Neonatal sepsis in alloimmune hemolytic disease of the fetus and newborn: a retrospective cohort study of 260 neonates

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TRANSFUSION COMPLICATIONS

TRANSFUSION

Neonatal sepsis in alloimmune hemolytic disease of the fetus and newborn: A retrospective cohort study of 260 neonates

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Abstract

Background: Among neonates with hemolytic disease of the fetus and newborn (HDFN), we aimed to describe the frequency of central-line use, indications for insertion, and incidence of confirmed and suspected sepsis, including antibiotic treatment over a 10-year surveillance period.

Study Design and Methods: All neonates with HDFN admitted to our neonatal intensive care unit between January 2012 and December 2021 were included in this retrospective, cohort study. Annual proportions of infants with a central-line and central-line-associated bloodstream infection (CLABSI) rates (per 1000 central-line days and per 100 infants) were evaluated. Numbers of confirmed and suspected early- and late-onset sepsis episodes were assessed over the entire study period.

Results: Of the 260 included infants, 25 (9.6%) were evaluated for suspected sepsis, with 16 (6.2%) having ≥1 confirmed sepsis episode. A total of 123 central-lines were placed in 98 (37.7%) neonates, with impending exchange transfusion (ET) being the most frequent indication. Of the 34 (34.7%) neonates in whom a central-line was placed due to impending ET, 11 (32.4%) received no ET. Overall CLABSI incidence was 13.58 per 1000 central-line days. Neonates with a central-line had a higher risk for confirmed late-onset infection (RR 1.11, 95% CI: 1.04–1.20) and sepsis work-up (RR 1.10, 95% CI: 1.03–1.17) compared to infants without a central-line.

Conclusions: Sepsis incidence among neonates with HDFN remains high, in particular in those with a central-line. Considering the substantial proportion of neonates with a central-line without eventual ET, central-line placement should be delayed until the likelihood of ET is high.

KEYWORDS

central-line, hemolytic disease of the newborn, neonates, sepsis

1 | INTRODUCTION

Hemolytic disease of the fetus and newborn (HDFN) is caused by destruction of fetal and neonatal antigen-positive erythroid cells by maternal alloantibodies.[1] In severe cases, HDFN results in fetal anemia, hydrops, and even perinatal death, for which timely intrauterine transfusion (IUT) forms the current cornerstone of antenatal management.[2,3] Postnatally, HDFN may lead to persisting neonatal anemia, hyperbilirubinemia, and bilirubin encephalopathy (kernicterus), with treatment consisting of intensive phototherapy, exchange transfusions (ET) or postnatal red blood cell transfusions.[4]

ET is indicated in neonates with continuously increasing bilirubin levels despite intensive phototherapy. Although highly effective, ET is associated with procedure-related morbidity, including hematological complications, biochemical abnormalities, and central-line associated bloodstream infections (CLABSI).[5] Bloodstream infections such as CLABSI, are a major cause of morbidity and mortality in neonatal intensive care units (NICU) worldwide, leading to prolonged hospital stays and increased health-care expenditures.[6]

Despite the numerous outcomes studied among neonates with HDFN including hematological and cardiorespiratory complications, long-term neurodevelopmental outcome, and mortality,[5,7–11] the incidence of culture-proven early-onset (EOS) and late-onset (LOS) sepsis, including CLABSI, is not well described. Moreover, in the context of an existing inherently low risk of infection, equivocal evidence regarding potential risk factors for sepsis evaluation and clinical indication for antibiotic therapy remains absent. As such, extending infection analyses to neonates with HDFN, including an evaluation of central-line use in the context of a potential risk for infection, is necessary to monitor performance and expand upon infection prevention and antimicrobial stewardship efforts.

In response to the implementation of more restrictive ET guidelines and overall improvement in the use of intensive phototherapy, a significant decline in the use of ET (67%–10%) was observed among neonates with HDFN over the past 20 years at our center.[7] It is plausible that this reduction may have also led to a concomitant decrease in central-line use and thereby risk of CLABSI. In view of the need to limit unnecessary antibiotic exposure in newborns and optimize treatment indication, the aim of this study was to therefore characterize in a cohort of newborns with HDFN the: (i) central-line use and indications for central-line placement, (ii) incidence of confirmed early- and late-onset sepsis, including CLABSI, (iii) difference in confirmed late-onset sepsis and sepsis evaluation risk between neonates with and without a central-line, and (vi) incidence of clinically suspected sepsis and subsequent antibiotic treatment over a 10-year surveillance period.

