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Management of Apnoea in Extremely Preterm Infants: A European Survey

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Abstract
Introduction: Episodes of apnoea are common in extremely preterm infants (EPIs) and usually treated with caffeine and respiratory support. Understanding differences in apnoea definitions, monitoring practices, and use of respiratory stimulants is essential to improve future treatment. ***Methods:*** Between March and July 2024, one lead consultant at European tertiary neonatal intensive care units (NICUs) was invited to complete a web-based survey on respiratory practices in EPIs. We sought information how they defined apnoea and monitored for it, and how they treated it with caffeine, doxapram, and non-invasive respiratory support. ***Results:*** We received replies from 447/721 (62%) NICUs across 24 European countries. Most NICUs (74%) use both electrocardiogram electrodes and pulse oximetry for apnoea monitoring. All NICUs reported using caffeine citrate, with 102 centres (23%) starting it in the delivery room. The median loading, maintenance and maximum maintenance doses used are 20 mg/kg, 5 and 10 mg/kg/day, respectively. Caffeine is occasionally given twice daily in some NICUs (30%) and stopped at 34–35 weeks of postmenstrual age at most of them (74%). Doxapram is used at 111 (25%) NICUs, with geographical differences. Strategies for the use and escalation of non-invasive respiratory support in case of persistent apnoea are not clearly defined. Automatic closed-loop oxygen delivery is used at 25% of NICUs. ***Conclusion:*** Despite consistency in the dosing and weaning of caffeine, there is much variation in the management of apnoea in preterm infants across Europe. Future research should focus on timing and dosage of caffeine, the use of doxapram, and strategies for optimising non-invasive respiratory support.

Introduction

Preterm infants have highly variable breathing patterns, characterised by fast respiratory rate with small tidal volumes, alternating with pauses and sigh breaths [1]. This reflects both the antenatal breathing pattern and a delay in the maturation of breathing control [2]. During antenatal life, intermittent breathing is functional to retain lung liquid volume and promote lung development [3]. After birth, recurrent apnoea episodes, often associated with bradycardia and hypoxaemia, are commonly observed in extremely preterm infants (EPIs) [4]. There is evidence that the burden of hypoxic episodes is associated with adverse neurodevelopmental outcomes [5].

The goal of treating apnoea is to improve respiratory stability, thereby preventing hypoxia and avoiding mechanical ventilation with its associated increased risk of respiratory morbidity [6]. After the seminal Caffeine for Apnoea of Prematurity (CAP) trial, showing a reduced incidence of bronchopulmonary dysplasia (BPD) and neurodevelopmental impairment [7], caffeine became the mainstay treatment of apnoea of prematurity in neonatal intensive care units (NICUs) [4]. However, questions remain regarding the start of treatment [8], the route of administration, dosing [9], and when to discontinue [10]. Moreover, other respiratory stimulants and various modes of non-invasive respiratory support are used to manage apnoea and to support spontaneous breathing in EPIs [11]. This survey aimed to identify current clinical practices in apnoea management of EPIs in NICUs across Europe to identify areas requiring further clinical research to improve outcomes.

Methods

A consortium from the pulmonology section of the European Society of Paediatric Research (ESPR) undertook a survey of respiratory practices in EPIs (gestational age (GA) <28 weeks) in Europe. Twenty-four countries were represented by at least one national principal investigator (PI): Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Lithuania, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, Turkey, and the UK.

The survey was divided into five sub-domains: (1) characteristics of participating NICUs, (2) practice in guiding transition after birth, (3) respiratory support strategies, (4) apnoea management, and (5) therapies for respiratory distress syndrome and evolving BPD. This paper reports on apnoea management. Data on other sub-domains will be reported separately. We asked specifically for apnoea definitions, apnoea

monitoring practices, use of caffeine and dosing recommendations, use of doxapram and use of non-invasive respiratory support for apnoea management. Five members of the consortium (A.L., J.H., C.H., R.S., C.K.) created the first draft of the survey, which was then distributed for feedback to a group of eight members (A.L., J.H., C.H., R.S., C.K., A.v.K., W.O., M.v.d.L.). Neonatologists at five centres tested the survey to improve clarity of content and design. Following three rounds of corrections, the final version was accepted in March 2024.

