

Original Research Article

Culture negative sepsis in neonate in a level III NICU of a community hospital in Brooklyn New York

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ABSTRACT

Background: Neonates often diagnosed with possible sepsis without any evidence of bacterial cause, known as “culture negative sepsis (CnS)”. Most data on neonatal sepsis focuses on culture proven sepsis but large number of neonates receives antibiotic for CnS and its epidemiological data is not accurately represented. Studies suggest that its incidence exceeds incidence of proven sepsis by 16 folds in United states and 50-fold in resource limited settings. According to recent estimates CnS contributes to 20% antibiotic usage in Neonatal intensive care units (NICUs). It is linked to adverse neurodevelopmental outcomes. We aim to identify the incidence and frequency of CnS in a community NICU.

Methods: It is a retrospective observational study between November 2023 to March 2024 in a level III NICU. Neonates admitted during 1st January 2023 till 30th June 2023 and required antibiotic were included. IRB approval was obtained. Data collected for gestational age, gender, diagnosis, blood culture, indication, type, number of days of antibiotic, length of stay, invasive device and duration, birth weight, blood culture and comorbid condition. Data was analyzed using SPSS 22.0. Frequencies and percentages calculated and Pearson Chi-square used to assess correlations, $p < 0.05$ considered statistically significant.

Results: The 95 neonates enrolled. Incidence of CNS was 64%. The 15% patients require invasive devices. Most common indication for antibiotic use was clinical SIRS (75%). The 49% of babies had comorbidities and most common comorbidity was prematurity (47%).

Conclusions: CnS has high incidence in community hospital NICU's then reported in literature.

Keywords: Culture negative sepsis, Community hospital, Neonatal intensive care unit

INTRODUCTION

Neonatal sepsis is a clinical manifestation of systemic infection in neonatal age group. It is further classified based on neonate age into early onset (<48-72 hours) and late onset (>48-72 hours).^{1,2} Neonatal Sepsis is most significant cause of neonatal mortality and morbidity worldwide.³ There is no consensual definition of neonatal sepsis.² Neonatal sepsis definition is mainly adapted from the consensual definition of pediatric and adult sepsis.^{2,3} Most widely accepted definition of neonatal sepsis is an

infant who has clinical and laboratory signs of infection and a positive blood culture from a usual sterile site such as blood, urine, or CSF.^{2,3} Gold standard for diagnosis of sepsis is blood culture but its sensitivity is suboptimal in neonate secondary to low level bacteremia, limited blood volume and inappropriate sampling.⁴ Finally, negative blood culture cannot totally exclude sepsis in neonate.⁴

Recently, there has been increased use of ancillary bio marker to help clinician in diagnosing sepsis such as CRP, Procalcitonin, leukocyte count, Bandemia,

Immature to total leukocyte ratio but no one in highly reliable.^{3,4} Therefore, many clinicians rely on their clinical assessment and systemic inflammatory response syndrome (SIRS) criteria for identification of sepsis.⁴ Hence, many neonates are diagnosed with possible or presumed sepsis without any evidence of bacterial cause, a condition known as CnS.^{2,3}

Very often, neonates specially in intensive care unit are started on antibiotics, after sending blood culture, based on clinical suspicion of infection. In some cases, blood culture remains negative, and neonate often received full course of antibiotic for CnS.¹⁻³ Most of the data on neonatal sepsis in high income countries focuses on culture proven sepsis but in reality, large number of neonates receives antibiotic for CnS and its epidemiological data is not accurately represented. Studies suggest that the incidence of CnS exceeds incidence of proven sepsis by 16 folds in United states and by 50-fold in resource limited settings.^{8,9} Incidence of culture proven sepsis is 0.4-0.8 cases per 1000 live born term infants and for CnS incidence is 6.4-12.8 cases per 1000 live born term infants in literature internationally.² This contributes to high rates of antibiotic consumption in NICU and wide variety of antibiotic usage in NICUs without any impact on attributable mortality and morbidity.² According to recent estimates CnS contributes to 20% antibiotic usage in NICUs.⁹⁻¹¹