2 | MATERIALS AND METHODS

2.1 | Study design and population

All neonates with HDFN admitted to the NICU of the Leiden University Medical Center (LUMC) between January 1, 2012 and December 31, 2021, were included in this retrospective, observational, descriptive cohort study. Treatment and complications have been described previously.[7] The LUMC is the national referral center for the perinatal management of severe HDFN in The Netherlands. In accordance with Dutch guidelines, all pregnant women with antibody-dependent cell-mediated cytotoxicity (ADCC) of ≥50% and/or antibody titer ≥16 in Rh-D immunization, an ADCC of ≥30% and/or antibody titer ≥2 in K-immunization, or an ADCC of ≥30% and/or antibody titer ≥16 for other antibody specifications, are referred to the LUMC for subsequent fetal blood group antigen typing, clinical monitoring and treatment with IUT, if indicated.[12,13]

2.2 | Data collection

Obstetric and neonatal data were collected from the patients' electronic medical records and included the following: gestational age, birth weight, delivery mode (i.e., vaginal delivery or caesarian section), sex, type of red cell alloimmunization (i.e., Rh D, C, c, E, K and other types), treatment with IUTs including number, treatment with ETs including number, hemoglobin level at birth, maximum total bilirubin level during admission, number of red blood cell transfusions during admission, length of hospital stay in days and mortality within the 28 days postpartum. Sepsis-related data included date and time of blood culture sampling, isolated pathogen, C-reactive protein (CRP) levels, date and time of CRP determination, number of sepsis evaluations for a suspected sepsis and antibiotic administration including duration in days. Central-line-related data included number of central-lines per infant including type (i.e., umbilical-venous, umbilical-arterial and/or peripherally-inserted central venous catheter), date and time of insertion and removal and indication for insertion. The study was approved by the medical ethics committee of the LUMC as exempt research (No. G20.096).

2.3 | Definitions

Antenatal HDFN was defined as the presence of maternal red blood cell alloantibodies and a fetus typed positive for the implicated antigen and an ADCC value or maternal antibody titer above the previously mentioned critical

values. The diagnosis of a confirmed early- and late-onset bloodstream infection was based on the presence of a positive blood culture obtained <72 h and ≥72 h after birth, respectively, in combination with clinical signs and symptoms of infection. CLABSI was defined according to the Dutch neonatal CLABSI Surveillance Criteria, with a central-line being at risk for infection if in place for >48 h, until the day of removal or discharge, whichever occurs first.[14] Infants with a blood culture positive for a common commensal as defined in the Center for Disease Control and Prevention's National Healthcare Safety Network (NHSN) Master Organisms list including but not limited to coagulase negative staphylococci (CoNS), were included as bacteremic cases in the presence of a CRP ≥10 mg/L within the first 36 h after start of infection or if a second blood culture was collected within 36 h after sampling of the first blood culture and which was positive for the same 5.[15] Necrotizing enterocolitis (NEC) was defined according to Bell's staging criteria and included stages ≥IIA.[16] Finally, suspected infection was defined as one in which the clinical course strongly suggested the presence of an infection and for which antibiotic therapy was administered for at least 48 h, despite negative culture results (adapted ICD-10-CM code P36.9).[17]

In our NICU, ETs are performed using irradiated, leuko-reduced blood products containing plasma from two different donors and hematocrit of 0.50–0.65 g/L, with exchange volumes ranging from 100 to 200 ml/kg.

2.4 | Outcomes

The primary outcome consisted of the frequency of central-line use and the number of confirmed early- and late-onset neonatal infection episodes, including CLABSI. Secondary outcomes included the number of suspected early- and late-onset infection episodes, indication for central-line placement, and antibiotic consumption rates.