The survey (online suppl. Material 1; for all online suppl. material, see https://doi.org/10.1159/000547546) was presented in English using Google Forms. It was headed by a brief description of the consortium and the study aim. There was a clear instruction that only one person in each NICU should complete the survey. The survey contained mainly closed questions, some with yes/no answers, and others with multiple-choice options. The number of questions varied, as the survey was designed with adaptive questioning. The estimated time to complete the survey was 10–15 min.

We collected responses between March and July 2024. Each national PI was responsible for identifying all NICUs in their country where EPIs are treated. They then emailed a link to the survey to a contact person at each NICU. Up to four email reminders were sent. We followed the checklist for reporting the results of Internet E-surveys [12]. We did not perform comparative analyses and report only descriptive data. We present quantitative variables as medians with interquartile ranges (IQRs) or frequencies (%), as appropriate.

Results

We distributed the survey to 721 NICUs in 24 countries. We received 465 replies and, after excluding 18 (14 from NICUs that had already responded, and 4 from units where EPIs were not treated), we included information from 447 completed surveys, a response rate of 62%. Median response rate per country was 81% (IQR 49–100). Participating NICUs reported a median of 13 NICU beds (IQR 9–20) and 30 EPI admissions per year (IQR 20–50). The lowest GA at which treatment was considered varied, with 18% reporting a lower limit at 24 weeks, 43% at 23 weeks, and 38% at 22 weeks.

The three most common definitions for apnoea used in participating NICUs were as follows: (i) cessation of breathing ≥ 15–20 s associated with oxygen desaturation and/or bradycardia (65%), (ii) cessation of breathing ≥ 15–20 s associated with oxygen desaturation (19%), and (iii) cessation of breathing ≥ 15–20 s (13%), respectively. The main cardiorespiratory monitoring technique was combined electrocardiogram and pulse oximetry (74%), while 26% relied on pulse oximetry only. In most NICUs, apnoea treatment is guided by a local protocol (55%), while over a quarter of NICUs (28%) follow a national protocol. The remaining NICUs (17%) did not report using a protocol.

All NICUs use caffeine as a pharmacological treatment for apnoea, mainly in the citrate formulation (414/447; 93%). In 102/447 centres (23%), caffeine is initiated in the delivery room (DR), and most commonly (90%) administered via a peripheral venous catheter and rarely via the umbilical vein (5%) or orally (5%). For the remaining NICUs, caffeine is commenced in the NICU and almost universally (96%) regardless of the type of respiratory support, with only a small minority (4%) reserving caffeine only to EPIs on non-invasive respiratory support. Almost all NICUs reported that caffeine was started intravenously (98%). Information on loading dose, maintenance doses, dosing frequency, serum concentration monitoring, and postmenstrual at discontinuation is reported in Table 1 and Figure 1. Some NICUs reported administering caffeine twice daily for the following reasons: the presence of an increased number of apnoeas throughout the day (74%); too high a single maintenance dose (17%), the presence of side effects with once daily dosing (4%); and older preterm infants (2%). A total of 316 NICUs (71%) indicated occasional use of an additional loading dose of caffeine. An increase in the number of apnoeas was given as the main reason (98%) for administering an additional loading dose of caffeine.

A total of 111/447 (25%) NICUs across Europe reported routine use of doxapram as an add-on therapy to caffeine, with large geographical differences (shown in Fig. 2). In 51 NICUs, doxapram is administered only intravenously, while the remaining 60 NICUs use either intravenous or oral administration. For intravenous doxapram administration, the median (IQR) starting dose and the maximum maintenance dose were 1 (1–2) and 2 (1.5–2) mg/kg/h, respectively. We also asked whether the NICUs had a standardised protocol to assess the maximal number of "physical stimulations" before increasing other support for apnoea, with only 21% reporting to have such.

