Clinical Guidelines for Management of Infants Born before 25 Weeks of Gestation: How Representative Is the Current Evidence?

Stacey Peart, MBBS[1,2,3], Mia Kahvo, MSc[4], Tugba Alarcon-Martinez, PhD[1], Kate Hodgson, PhD[1,2,3], Helen S. Eger, PhD[5], Susan Donath, MA[3], Louise S. Owen, PhD[1,2,3], Peter Graham Davis, PhD[1,2,3], Charles C. Roehr, PhD[6,7,8,*], and Brett J. Manley, PhD[1,2,3,*]

Objective To determine whether management guidelines for infants born extremely preterm are representative for those infants <25 weeks of gestation.

Study design Three guidelines were reviewed: the 2022 European Consensus Guidelines on the Management of Respiratory Distress Syndrome, the 2017 American Academy of Pediatrics Guidelines for Perinatal Care, and the 2020/2021 International Liaison Committee on Resuscitation guidelines. All referenced studies for overlapping recommendations were reviewed. Data extracted included the total number and proportion of infants <25 weeks of gestation in the original articles referred in the guidelines. Where the exact number of infants <25 weeks of gestation was unobtainable, this was conservatively estimated by statistical deduction.

Results Eight recommendations were included in 2 or more guidelines: (1) antenatal corticosteroids, (2) antenatal magnesium sulfate, (3) delayed cord clamping, (4) thermoregulation at birth, (5) initial oxygen concentration at birth, (6) continuous positive airway pressure, (7) surfactant, and (8) parenteral nutrition. In total, 519 studies (n = 409 986) informed these 8 recommendations, of which 335 (64.5%) were randomized controlled trials (n = 78 325). Across all studies, an estimated 59 360 (14.5%) infants were <25 weeks of gestation. Within randomized controlled trials alone, an estimated 5873 (7.5%) infants were <25 weeks of gestation. A total of 196 (37.8%) studies did not include any infants <25 weeks of gestation.

Conclusions Infants born <25 weeks of gestation are not well-represented in the evidence used to develop major clinical guidelines for infants born extremely preterm. Future studies should provide evidence for this population as a distinct cohort. *(J Pediatr 2025;278:114423)*.

Globally, there has been no improvement in rates of extremely preterm birth before 28 weeks of gestation.[1] With advances in neonatal care, survival rates of infants born extremely preterm are also increasing,[2,3] and intensive care currently is being offered to infants born as early as 22 weeks of gestation in some centers.[4-6] Compared with their term-born counterparts, children born extremely preterm have greater rates of cerebral palsy, cognitive impairment, visual and hearing impairment, and behavioral and learning difficulties,[7-14] with the incidences being inversely proportional to gestation. Importantly, rates of these outcomes in the infants born most preterm, defined as those born before 25 weeks of gestation, vary considerably, reflecting different philosophies, practices, and experience in providing active care to these infants.[4,15-17]

Although much research has focused on the population of infants born extremely preterm, this subset at greatest risk is not well represented in clinical trials. A systematic review by Pavlek et al demonstrated that since 2010, only 1% of all infants included in randomized controlled trials (RCTs) that aimed to enroll infants defined as extremely preterm were born at <24 weeks of gestation.[18] However, according to recent Australian and New Zealand data, infants born <25 weeks constitute 28% of all extremely preterm births.[19] Infants born <25 weeks of gestation face greater challenges than infants born preterm at 25-27 weeks of gestation. As fetal development is a continuum, the physiology and responses to treatment of the infants born most preterm likely differ from those seen in more mature infants born extremely preterm, and uncertainty about these differences has led to inconsistent clinical practices in their care.[20]

It cannot be assumed that management guidelines for infants born extremely preterm are appropriate for infants born <25 weeks of gestation. The aim of this study was to determine whether important management guidelines aimed at