2.5 | Sub-analyses

In April 2015, an adaptation of the ET guidelines was made at our center. According to the American Academy of Pediatrics (AAP) guideline, proven blood group incompatibility is deemed a major risk factor for severe hyperbilirubinemia and should therefore be classified as "high risk" for the development of bilirubin encephalopathy.[18] However, based on the notion that the function of the blood–brain barrier does not decline in the presence of red cell alloimmunization, our medical team unanimously decided to classify neonates with confirmed alloimmunization as "standard risk" as appropriate threshold for phototherapy and ET. Under the assumption that this change in ET guidelines would result in fewer neonates in need of an ET and thereby a central-line, sub-analyses evaluating central-line use and CLABSI incidence before (January 2012–March 2015) and after (April 2015–December 2021) the change in ET guidelines were likewise performed.

2.6 | Statistical analysis

Descriptive statistics, including absolute numbers and percentages, mean and standard deviation (SD), or median and interquartile range (IQR), were used to summarize demographic, clinical, and infection-related data. CLABSI rates were calculated per 1000 central-line days (incidence density) and per 100 infants (cumulative incidence rate). Distribution of causative pathogens from culture-confirmed infections was evaluated by calculating the overall frequency of observed major pathogens. Antibiotic consumption rates were quantified as DOT (days of treatment) and LOT (length of treatment) rates per 1000 patient days. DOT represents the aggregate number of days a single antibiotic agent is administered (i.e., 2 different antibiotics administered for 3 days amounts to 6 DOTs). LOT represents the total number of days at least one antibiotic agent is administered. As part of the subanalyses, central-line related outcomes including the proportion of infants with a central-line and cumulative and overall CLABSI incidence rates were stratified in 2 periods according to the ET guideline change in April 2015, namely period 1 (January 2012–March 2015), period 2 (April 2015–December 2021). Differences in the proportion of neonates with a central-line before and after guideline change were calculated using the Chi-square test or Fisher's exact test, as appropriate. Differences in CLABSI rates in Poisson distribution between the two study periods were assessed via Poisson regression with period added as explanatory variable. Statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 26 for Windows (SPSS Inc, Chicago, IL, USA).

3 | RESULTS

3.1 | Baseline characteristics

Between January 1, 2012 and December 31, 2021, 260 neonates with an antenatal diagnosis of severe HDFN were admitted to our NICU. Baseline characteristics of the included infants are shown in Table 1. D-mediated HDFN was the most common type of red cell alloimmunization (75.8%), followed by K (12%) and c (8.4%). The majority of the included infants were treated with IUT (60.8%), with a median of 2 (IQR 2)

TABLE 1 Neonatal baseline characteristics

Characteristic	$N = 260$
Sex (male)	126 (48.5%)
Gestational age (weeks)	36 [1]
Birth weight (grams)	2886 ± 493
Caesarian delivery	70 (26.9%)
Primary type of red cell alloimmunization	
Rh D	197 (75.8%)
Rh C	1 (0.4%)
Rh c	22 (8.4%)
Rh E	5 (1.9%)
K	31 (12%)
Fy(a)	3 (1.2%)
Antenatal IUT	158 (60.8%)
Number of IUTs per neonate	2 [2]
Hemoglobin level at birth (g/dL)[a]	8.4 ± 1.72
Maximum unconjugated bilirubin level (μmol/dL)[b]	243 ± 87
RBC transfusion	59 (22.7%)
Number of RBC transfusions per neonate	1 [1]
Length of hospital stay per neonate (days)	6.0 [3]
Mortality	4 (1.5%)

Note: Results are presented as *n* (%), mean ± SD or median [IQR].
Abbreviations: ET, exchange transfusion; IUT, intrauterine transfusion; RBC, red blood cell.
[a]5 missing values.
[b]1 missing value.

TABLE 2 Central-line and infection-related outcomes

Outcome	
Number of neonates treated with ET[a]	32 (12.3%)
Median number of ET	1 [1]
Total number of neonates with a central-line[a]	98 (37.7%)
Number of central-lines	123
Indication for central-line placement	
Impending ET	34 (34.7%)
Difficulty obtaining peripheral vascular access	22 (22.4%)
Large volume of intravenous fluid supplementation	10 (10.2%)
Combination[b]	5 (5.1%)
Others[c]	3 (3.1%)
Unknown	24 (24.5%)
Line-days per neonate	3.66
Line-days per line	3.44
Total line-days	395.9
Age at insertion (days)	1.10 [1.26]
Number of neonates with CLABSI[d]	6 (6.12%)
CLABSI episodes	6
Number of neonates with confirmed sepsis	16 (6.2%)
Early-onset (< 72 h)	2
Late-onset (≥ 72 h)[e]	10
NEC	4
Duration of antibiotic therapy for confirmed sepsis (days)[f]	14 [8]
Number of neonates with clinically suspected sepsis	25 (9.6%)
Number of clinically suspected sepsis episodes	29
Early-onset (<72 h)	17
Late-onset (≥72 h)	12
Duration antibiotic therapy for suspected sepsis (days)	2 [1]