Table 1. Caffeine practice of participating NICUs

Practise	*N* (%)/median (IQR)
Location of caffeine initiation	
In the delivery room	102 (23%)
In the NICU	345 (77%)
Dosing frequency	
Once daily	286 (64%)
Twice daily	25 (6%)
Sometimes twice daily	136 (30%)
Loading dose, mg/kg	20 (0), total range 5–40
Maintenance dose, mg/kg/day	5 (5–10), total range 2.5–20
Maximum maintenance dose, mg/kg/day	10 (10–15), total range 5–40
Monitoring serum concentration	
No	395 (89%)
Yes	6 (1%)
Sometimes	46 (10%)
Cessation of caffeine therapy	
At PMA 32–33 weeks	37 (8%)
At PMA 34–35 weeks	330 (74%)
At PMA 36–37 weeks	44 (10%)
No specific local guideline regarding PMA	36 (8%)

All data are number (%) or median (IQR) if not otherwise stated. All values are for caffeine citrate, and if caffeine base was used, these values are converted to citrate. PMA, postmenstrual age; NICU, neonatal intensive care unit; IQR, interquartile range.

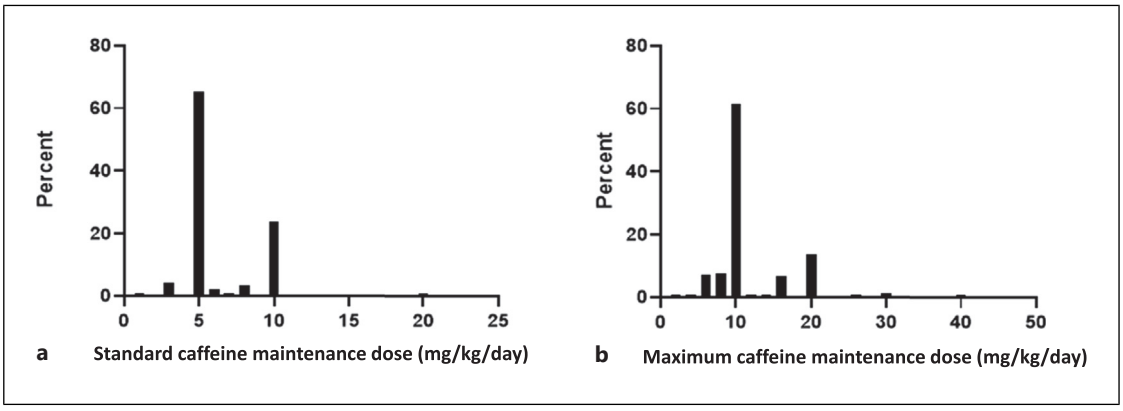

Fig. 1. Reported standard (**a**) and maximum (**b**) caffeine citrate maintenance dose (mg/kg/day) in EPIs in 447 NICUs across Europe.

In case of persisting apnoeas in EPIs receiving nasal continuous positive airway pressure (nCPAP), most NICUs (72%) reported switching to another mode of non-invasive respiratory support, a minority (25%) attempting to increase the nCPAP level first, and the remaining not having standardised the respiratory support management. When switching to another form of non-invasive respiratory support is made, the following modes were reported: non-synchronised nasal intermittent positive pressure ventilation (nIPPV) (48%), followed by synchronised nIPPV (31%), bi-level CPAP (17%), nasal-high frequency oscillation (2%), and not specified (2%). Most NICUs (75%) did not use automatic closed-loop oxygen delivery during non-invasive respiratory support for infants with frequent apnoeas.

