later invasive MRSA infections. A negative MRSA screen almost excluded a later MRSA infection with a negative predictive value (NPV) of 97.8%. A positive MRSA screen had a sensitivity = 62.5%.

Discussion

This study examined the clinical factors and bacterial genera associated with neonatal sepsis in our center over a 10-year period. *E. coli,* GBS and *S. aureus* were identified most frequently but remained similar year-to-year throughout the study period. Considering that some *Klebsiella* isolates are now being identified, we need to carefully monitor these numbers to determine whether there could be a need for modifications in antibiotic management of suspected sepsis before the culture reports become available.[15]

In EOS, our frequent identification of GBS and *E.coli* is consistent with existing literature.[3] We need to continuously monitor maternal and neonatal information at all centers to validate the protocols for perinatal prophylaxis and treatment of suspected neonatal sepsis.[16] Currently, the antibiotic susceptibility patterns of bacteria isolated in our NICU are reassuring for continued empiric use of ampicillin and gentamicin for suspected EOS before culture results become available, as recommended by the American Academy of Pediatrics (AAP).[8,9] However, if *E. coli* or *Klebsiella* species emerge as important causes of EOS, the antibiotic protocols may need to be updated.[10,11] The concerns about ampicillin resistance in our *E. coli* isolates call for continuous monitoring.[17] Our current regimen of vancomycin and gentamicin for LOS is effective effective as most *E. coli* strains are susceptible to gentamicin.[18] However, the clinical utility and long-term safety of gentamicin monotherapy when secondary