Note: Results are presented as *N*, *n* (%), or median [IQR].
Abbreviations: CLABSI, central-line associated bloodstream infection; ET, exchange transfusion; h, hours; NEC, necrotizing enterocolitis.
[a]Percentage based on total study cohort (n = 260).
[b]Encompass impending ET in combination with difficulty in obtaining peripheral access, large volume of intravenous fluid supplementation, need for inotropic support, or the need for frequent blood sampling.
[c]Encompass the need for acute vascular access during resuscitation and poor/failed neonatal transition with chronic fetal anemia with PPHN.
[d]Percentage based on neonates with a central-line.
[e]Consists of 4 late-onset bacteremias and 6 CLABSI episodes.
[f]Based on 14 due to 2 missing values as a result of transfer to another hospital during treatment for an infection.

transfusions per neonate. Overall mortality was 1.5% (4/260), with causes being pulmonary hypoplasia of unknown etiology complicated by NEC, bowel perforation associated with NEC, progressive neonatal liver failure, bowel perforation with therapy-resistant persistent pulmonary hypertension, and systemic hypotension.[19]

3.2 | Central-line characteristics and CLABSI outcomes

Central-line and infection-related outcomes are presented in Table 2. Over the 10-year study period, 32 (12.3%) neonates were treated with an ET. A total of 123 central-lines covering 395.9 central-line days were placed in 98 (37.7%) infants, with the proportion of neonates with a central-line varying from 46.4% in 2013 to 32.4% in 2021. The primary indication for insertion was impending ET (34.7%) followed by difficulty in obtaining peripheral vascular access (22.4%). Of the 34 neonates in whom a central-line was placed by reason of an impending ET, 23 (68%) ultimately received an ET (data not shown). The median postnatal age at line insertion over the entire study period was

1.10 days (IQR 1.26), with 52 (53%) infants having received the central-line within 24 h after birth (data not shown). Four (4.3%) infants had one or more central-lines removed <24 h after initial placement, with primary reasons for removal being catheter malposition and malfunction. Over the entire study period, a total of 6 CLABSI episodes were identified in 6 infants, with the incidence density and cumulative incidence rates being 13.58 per 1000 central-line days and 5.52 per 100 neonates, respectively. Of the 32 infants treated with an ET, 2 (6.3%) were diagnosed with CLABSI, although no difference was found in the number of CLABSI episodes between neonates with and without an ET (2 vs. 4 episodes, $p = 0.58$, data not shown).

3.3 | Overall sepsis- and antibiotic consumption-related outcomes

Throughout the 10-year study period, 12 microbiologically-confirmed sepsis episodes were recorded in 12 neonates, 2 and 10 of which were acquired <72 h and ≥72 h after birth, respectively (Table 2). Neonates with a central-line were found to have a significantly higher risk for late-onset infection compared to those without a central-line, with all late-onset infection episodes occurring in the former group (RR 1.11, 95% CI: 1.04–1.20). Both EOS episodes were caused by group B streptococci, with *Staphylococcus aureus* accounting for 40% ($n = 4$) of all late-onset infections. Remaining late-onset infection episodes were caused by group B streptococci ($n = 1$), CoNS ($n = 1$), *E.coli* ($n = 3$) and *Klebsiella pneumoniae* ($n = 1$). There were 4 radiologically-confirmed cases of NEC, all of which had concomitant negative blood cultures.[19] No infant acquired more than one confirmed infection. A total of 29 sepsis evaluations were performed in 25 neonates (9.6%), of which 17 and 12 were performed in the context of a suspected perinatal and late-onset infection, respectively. Neonates with a central-line were found to have a significantly higher risk for sepsis evaluation and thereby antibiotic treatment compared to those without a central-line (RR 1.10, 95% CI: 1.03–1.17).