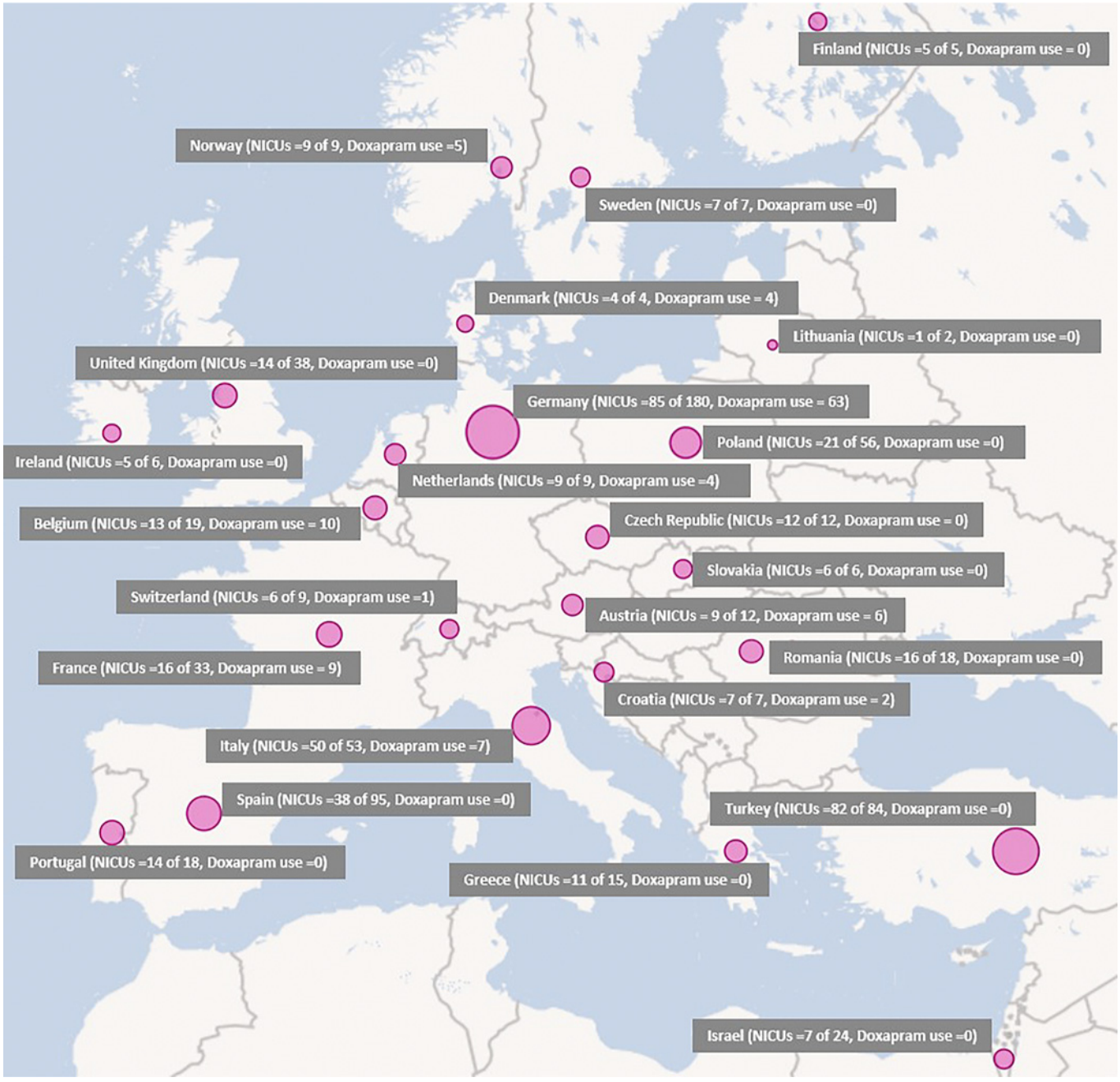

Fig. 2. Rate of doxapram use in European countries in participating NICUs. The size of the dots on the map is proportional to the number of participating NICUs in the survey. For each country, we specified the number of centres that responded and the number of NICUs using doxapram.

Discussion

This survey, which included responses from >400 NICUs, showed that caffeine is the main pharmacological treatment for apnoea in EPIs across Europe. However, variations exist in the dosing regimen, frequency of administration, and cessation of treatment. Doxapram, a pharmacological add-on therapy when caffeine is not sufficient to control apnoeas, is applied in a quarter of all centres, with great variations between countries. No agreement exists about the escalation of non-invasive respiratory support in EPIs on nCPAP with inadequate control of apnoeic episodes.

Most of the respondents defined "apnoea" as a cessation of breathing associated with desaturation and/or bradycardia. Thus, to assess the apnoeic episodes, three-quarters of the participating NICUs employ both pulse oximetry and electrocardiogram electrodes to monitor transthoracic impedance. Of note, transthoracic impedance may fail to detect apnoeic events by mistaking fluctuations in cardiac impedance for respiratory signals and cannot detect primary obstructive apnoea [13]. The majority of units used either a local or national protocol for apnoea management, highlighting both the perceived clinical relevance of apnoea in EPIs and the need for guidance. Most European NICUs use caffeine citrate formulation, but both caffeine base and citrate share similar efficacy and safety profiles [14].