ANS	Antenatal corticosteroids
RCT	Randomized controlled trial

From the [1]Newborn Services and Newborn Research, Royal Women's Hospital, Melbourne, Australia; [2]Department of Obstetrics, Gynaecology and Newborn Health, The University of Melbourne, Melbourne, Australia; [3]Department of Clinical Sciences, Murdoch Children's Research Institute, Melbourne, Australia; [4]Regional Neonatal Intensive Care Unit, St Michael's Hospital, Bristol, United Kingdom; [5]Division of Children and Adolescent Medicine, Oslo University Hospital, Oslo, Norway; [6]National Perinatal Epidemiological Unit, Oxford Population Health, University of Oxford, Oxford, United Kingdom; [7]Newborn Services, Southmead Hospital, Bristol, United Kingdom; and [8]Faculty of Health Sciences, University of Bristol, Bristol, United Kingdom

*Contributed equally.

https://doi.org/10.1016/j.jpeds.2024.114423

infants born extremely preterm are representative of the most infants born preterm.

Methods

Data Sources

Three recent international guidelines for the clinical management of infants born preterm were reviewed: the 2022 European Consensus Guidelines on the Management of Respiratory Distress Syndrome[21]; the 2017 American Academy of Pediatrics Guidelines for Perinatal Care[22]; and the 2020 International Liaison Committee on Resuscitation guidelines (including the 2021 update).[23,24] After a search for guidelines regarding the management of infants born preterm, these widely cited guidelines were selected for their international importance, geographic representation, and impact on clinical care through the delivery of comprehensive evidence-based recommendations. No explicit inclusion or exclusion criteria were applied in this selection.

Recommendations that were made in at least 2 of these 3 guidelines were included in the study. All original citations for a particular recommendation that included infants born <37 weeks of gestation and were published in English were reviewed. Relevant primary references that were not an original study were screened for secondary references, with the process repeated to identify tertiary references. Studies were excluded if they were studies in animals, did not report a neonatal outcome, were of no direct relevance to the recommendation, or were exclusive to infants born at term. For publications reporting follow-up studies or substudies of already-included RCTs, only the original study was included in the analysis. All studies were checked for published retractions.

Data Extraction

Data were independently extracted by the authors using a designed data collection form. For each article, the following data were collected: year of publication, country (including economic resource level: low- to middle-income country or high-income country, as defined by the World Bank[25]), single or multicenter study, study design, gestational age inclusion criteria, number of participants, the mean and SD or median and IQR gestational age of participants, proportion of included infants <25 weeks of gestation, and the primary outcome.

In cases in which the exact number of included infants <25 weeks of gestation was not reported, authors of papers that were published within the last 10 years were contacted with requests for this information. For older papers, or if these data were unavailable, the number of infants <25 weeks of gestation was estimated using an algorithm determined on the basis of the mean (SD)/median (IQR) gestational age reported in the study (**Supplementary Material Section 1**, available at www.jpeds.com). This algorithm was designed to predict the maximum number of infants born <25 weeks of gestation who could have been enrolled. The estimated number of infants <25 weeks of gestation was always rounded up to the nearest whole number of infants. Studies that reported neither the exact number of infants <25 weeks of gestation enrolled nor the mean (SD)/median (IQR) gestational age of enrolled infants (to allow for the estimation algorithm to be used) were excluded.

Data Synthesis

For each guideline recommendation, the following variables are presented as counts (%) or median (range) where appropriate: number of studies; number of RCTs; studies with known number of infants <25 weeks of gestation; studies that enrolled zero infants <25 weeks of gestation; studies that exclusively (only) enrolled infants <25 weeks of gestation; total number of infants included across all studies; total number of infants born <25 weeks of gestation included across all studies; total infants included across all RCTs; and total infants born <25 weeks of gestation included across all RCTs.