A total LOT and DOT of 238 and 435 days, respectively, were registered over the entire study period. DOT and LOT rates ranged from 56.5 to 435.2 and 43.1 to 213.4 per 1000 patient-days, respectively, with no evident increasing or decreasing trend over time. Median duration of antibiotic treatment for a confirmed infection was 14 days (IQR 8.0). For a suspected infection, median duration of antibiotic therapy was 2 days (IQR 1), which is in line with hospital policy to discontinue treatment in infants with possible sepsis and negative cultures at 48 h after start infection.

3.4 | Guideline change

No significant change in the proportion of neonates with a central-line was found before and after the ET guideline change (period 1: 39% vs. period 2: 37%, $p = 0.84$) (Figure 1). No significant difference was likewise observed in both the incidence density (15.40 vs. 15.04 per 1000

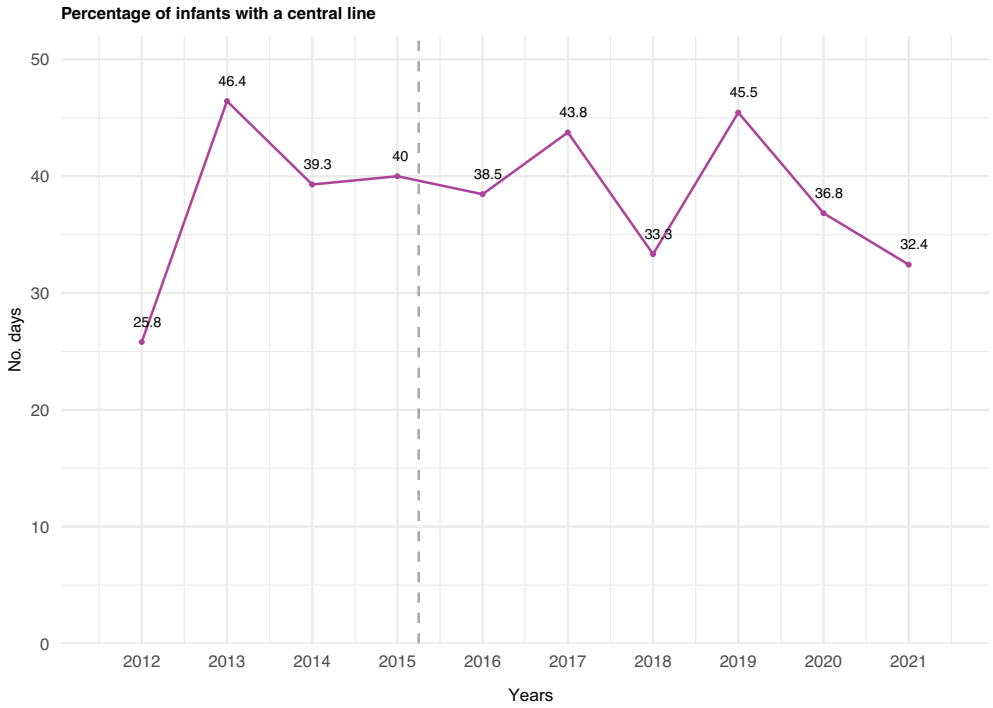

FIGURE 1 Percentage of infants with a central-line. ET guideline change indicated by vertical, dashed line. [Color figure can be viewed at wileyonlinelibrary.com]