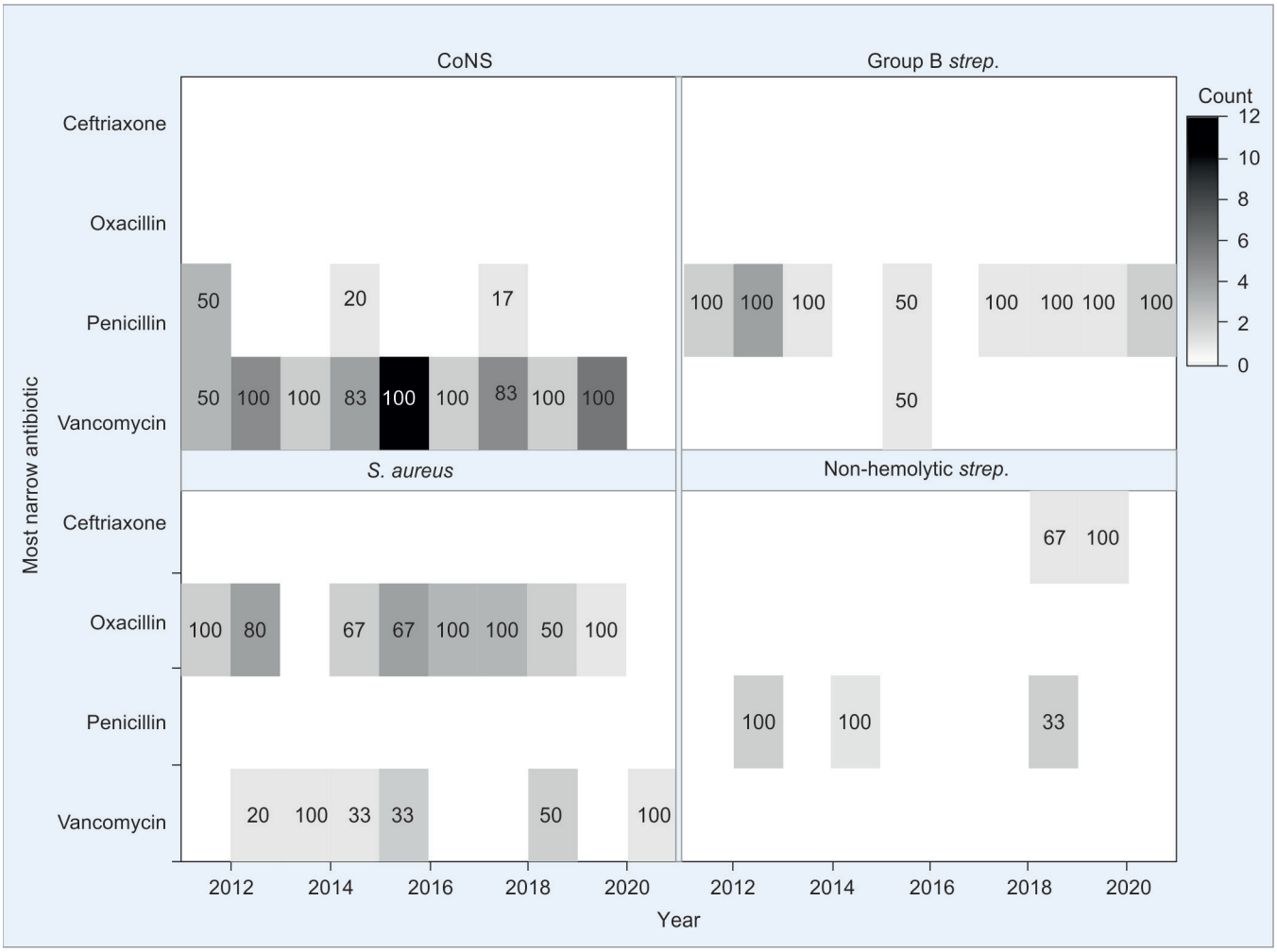


Fig. 3: Susceptibility patterns of most prevalent gram-positive organisms
Above figure shows a heatmap of the antibiotic susceptibility of the most common gram-positive organisms (CoNS, Group B *Streptococcus*, *Staphylococus aureus* and non-hemolytic *Streptococcus*) by year. Color intensity corresponds to the number of infections treated by each antibiotic for each organism. Antibiotic susceptibility percentage is shown within each cell.

resistance is considered, remains controversial.[19,20] We may need to consider revising our empiric antibiotic panels for use prior to the availability of culture/sensitivity results if Gram-negative organisms or ampicillin resistance is seen more frequently.[21]

In patients presenting with LOS, Gram-positive organisms such as CoNS and *S. aureus* were seen frequently during the entire study period. These data resemble those from the entire United States.[2,22,23] Most of our *S. aureus* isolates show oxacillin susceptibility, with resistance in about 25% of the strains. Studies show MRSA rates varying between <1 and 23% between centers.[2] Currently, our empiric regimen covers for MRSA with vancomycin, although some recent studies have found oxacillin to be effective for LOS Gram-positive coverage.[24] These steps are attractive for less adverse effects and limiting bacterial resistance due to overuse of broad spectrum antibiotics.[25] In our patients, a negative MRSA nasal screen showed a strong NPV in identifying patients who would be less likely to develop MRSA infections and hence, the need for using vancomycin. On the other hand, infants who have central lines and are started on empiric oxacillin for suspected sepsis should be switched to vancomycin once the blood cultures are confirmed as positive for CoNS.[26] Finally, many recent studies have noted an increasing frequency of *Klebsiella* spp. in neonatal sepsis.[22,23] Hence, many centers have either actively considered or included a first-generation cephalosporin to broaden empiric antibiotic therapy in a decompensating patient.[15]

Infection prevention is key to minimizing infections and preventing antibiotic resistance. One strength of our study is that every single patient who qualified by the inclusion criteria was included.[27] We acknowledge that there have been changes in our practice over the 10-year period of the study. There are some steps that we have applied very stringently in our NICU and could affect the number of infants who have tested positive and hence, included in the study.[28] We perform weekly MRSA nasal screens in all NICU patients, and those who test positive are immediately placed on contact precautions.[29] Procedures such as central line insertion, initiation of fluid administration, or obtaining blood cultures are performed after sequentially wiping the site with alcohol and povidone-iodine or lately with chlorhexidine.[30–32] Each step is performed only after the site has dried after the previous step.[33,34] Irrespective of the disinfection protocol, we have included every patient who were treated for a positive culture infection related to EOS or LOS. These practices could have altered the spectrum

of organisms isolated in cultures as compared to other NICUs. Our practices could also have minimized the overlap between bacteria isolated in EOS vs LOS.[23]