Results

Eight recommendations appeared in at least 2 of the 3 guidelines and were included in this study (**Table I**): (1) antenatal corticosteroids (ANS); (2) antenatal magnesium sulfate; (3) delayed umbilical cord clamping; (4) thermoregulation measures; (5) initial oxygen concentration when commencing respiratory support at birth; (6) early continuous positive airway pressure; (7) surfactant administration; and (8)early parenteral (intravenous) nutrition. The **Figure** depicts the total number of identified, screened, and included studies for all the aforementioned recommendations, combined. A total of 519 studies spanning from 1972 to 2022, enrolling 409 986 infants born preterm informed the 8 recommendations and were included (**Table II**). Of these 519 studies, 335 (64.5%) were RCTs that enrolled a total of 78 325 infants born preterm. Most studies (81.7%) were performed in high-income countries (**Supplementary Material Section 2: Tables I** and **II**, available at www.jpeds.com).

Across all studies, there were an estimated 59 360 (14.5%) infants born at <25 weeks of gestation. Within RCTs alone, there were an estimated 5873 (7.5%) infants born at <25 weeks of gestation included. Of the 519 studies, 196 (37.8%) did not include any infants born at <25 weeks of gestation, 323 (62.2%) were estimated to have included at least 1 infant born at <25 weeks of gestation, and 5 studies (1%)[26-30] exclusively enrolled infants born at <25 weeks of gestation (**Table II**). When only RCTs were considered, 139 of 335 RCTs (41.5%) did not include any infants born at <25 weeks of gestation, 196 (58.5%) were estimated to have included at least 1 infant born at <25 weeks of gestation, and 1 (0.3%) RCT exclusively enrolled infants born at <25 weeks of gestation (**Table III**). Overall, 11 studies, of antenatal corticosteroids (10 studies), and early continuous positive airway pressure (1 study), stratified participants at randomization into <25 weeks and

Table I. Guideline recommendations

Type of recommendations	Recommendation	Referenced guideline
ANS	ANS should be administered to all women at risk of preterm birth occurring at a viable gestational age up to 34 weeks of gestational age, ideally at least 24 hours before birth. ANS may be considered for women up to $36^{6/7}$ weeks of gestational age. A single repeat course may be given if ongoing risk of preterm birth and the first course was at least 1-2 weeks prior. Regularly scheduled repeat courses are not recommended.	*,†
Antenatal magnesium sulfate	Magnesium sulfate should be administered to women with imminent delivery before 32 weeks of gestation	*,†
Delayed cord clamping	Delayed cord clamping for at least 30-60 seconds is recommended for infants born <34 weeks of gestational age who do not require immediate resuscitation at birth. When delayed cord clamping is not feasible, consider umbilical cord milking in infants >28 weeks of gestational age. Umbilical cord milking is not recommended for infants <28 weeks of gestational age.	*,‡
Thermoregulation measures	Infants born preterm at <32 weeks of gestational age should be placed under a radiant warmer and have a combination of interventions used to avoid hypothermia, including being placed in a plastic wrap without drying, cap, thermal mattress, and humidified gases.	*,†,‡
Initial oxygen concentration	Infants born preterm at <35 weeks of gestational age receiving respiratory support should be commenced in an initial oxygen concentration of 21%-30%.	*,†,‡
CPAP	Spontaneously breathing infants born preterm with respiratory distress requiring respiratory support in the delivery room should be commenced on CPAP rather than intubation and intermittent positive pressure ventilation.	*,‡
Surfactant	Infants born at <30 weeks of gestational age who require intubation should receive surfactant, with a recommendation for 200 mg/kg of an animal-derived surfactant preparation. Spontaneously breathing infants born preterm with respiratory distress syndrome should receive surfactant via the less-invasive surfactant administration method. Rescue surfactant should be administered early when an infant is requiring >30% oxygen on a CPAP >6 cmH_2O. A second and occasionally a third dose of surfactant (100 mg/kg) should be given if there is ongoing evidence of respiratory distress syndrome.	†,‡
Parenteral nutrition	Parenteral nutrition should be commenced as soon as possible after birth for infants who weigh less than <1500 g.	*,†

ANS, antenatal corticosteroids; *CPAP*, continuous positive airway pressure.
*2022 European Consensus Guidelines on the Management of Respiratory Distress Syndrome.
†2017 American Academy of Pediatrics Guidelines for Perinatal Care.
‡2020 International Liaison Committee on Resuscitation (ILCOR) guidelines (including the 2021 update).