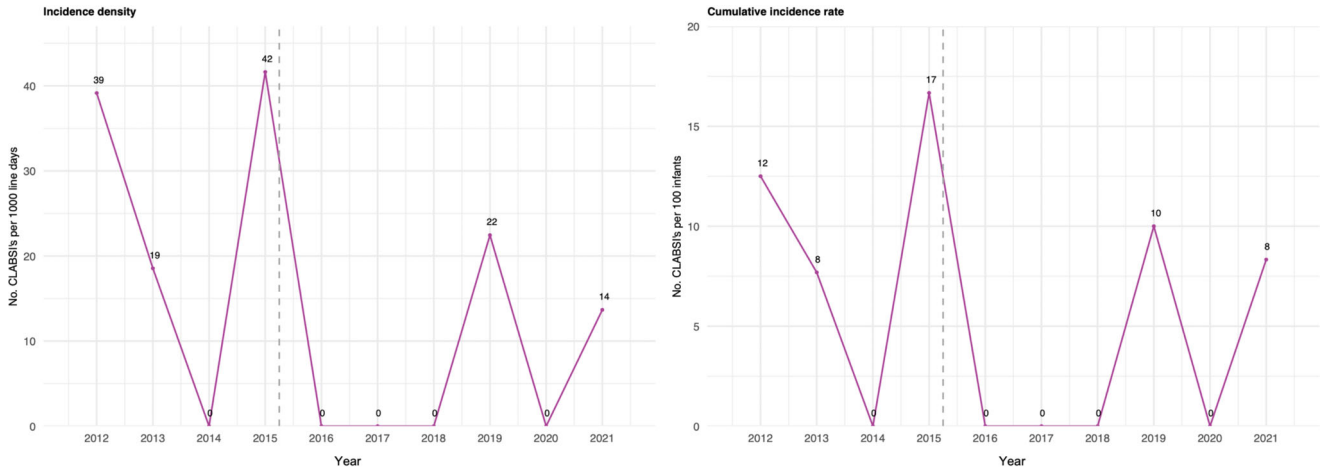

FIGURE 2 Incidence density and cumulative incidence rate of CLABSI. ET guideline change indicated by vertical, dashed line. [Color figure can be viewed at wileyonlinelibrary.com]

central-line days, $p = 0.95$) and cumulative incidence rates (5.56 vs. 6.45 per 100 neonates, $p = 0.80$) (Figure 2).

4 | DISCUSSION

In this study, we evaluated central-line utilization and the incidence of confirmed and suspected EOS and LOS, including CLABSI, in relation to the increasingly uncommon ET procedure among neonates with severe HDFN. Despite the previously reported decrease in ET over the years,[7] we observed no concomitant decrease in the number of infants with a central-line nor CLABSI rate. Laboratory-confirmed sepsis was found in 16 neonates, the majority of which occurred ≥72 h after birth. Group B Streptococcus and *Staphylococcus aureus* were the most frequently isolated pathogens in early-onset and late-onset infections, respectively. Similarly, 29 sepsis work-ups were performed in 25 infants clinically suspected of infection with no evident decrease in overall antibiotic consumption as expressed by the DOT and LOT rates seen over time. Neonates with a central-line were found to be at a higher risk for both a confirmed late-onset infection and sepsis evaluation with subsequent antibiotic treatment.

To the best of our knowledge, this is the first study to assess the burden of confirmed and suspected sepsis, including central-line use and the risk of CLABSI, among neonates with HDFN. Numerous studies have assessed the risk of infection after ET, reporting substantial variation in incidence rates. As previously reported by our group in a retrospective observational study investigating the occurrence of complications during admission in neonates with HDFN, infants treated with ET were shown to have a significantly higher risk of proven sepsis compared to those without the need for ET (8.2% vs. 1.4%, adjusted OR 8.3, 95% CI: 1.7–40.3).[5] Similarly, Steiner et al. reported a sepsis rate of 12% among infants who received single- or double volume ET.[20] Even though the proven overall sepsis rate of 6.2% in our study is lower than those reported by two previously mentioned studies, a number of factors compromise accurate comparison. First, available evidence on sepsis among infants with HDFN has thus far exclusively pertained to studies conducted in relation to ET, making the overall infection prevalence among this population unknown. Although infection may indeed be associated with ET, particularly in the context of central-line requirement, the exact cause of the increased infection risk remains unknown. Other potential causes such as pre-existing morbidity, maternal risk factors and poor adherence to infection-control measures should also be taken into consideration. Second, considerable variation exists with regards to the definitions used to confirm neonatal sepsis. Definitions vary from culture-confirmed infections in combination with biochemical and/or clinical signs of infection to the presence of signs and symptoms alone,[5,21,22] without any clear distinction made between early- and late-onset infections despite their distinct underlying etiologies. Moreover, few studies have investigated presumed (i.e., culture-negative) sepsis, even though this diagnostic entity is an important indicator for antibiotic use. By diagnosing infection episodes using established surveillance criteria we were able to evade issues related to inaccurate infection detection and reporting. In contrast to studies exclusively pertaining to neonates with HDFN however, our sepsis rate seems to be approximately 5–10 times higher as compared to those reported among general late-preterm to full-term neonates. In a large national study conducted by Cohen-Wokowiez et al. 0.6% of late-preterm infants (34–36 weeks' gestation) were found to have culture-proven LOS.[23] Similarly, Aziz et al. found that 2.5% of infants ≥1500 grams were diagnosed with nosocomial sepsis during NICU

admission.[24] It can therefore be speculated that many of the infection episodes in our study may have ensued from the presence of an intravascular device, supporting the need to further optimize prevention efforts.