There are limitations to our study. It is a single center retrospective study with a limited number of subjects and therefore may not be generalizable to other NICUs.[35] However, in discussions in the Global Newborn Society, such small unit-specific studies will very likely be needed in NICUs all over the world.[36] In large consortia of NICUs, even though the number of enrolled infants is larger, there is considered center-to-center variability.[37] Differences in host genetic susceptibility, bacterial flora, environmental factors, previously-administered and ongoing drugs, nutrition, and systems management all likely vary in different parts of the world thus making generalizable studies challenging. Furthermore, due to our evaluation of only patients with positive cultures, we were unable to clearly identify the patients who would be at risk for infection and risk factors for resistant organisms in the overall NICU population. Shortly after this study was concluded, the change in skin disinfectants in our NICU could shift the microflora in our unit.[38] During this time, we also did not have antibiotic guidelines for late-onset neonatal infections. This could have led to unrecognized but possibly suboptimal overuse of broad-spectrum antibiotics leading to emergence of resistant pathogens.[39] The overuse of antibiotics in NICUs is a topic of concern due to the increased risk of antimicrobial resistance in addition to associations with alternations in the gut microbiome. We have been very cautious in our empiric antibiotic use for EOS by using risk-of-sepsis calculators to minimize unnecessary antibiotics.[40,41] We still need strong risk-assessment tools for LOS.

Conclusion

In our retrospective review, the spectrum of bacteria causing neonatal sepsis did not change significantly over the 10-year study period. Although no significant trends were observed in the frequency of susceptibility patterns, the NICU staff expressed a concern about the need to monitor for drug resistance in Gram-negative pathogens such as *E. coli* and the total number of *Klebsiella* infections requiring cephalosporin therapy. At this time, we do not have strong evidence for an immediate need for a change in antibiotic protocols, but we are continuing with QI efforts to monitor the spectrum of bacterial isolates. The development of a Global Newborn Society-wide patient database with records of infections and a standardized antimicrobial stewardship program could help but considering the heterogeneity in different parts of the world, we might still need advanced prediction-focused statistical tools.[42] If the heterogeneity precludes the derivation of major conclusions, alternative methods such as systemic reviews/meta-analysis of small, comparable studies could help.[43] To facilitate this idea, performing a well-considered single-center study could provide a template for multiple, similarly-structured small studies all over the world to improve precision.[44,45]

Ethical Approval

This study was approved by the Hackensack Meridian Health IRB. The protocol number for approval is Pro2021-0879. This study was conducted in accordance with the Declaration of Helsinki.