There is high certainty level evidence that caffeine for EPIs prevents the development of BPD and reduces adverse long-term neurodevelopmental outcomes [7]. Our data demonstrate a universal adherence across Europe to this evidence and that caffeine is started prophylactically in most centres, i.e., irrespective of the presence of apnoea or mode of respiratory support. A subgroup analysis of the CAP trial revealed a greater benefit in reducing BPD when caffeine is commenced <3 days versus ≥3 days after birth [15]. A large US cohort study confirmed a lower rate of BPD, haemodynamically significant patent ductus arteriosus, and a shorter duration of mechanical ventilation with early caffeine administration [16]. Accordingly, we found homogeneity among the centres in starting caffeine within the first days after birth. However, in the current era of less invasive surfactant administration, a more liberal and very early caffeine treatment strategy has emerged [17]. A quarter of the participating NICUs start caffeine in the DR despite only a few pilot trials testing the efficacy and safety of this approach [18, 19]. In one study of 30 infants (GA 24–30 weeks), a caffeine loading dose given within 5 min from birth significantly improved ventilation during respiratory stabilisation but had no impact on oxygenation or other short-term clinical outcomes [18]. Another study of 38 infants (GA <30 weeks) found no difference in caffeine blood levels or clinical outcomes between those receiving enteral or intravenous caffeine in the DR [19]. The intravenous route is preferred for initial caffeine administration in EPIs, probably given that these vulnerable infants usually require venous access in the first days of life and since feeding intolerance is relatively common. Nevertheless, oral caffeine is absorbed in the upper gastrointestinal tract with almost a complete bioavailability [14].

The loading and maintenance doses of caffeine citrate in European NICUs are in line with the CAP trial, with a median dose of 20 mg/kg and 5 mg/kg/day, respectively. The highest median maintenance dose was 10 mg/kg/day but ranging up to 30 mg/kg/day. In a meta-analysis, higher caffeine doses have been associated with a further reduction in BPD rates, but with no effect on mortality or neurodevelopmental impairment [9]. The quality of evidence for higher caffeine dosing is low. This may explain the observed variation in higher dosing strategies across participating units. According to the survey, caffeine is generally given once daily in line with the CAP trial and reflecting serum half-life of up to 100 h in preterm infants [14]. However, most participating centres (71%) administered additional loading doses when apnoeas increased. This may be a result of caffeine clearance increasing as half-life decreases during the first postnatal weeks. Very few centres (6%) routinely use caffeine twice a day, but in nearly a third of participating NICUs, dosing twice daily was used when "deemed necessary for various reasons". However, there is no pharmacological or clinical evidence supporting more frequent dosing [20]. Almost none of the centres perform drug-level monitoring, reflecting the high therapeutic index of caffeine.

Apnoea of prematurity generally resolves by 35–40 weeks of postmenstrual age (PMA), but those born <28 weeks of gestation or affected by BPD may present a delayed maturation in the control of breathing. The variability in apnoea resolution complicates decision-making with respect to caffeine discontinuation. Various approaches have been suggested, including discontinuation at a certain PMA or following an apnoea-free period. According to our survey, caffeine is mostly stopped related to PMA, predominantly at around 34–35 weeks of PMA. Current evidence does not support a clear and unequivocal timing for when caffeine therapy should be discontinued. However, caffeine administration to EPIs often is prolonged to at least 36 weeks of PMA [21].

If apnoea is refractory to standard caffeine therapy, doxapram may be considered as an additional therapy to prevent intubation [22]. A quarter of all centres that responded used doxapram in EPIs, but we observed substantial variation both within and between countries across Europe. Large countries like Turkey, Spain, and the UK, reported not to use doxapram. Some studies suggest that doxapram may alter brain activity potentially leading to seizures [23]. However, a large retrospective study did not report any association between doxapram and altered neurodevelopment [24]. An ongoing placebo-controlled randomised trial will provide more evidence on efficacy and safety of doxapram in the management of apnoea in EPIs (NCT04430790).