The consequences of CnS are not well established. Limited studies suggest there is no increased mortality or morbidity associated with it.¹² While other studies link it to adverse neurodevelopmental outcomes in neonates. In a study by Mukhopadhyay, extremely low birth weight infant (<1000 gm) who were treated for CnS have 17% higher incidence of neurodevelopmental morbidities at 2 years of age.⁴ But in study by Schlapbach et al there was no association found between CnS and Poor neurodevelopmental outcome.¹³

Recently, American Academy of pediatrics also recognizes the increasing use of antimicrobial for CnS and attributes it to incorrect assumptions on the clinician part and recommends to End the culture of CnS in NICU.¹⁴

Currently, many researchers have described the incidence of CnS in various NICU in resource rich setting.¹⁻⁷ Cantey et al also devised a framework for the management of CnS.³ Researchers have described the incidence of CnS in various NICU in resource rich setting but actual incidence of CnS is even higher in community hospital in US than reported.¹⁻³ We hypothesized that the incidence of CnS is higher in community hospital NICU then reported.

Research question/aim

Incidence of CnS in level III NICU of community hospital in Brooklyn New York.

Primary outcome-percentages of CnS in neonate and secondary outcome: Duration, indication and type of antibiotic used.

Hypothesis

There is higher incidence of CnS in neonate in community hospital's NICU then reported in literature.

Operational definitions

SIRS: For this study we used international pediatric sepsis consensus conference criteria published in 2005.⁴ Specificity of this criteria is 69 while sensitivity is 60. Positive predictive value is 59 and negative predictive value is 70.¹⁸ Criteria is as follows: Presence of the findings listed under at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count. Temperature-core temperature of $>38.5^{\circ}\text{C}$ or $<36^{\circ}\text{C}$. Heart rate-tachycardia, defined as a mean HR >2 SD above normal for age. In the absence of external stimulus, chronic drugs, or painful stimuli. Otherwise, unexplained persistent elevation over a 0.5- to 4-h time period-Bradycardia, defined as a mean HR $<10^{\text{th}}$ percentile for age. In the absence of external vagal stimulus, b-blocker drugs, or congenital heart disease. Otherwise, unexplained persistent depression over a 0.5-h time period. Respiratory rate-mean respiratory rate >2 SD above normal for age. Mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia. Leukocyte count-Leukocyte count elevated or depressed for age and $>10\%$ immature neutrophils.

Sepsis: SIRS in presence of or as a result of suspected or proven infection.⁴

CnS: SIRS in presence of or as a result of suspected infection with negative blood culture

Culture proven sepsis: SIRS in presence of or as a result of proven infection with positive blood culture.

Invasive devices: Central line including peripherally inserted central catheters (PICC) and umbilical lines, endotracheal tube, tracheostomy tube and urinary catheter.

METHODS

We conducted a retrospective observational study of 6 months duration (November 2023 till April 2024) in a level III NICU of Brookdale hospital medical center. All neonates admitted in NICU from 1st January 2023 till 30th June 2023 and required antibiotic therapy included in the study. All neonate admitted to NICU and does not require antibiotic excluded. Predictor variables were gestational age of neonate, birth weight, gender, presence of culture proven sepsis, comorbid condition including congenital heart defects, congenital anomaly, respiratory pathology,

indication of antibiotic and duration of antibiotic, Invasive device used and duration of invasive device. Outcome variables were percentages of CnS, Number of days of antibiotic used, type of antibiotic used and length of stay of neonate. For this study we used SIRS criteria published in international pediatric sepsis consensus conference criteria in 2005.⁴

Procedures

After IRB approval we reviewed the electronic health records of the patients admitted to NICU during study period and fulfilled inclusion criteria. Principal investigator reviewed the patients charts in epic and collected data in excel sheet for gestational age, gender, diagnosis, blood culture, antibiotic used, number of days of antibiotic, length of stay and invasive device used. All identified data will be kept in hospital computer with password protection. Principal investigator will only have access to the files with identified information. All the data will be deidentified before submitting to the statistician for data analyses or for publications.