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References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1789–1858. DOI: 10.1016/S0140-6736(18)32279-7.
2. Coggins SA, Glaser K. Updates in late-onset sepsis: Risk assessment, therapy, and outcomes. Neoreviews. 2022;23(11):738–755. DOI: 10.1542/neo.23-10-e738.
3. Schrag SJ, Farley MM, Petit S, et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. Pediatrics 2016;138(6):e20162013. DOI: 10.1542/peds.2016-2013.
4. Dong Y, Speer CP. Late-onset neonatal sepsis: Recent developments. Arch Dis Child Fetal Neonatal Ed 2015;100(3):F257–F263. DOI: 10.1136/archdischild-2014-306213.
5. Sgro M, Kobylianskii A, Yudin MH, et al. Population-based study of early-onset neonatal sepsis in Canada. Paediatr Child Health. 2019 May;24(2):e66-e73. PMID: 30996609. doi: 10.1093/pch/pxy018.
6. ACOG. Prevention of Group B Streptococcal Early-Onset Disease in Newborns: ACOG Committee Opinion, Number 797. Obstet Gynecol 2020;135(2):e51–e72. DOI: 10.1097/AOG.0000000000003668.
7. Bizzarro MJ, Raskind C, Baltimore RS, et al. Seventy-five years of neonatal sepsis at Yale: 1928–2003. Pediatrics 2005;116(3):595–602. DOI: 10.1542/peds.2005-0552.
8. Puopolo KM, Benitz WE, Zaoutis TE. Committee on Fetus, Newborn, Committee on Infectious Diseases. Management of neonates born at ≥35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. Pediatrics 2018;142(6):e20182894. DOI: 10.1542/peds.2018-2894.
9. Puopolo KM, Benitz WE, Zaoutis TE. Committee on Fetus, Newborn, Committee on Infectious Diseases. Management of neonates born at </=34 6/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. Pediatrics 2018;142(6):e20182896. DOI: 10.1542/peds.2018-2896.
10. Flannery DD, Chiotos K, Gerber JS, et al. Neonatal multidrug-resistant gram-negative infection: Epidemiology, mechanisms of resistance, and management. Pediatr Res 2022;91(2):380–391. DOI: 10.1038/s41390-021-01745-7.
11. Kuster SP, Ruef C, Bollinger AK, et al. Correlation between case mix index and antibiotic use in hospitals. J Antimicrob Chemother 2008;62(4):837–842. DOI: 10.1093/jac/dkn275.
12. Mendez CM, Harrington DW, Christenson P, et al. Impact of hospital variables on case mix index as a marker of disease severity. Popul Health Manag 2014;17(1):28–34. DOI: 10.1089/pop.2013.0002.
13. MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev 2005;18(4):638–656. DOI: 10.1128/CMR.18.4.638-656.2005.
14. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: A clinical update. Clin Microbiol Rev 2005;18(4):657–686. DOI: 10.1128/CMR.18.4.657-686.2005.
15. Mukherjee S, Mitra S, Dutta S, et al. Neonatal sepsis: The impact of carbapenem-resistant and hypervirulent klebsiella pneumoniae. Front Med (Lausanne) 2021;8:634349. DOI: 10.3389/fmed.2021.634349.
16. Zhou P, Zhou Y, Liu B, et al. Perinatal antibiotic exposure affects the transmission between maternal and neonatal microbiota and is associated with early-onset sepsis. mSphere 2020;5(1). DOI: 10.1128/mSphere.00984-19.
17. Friedman S, Shah V, Ohlsson A, et al. Neonatal escherichia coli infections: Concerns regarding resistance to current therapy. Acta Paediatr 2000;89(6):686–689. DOI: 10.1080/080352500750044007.
18. Chu A, Hageman JR, Schreiber M, et al. Antimicrobial therapy and late onset sepsis neoreviews. 2012;13(2):e94–e102. DOI: 10.1542/neo.13-2-e94.
19. Stoll BJ, Puopolo KM, Hansen NI, et al. Early-onset neonatal sepsis 2015 to 2017, the Rise of Escherichia coli, and the need for novel