Most EPI will routinely receive non-invasive respiratory support in the management of apnoea of prematurity [11]. Nasal CPAP still represents the most commonly used mode of non-invasive respiratory support and is most effective for

apnoeas with an obstructive component [11]. More advanced non-invasive respiratory modes may both support ventilation and stimulate the spontaneous respiratory drive [11]. In our survey, most of the respondents would escalate the support by changing to a different non-invasive ventilation mode. Synchronised NIPPV modes, such as NIV NAVA, reduce apnoeic episodes by promoting effective ventilation and by applying backup ventilation in case of central apnoea [11]. However, only one-third of the NICUs would apply synchronised NIPPV as this mode is often not available. Similarly, the use of automatic closed-loop oxygen delivery during non-invasive respiratory support, which has been associated with decreasing hypoxic events and apnoea, is still limited [25].

The strength of this study is that almost 450 NICUs responded from 24 European countries, with a median response rate of more than 80% per participating country. However, for a few countries (UK and Spain), a response rate of around 40% limits generalisability. Still, we believe the responses reflect true clinical practice across units, and a high conformity with current evidence was found, in particular for the use of caffeine. Although our survey asked for policies on apnoea management in the NICU, the fact that a single neonatologist provided this information may have resulted in some personal bias. Other possible limitations – intrinsic to the study design – were the use of adaptive questioning to reduce complexity, but with loss in specific practice details and potentially acquiescence bias.

Conclusions

This large European survey identifies several inconsistencies in the current apnoea management of EPIs. The timing – both starting and stopping – and the use of higher doses of caffeine merit further study. The role of doxapram as a respiratory stimulant is still unclear, and more studies are needed. Finally, research on optimisation and escalation of advanced modes of non-invasive respiratory support, including apnoea detection with back-up support, improved synchronisation, and automatic closed-loop oxygen delivery, holds promise to improve the management of apnoea in vulnerable EPIs in the future.

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Statement of Ethics

We did not seek formal approval by the Local/National Ethics Committees as this study only collected information on policies and did not include data from patients. In the survey, we stated the following: "We greatly appreciate your participation in this online survey, which we expect to take no more than 10–15 min to complete. Replies will be treated with strict confidentiality and results will be made public in summarised form only. Data will be accessible only to members of the research team and will be stored safely for a maximum of 15 years. By completing the survey, you consent to the conditions mentioned above".

Conflict of Interest Statement

A.L. has been a consultant for Chiesi S.p.A, Vyaire Medical, and ZOLL. C.H. and C.K. has received honoraria from Chiesi as member of the board for the Nordic Neonatal Meeting. T.S. is the president of Polish Neonatal Society. He has received speakers' honoraria from the following companies: Masimo, Medtronic, AstraZeneca, and Sanofi. H.S. received honoraria from Getinge. A.L., H.E., K.B., and C.K. were all members of the journal's Editorial Board at the time of submission. All the other authors have no conflicts of interest to declare.

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Author Contributions

The authors' contributions to each term of the research are as follows – conceptualisation: C.K., A.L., C.H., R.S., and J.H. Methodology/study design: M.L., C.K., A.L., C.H., R.S., J.H., W.O., and AK. Software, validation, and formal analysis: M.L., J.H., and W.O. Investigation and resources: M.L., C.K., A.L., C.H., R.S., J.H., W.O., A.K., A.A., H.E., M.C., T.S., V.S., G.R., M.W., H.S., O.D., T.D., M.C., A.C., G.D., B.B., B.F., R.H., U.T., K.B., G.L., S.S., R.P., R.T., and C.O.D. Data curation and visualisation: M.L., C.K., A.L., C.H., R.S., and J.H. Writing – original draft: A.L. and J.H. Writing – review and editing: C.K., R.S., C.H., A.K., M.L., W.O., and C.O.D. Supervision: C.K., R.S., A.K., and W.O. Project administration: A.K. and M.L. Funding acquisition: A.L.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the data sharing committee upon request.

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