Despite the decline in ET as previously reported by our group,[7] we observed no concomitant decrease over time in the number of neonates with a central-line, suggesting that there is still a relatively high tendency towards preemptive central-line placement among neonates with HDFN. Even though evidence regarding central-line utilization and prevalence of CLABSI has primarily focused on (extremely) preterm infants or the NICU population in its entirety, our rates are higher than those reported by a previous study from our center, which found a CLABSI incidence of 12.3, 10.6, and 5.3 per 1000 central-line days for femoral-venous, umbilical-venous, and peripherally-inserted central catheters, respectively, among neonates born ≥34 weeks' gestation.[25] Similarly, a summary report published by the National Healthcare Safety Network found a pooled mean rate of 0.6–0.8 per 1000 central-line days among neonates with a birth weight ≥1501 grams admitted to level III NICUs.[26] A potential reason for this large discrepancy in incidence rates may be the exclusive and thus perhaps limited indications for central-line placement among infants with HDFN compared to the overall NICU population which may have resulted in an overestimation of the CLABSI incidence due to the substantially lower number of central-line days. Moreover, variation in CLABSI criteria, surveillance methods and blood culture practices used for (local) monitoring must also be taken into account. Given that core aspects of the work environment (e.g., workload, staff interplay with the organization) and compliance to and composition of evidence-based bundle practices (especially regarding the timely removal of the central-line), are important precursors to lower CLABSI rates, we anticipate that discrepancies in these areas may have also contributed to interinstitutional variation in incidence rates.

It is important to note that ET was deemed not necessary in nearly one-third of infants who received a central-line due to an imminent ET, implicating that an invasive device carrying a potential infection risk may have been unnecessarily placed. In consequence, two-thirds of the CLABSI episodes occurred in infants in whom an ET was not performed. Moreover, difficulty in securing peripheral vascular access formed an additional, common reason for central-line placement, suggesting that optimizing management strategies such as utilizing advanced visualization techniques or enlisting experienced staff may aid in restraining otherwise unnecessary central-line use. As such, reserving central-line use for infants whose total serum bilirubin levels have (closely) approached the ET threshold and will therefore almost certainly necessitate an ET, as well as tackling intravenous drip cannulation issues are recommended measures to limit the use of central-lines and consequent CLABSI risk.

4.1 | Strengths and limitations

This study has several strengths and limitations. A primary strength is the specialized- and centralized-care setting in which the study was conducted, providing us with a homogeneous and consolidated study population with an increasingly rare disease. Our results must nevertheless be interpreted with caution and not directly extrapolated given the selection of severe HDFN cases based on our national referral guidelines. Another strength is the well-defined, unified criteria used to confirm neonatal CLABSI cases, enabling further collaborative research and benchmarking, as well as the details of indications for central-line use. In addition to its retrospective nature, a limitation of this study includes the small sample size, hindering our ability for risk factor assessment. Nevertheless, this is the largest and only cohort thus far to have addressed the burden of sepsis and central-line utilization among infants with HDFN. Moreover, the indication for central-line insertion was unknown in nearly one-fourth of neonates with a central-line, indicating that the number of infants in whom a central-line was unnecessarily placed due to an impending ET without eventual ET may have been greater.

5 | CONCLUSION

In summary, this study indicates that neonates with HDFN carry an important risk of infection and antibiotic treatment, particularly those with a central-line. Moreover, no difference in central-line utilization and CLABSI rates before and after a more restrictive ET guideline change was observed. The occurrence of CLABSI, therefore, remains a cause for concern, particularly considering that a substantial proportion of neonates who received a central-line by reason of an impending ET ultimately did not require an ET. Limiting central-line use to those with a legitimate risk for ET, improving peripheral vascular access management, and implementing well-established CLABSI prevention strategies are needed to achieve and sustain low infection rates.

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CONFLICT OF INTEREST

There is no potential conflict of interest to disclose.

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