prevention strategies. JAMA Pediatr 2020;174(7):e200593. DOI: 10.1001/jamapediatrics.2020.0593.
20. Verani JR, McGee L, Schrag SJ. Division of Bacterial Diseases NCfI, Respiratory Diseases CfDC, Prevention. Prevention of perinatal group B streptococcal disease–Revised guidelines from CDC, 2010. MMWR Recomm Rep 2010;19;59(RR-10):1–36. PMID: 21088663.
21. Sands K, Carvalho MJ, Portal E, et al. Characterization of antimicrobial-resistant Gram-negative bacteria that cause neonatal sepsis in seven low- and middle-income countries. Nat Microbiol 2021;6(4):512–523. DOI: 10.1038/s41564-021-00870-7.
22. Flannery DD, Edwards EM, Coggins SA, et al. Late-onset sepsis among very preterm infants. Pediatrics 2022;150(6):e2022058813. DOI: 10.1542/peds.2022-058813.
23. Russell N, Barday M, Okomo U, et al. Early-versus late-onset sepsis in neonates - time to shift the paradigm? Clin Microbiol Infect 2024;30(1):38–43. DOI: 10.1016/j.cmi.2023.07.023.
24. Domaracki BE, Evans AM, Venezia RA. Vancomycin and oxacillin synergy for methicillin-resistant staphylococci. Antimicrob Agents Chemother 2000;44(5):1394–1396. DOI: 10.1128/AAC.44.5.1394-1396.2000.
25. Magers J, Prusakov P, Speaks S, et al. Safety and efficacy of nafcillin for empiric therapy of late-onset sepsis in the NICU. Pediatrics 2022;149(5):e2021052360. DOI: 10.1542/peds.2021-052360.
26. Dao TH, Alsallaq R, Parsons JB, et al. Vancomycin Heteroresistance and clinical outcomes in bloodstream infections caused by coagulase-negative staphylococci. Antimicrob Agents Chemother 2020;64(11). DOI: 10.1128/AAC.00944-20.
27. Lohr KN. Rating the strength of scientific evidence: relevance for quality improvement programs. Int J Qual Health Care 2004;16(1): 9–18. DOI: 10.1093/intqhc/mzh005.
28. Vassar M, Holzmann M. The retrospective chart review: Important methodological considerations. J Educ Eval Health Prof 2013;10:12. DOI: 10.3352/jeehp.2013.10.12.
29. Goldstein ND, Jenness SM, Tuttle D, et al. Evaluating a neonatal intensive care unit MRSA surveillance programme using agent-based network modelling. J Hosp Infect 2018;100(3):337–343. DOI: 10.1016/j.jhin.2018.05.002.
30. Cho HJ, Cho HK. Central line-associated bloodstream infections in neonates. Korean J Pediatr 2019;62(3):79–84. DOI: 10.3345/kjp.2018.07003.
31. Lepelletier D, Maillard JY, Pozzetto B, et al. Povidone iodine: Properties, mechanisms of action, and role in infection control and staphylococcus aureus decolonization. Antimicrob Agents Chemother 2020;64(9):e00682–20. DOI: 10.1128/AAC.00682-20.
32. Silvestri DL, McEnery-Stonelake M. Chlorhexidine: Uses and adverse reactions. Dermatitis 2013;24(3):112–118. DOI: 10.1097/DER.0b013e3182905561.
33. Bagheri I, Bahare F, Dadgari A, et al. A literature review of selection of appropriate antiseptics when inserting intravenous catheters in premature infants: The challenge in neonatal intensive care unit. J Clin Neonatol 2020;9(3):162–167. DOI: 10.4103/jcn.JCN_135_19.
34. Kucuker H, Cakir SC, Koksal N, et al. A comparison of chlorhexidine and povidone-iodine solutions in neonatal intensive care units. Pediatr Int 2023;65(1):e15552. DOI: 10.1111/ped.15552.
35. Song JW, Chung KC. Observational studies: Cohort and case-control studies. Plast Reconstr Surg 2010;126(6):2234–2242. DOI: 10.1097/PRS.0b013e3181f44abc.
36. GNS. Global Newborn Society Clarksville, Maryland, USA: Global Newborn Society; 2022. [online] Available from: https://www.globalnewbornsociety.org/. [Last accessed February, 2025].
37. Fitzgerald DC, Simpson AN, Baker RA, et al. Determinants of hospital variability in perioperative red blood cell transfusions during coronary artery bypass graft surgery. J Thorac Cardiovasc Surg 2022;163(3):1015–1024 e1. DOI: 10.1016/j.jtcvs.2020.04.141.
38. Bokulich NA, Mills DA, Underwood MA. Surface microbes in the neonatal intensive care unit: Changes with routine cleaning and over time. J Clin Microbiol 2013;51(8):2617–2624. DOI: 10.1128/JCM.00898-13.
39. Cizman M, Plankar Srovin T. Antibiotic consumption and resistance of gram-negative pathogens (collateral damage). GMS Infect Dis 2018;6:Doc05. DOI: 10.3205/id000040.
40. Jon Widding Fjalstad, Eirin Esaiassen, Lene Kristine Juvet, John N van den Anker, Claus Klingenberg, Antibiotic therapy in neonates and impact on gut microbiota and antibiotic resistance development: A systematic review. Journal of Antimicrobial Chemotherapy 2018;73(3):569–580. DOI: 10.1093/jac/dkx426.
41. Kaiser Permanente Research. Neonatal early-onset sepsis calculator. California: United States; 2025. [online] Available from: https://neonatalsepsiscalculator.kaiserpermanente.org/. [Last accessed February, 2025].
42. Efthimiou O, Hoogland J, Debray TPA, et al. Measuring the performance of prediction models to personalize treatment choice. Stat Med 2023;42(8):1188–1206. DOI: 10.1002/sim.9665.
43. Delgado-Rodriguez M. Systematic reviews of meta-analyses: Applications and limitations. J Epidemiol Community Health 2006;60(2):90–92. DOI: 10.1136/jech.2005.035253.
44. Gidh-Jain M, Parke T, Konig F, et al. Developing generic templates to shape the future for conducting integrated research platform trials. Trials 2024;25(1):204. DOI: 10.1186/s13063-024-08034-8.
45. Indrayan A, Mishra A. The importance of small samples in medical research. J Postgrad Med 2021;67(4):219–223. DOI: 10.4103/jpgm.JPGM_230_21.