≥25 weeks of gestation subgroups and reported outcomes by subgroups. One of these studies was an RCT.[31]

Overall, the exact number of enrolled infants born at <25 weeks of gestation was known in 199 of 519 (38.3%) studies, of which 161 (80.9%) studies contained zero infants born at <25 weeks of gestation and 38 (19.1%) studies enrolled at least 1 infant born at <25 weeks of gestation (**Supplementary Material Section 3: Tables III** and **IV**, available at www.jpeds.com). The remaining 320 studies (61.7%) required estimation of infants born at <25 weeks of gestation using the algorithm.

The greatest representation of infants born at <25 weeks of gestation was in studies of ANS (estimated 48 248 of 281 742 [17.1%] infants). The lowest representation of infants born at <25 weeks of gestation was in studies of antenatal magnesium sulfate (estimated 1421 of 25 589 [5.6%] infants). Conversely, when only RCTs were considered, the lowest proportion of infants born at <25 weeks of gestation was in studies of ANS (estimated 179 of 14 303 [1.3%] infants), whereas the greatest proportion was in studies of parenteral nutrition (estimated 481 of 3567 [13.5%] infants). On review of studies that explicitly reported the number of infants born at <25 weeks of gestation enrolled, there were no apparent trends observed regarding the inclusion of infants born at <25 weeks of gestation in RCTs over time.

Discussion

This study systematically reviewed the evidence that has informed 3 major international guidelines regarding the care of infants born extremely preterm. Only 7.5% of infants born preterm enrolled in RCTs informing important clinical guidelines were estimated to be born <25 weeks of gestation. Current "evidence-based" clinical recommendations may therefore not represent the most immature group of infants, even for the most common, best-studied, and most highly recommended therapies. Although almost two-thirds of studies overall included some infants <25 weeks of gestation, the median number of enrolled infants per study was very low: range of medians 0-8 infants <25 weeks of gestation (**Table II**). Of the 196 studies that did not include any infants <25 weeks, 44 (22.4%) were primary references, with a further 133 (67.9%) included in a Cochrane or systematic review that formed a primary or secondary reference. These studies lack representation of infants <25 weeks but are being used as references to guide treatment recommendations for these infants. Very few studies, 5 of 519 (1%), of which only 1 was an RCT, exclusively enrolled infants born at <25 weeks of gestation. This suggests that data from this cohort are insufficient, a fact acknowledged in the latest edition of the European Consensus Guideline on the Management of Respiratory Distress Syndrome, which explicitly advises caution when applying the current recommendations to the infants born most preterm.[21]

These results highlight the urgent need for more studies that include, and specifically enroll, infants from this greatest-risk cohort of infants <25 weeks of gestation. With extremely preterm birth rates increasing, and increasingly immature infants being offered neonatal intensive care,