Statistical analyses

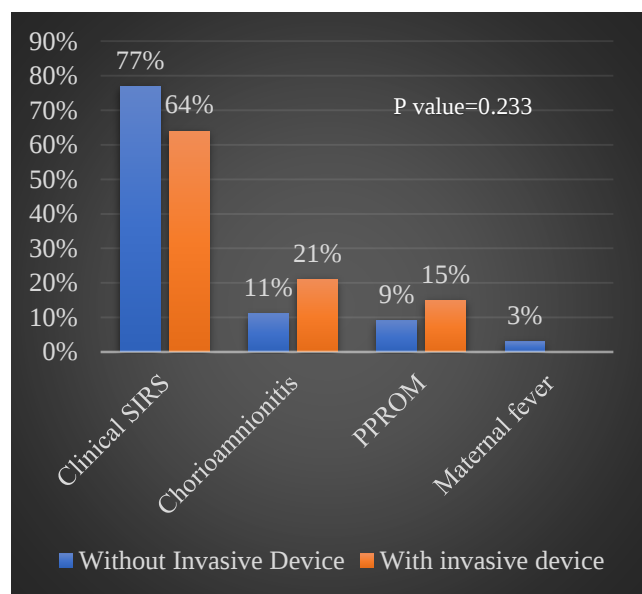
All data was analyzed using SPSS 22.0, coded, de-identified and cleaned from missing data and duplicates. Patient demographics and clinical characteristics will be expressed as median, interquartile range, mean and standard deviation. Frequencies and percentages will be calculated for categorical variables including gender, birth weight, culture positive sepsis, CnS, Invasive device used, comorbid condition, indication of antibiotic and type of antibiotic used. Mean with standard deviation and interquartile ranges will be calculated for duration of invasive device, gestational age of neonate, number of days of antibiotic used, and length of stay of neonate. Pearson Chi-square was used to assess correlations and a $p < 0.05$ will be considered statistically significant.

RESULTS

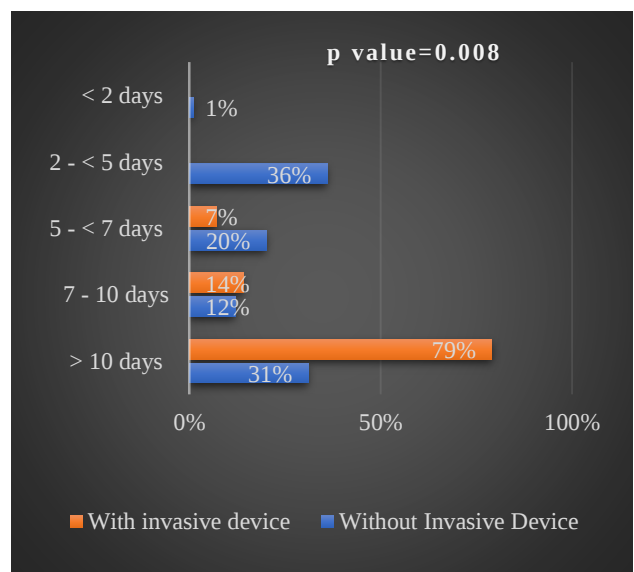
The 148 neonates admitted during study period. 95 received antibiotic and included in the study. The 52% were female. The 52.6% born via C-section median (Patient characteristics are mentioned in Table 1). Out of all initial culture sent only one came out positive. Hence, incidence of CNS was 64% overall. The 14 (15%) patients required invasive device and received antibiotics, none of them had positive blood culture. Most common indication of antibiotic was clinical SIRS (75%) (Figure 1). Mean length of stay (LOS) was 17 days while median (IQR) LOS was 7 days (4-15 days) (Figure 2). Neonates with invasive devices had statistically significant higher LOS. Mean antibiotic duration was 4 days (SD 2.6 days), median (IQR) antibiotics duration 2 days (2-5 days). Neonates with invasive device receive longer duration of antibiotics (Figure 3). The 49% of babies had comorbidity and most common comorbidity prematurity (47%). Antibiotic exposure was 2.5 days.

Table 1: Patient characteristics, (n=95).

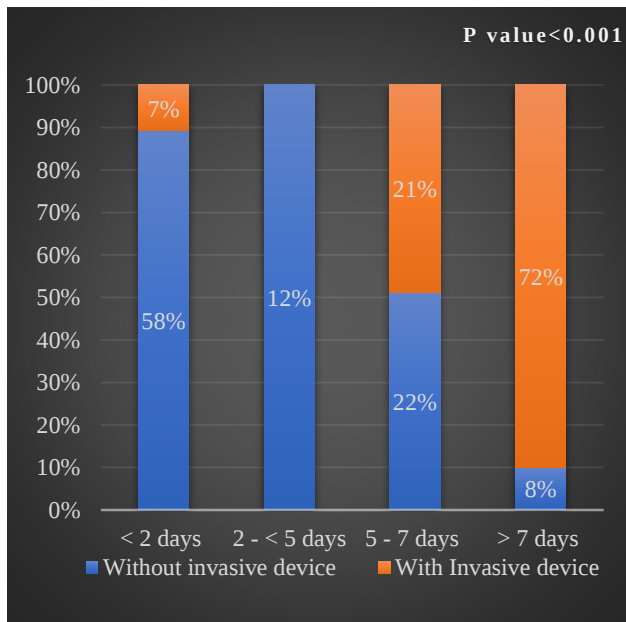
Variables	N (%)
Gender	
Male	46 (48)
Female	49 (52)
Mode of delivery	
C-section	50 (53)
NVD	45 (47)
Median LOS (IQR)	7 days (4-15 days)
Median birth weight (IQR)	2900 gm (2021-3383 gm)
Median gestational age (IQR)	37 weeks (34-39 weeks)
Median antibiotic duration (IQR)	2 days (2-5 days)



Figures 1: Indication for antibiotic.



Figures 2: Length of stay.



Figures 3: Duration of antibiotic.

DISCUSSION

CnS is highly prevalent condition specially in intensive care units. Many neonates because of presumed vulnerability to infection and higher chances of worse outcomes receive antibiotics without positive culture or growth of organism which expose them to unnecessary antimicrobials and increases chances of medication adverse effects or antimicrobials resistance. Incidence of CnS is higher in community hospital where there is less robust institutional guidelines and variety of experience in attendings as seen in this study.

In our study, incidence of CnS is even higher in neonate on invasive devices as most of these neonates were critically ill and had unstable hemodynamics and neonatologist had low threshold for introduction of antimicrobials in case of clinical deterioration or worsening. Some of them already had central lines in place. But during this study no neonate with invasive device including central line had positive blood culture but still received treatment for presumptive central line infection.

Most common indication for initiating antibiotic in our study was based on SIRS criteria and clinical assessment. There is no valid criteria for SIRS in neonate and available criteria is mainly derived from the pediatric definition. It has low positive predictive value in neonatal population, and this may be the reason for increased use of antibiotic in our study based on SIRS criteria alone.¹⁷

Similar to findings in our study a survey by park et al showed neonatologists' years of experience also play a significant role in deciding length of therapy for CnS as well as having standardized institutional guidelines also limit the duration.¹⁸ In our institute there is no guidelines

for CnS and duration varies according to the attending neonatologist and patient clinical condition. Neonates on invasive device especially central line ends up receiving higher days of therapy even if the culture is negative.

In our study, patient with invasive devices and CnS received longer duration of antibiotics and were stayed longer in NICU as compared to neonate without invasive devices which is statistically significant ($p < 0.05$). This observation is likely secondary to perception of treating neonatologist for higher incidence of infection in neonates with invasive devices and increase risk of deterioration.

Limitation of this study includes single center study; retrospective study design and we did not follow the patient after being discharged. There is need for future research to address the issue of CnS with more education and institutionalized protocol for antibiotic stewardship in NICUs.

CONCLUSION

Incidence of CnS is higher in community hospital then reported in literature. Neonates with invasive devices received longer duration of antibiotic and has longer length of stay.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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