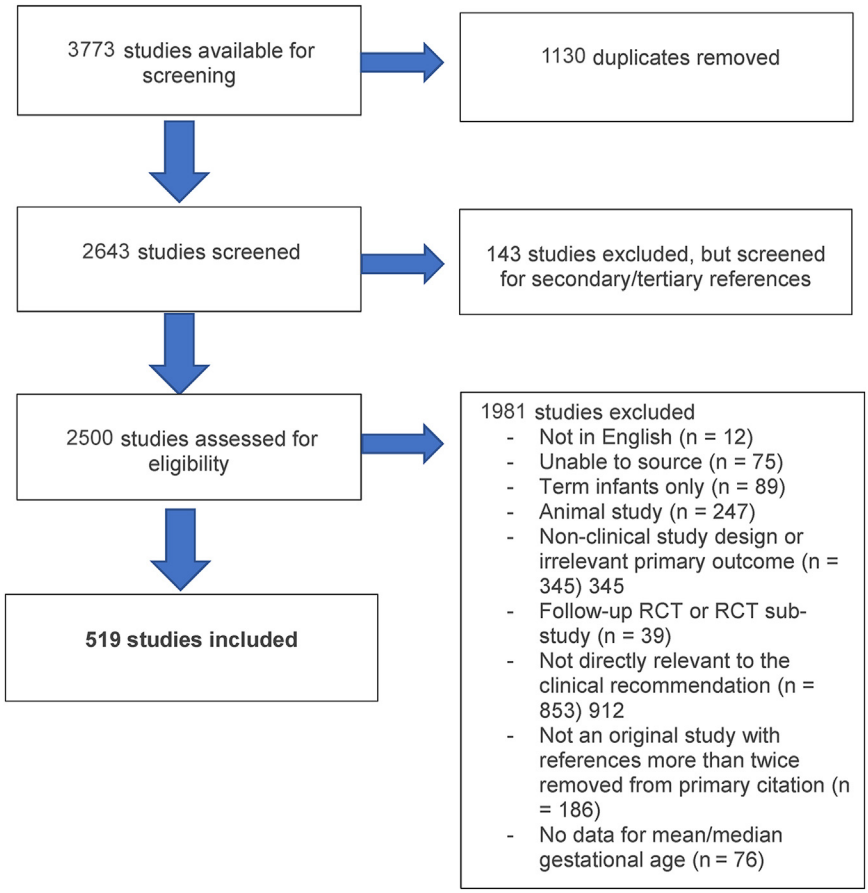

Figure. PRISMA flow diagram.

targeted research is critical to guide and achieve consistency in practice. The challenges in recruiting infants into large RCTs are many. This subgroup of infants is a relatively small population in whom obtaining prospective consent can be challenging. Extremely preterm birth is a complex and stressful event that often occurs after-hours. National and

Table II. Summary data of each recommendation: all studies

Recommendations	Studies, No.	Studies that included at least 1 infant <25 wk,* No. (%)	Studies including only infants <25 wk,* No. (%)	Total no. infants, No.; median per study (range of total no. infants/study)	Total no. infants <25 wk,* No. (%); median no. infants <25 wk/study (range of total no. infants/study)
Antenatal corticosteroids	139	85 (61.1)	4 (2.9)	281 742; 253 (25-29 932)	48 248 (17.1); 5 (0-29 932)
Antenatal magnesium sulfate	32	26 (81.2)	0 (0)	25 589; 166 (24-12 876)	1421 (5.6); 8 (0-293)
Delayed cord clamping	57	35 (61.4)	0 (0)	8166; 66 (19-1566)	567 (6.9); 2 (0-142)
Thermoregulation measures	43	32 (74.4)	1 (2)	29 855; 91 (28-9833)	2950 (9.9); 8 (0-685)
Initial oxygen concentration 21%-30%	48	28 (58.3)	0 (0)	9091; 77 (4-2326)	1030 (11.3); 3 (0-465)
Early CPAP	50	18 (36)	0 (0)	12 323; 101 (33-2823)	612 (5); 0 (0-199)
Surfactant	101	70 (69.3)	0 (0)	37 513; 125 (15-6757)	3834 (10.2); 5 (0-816)
Early parenteral nutrition	49	29 (59.2)	0 (0)	5707; 100 (14-1018)	698 (12.2); 4 (0-237)
Total	519	323 (62.2)	5 (1)	409 986; 117 (4-29 932)	59 360 (14.5); 3 (0-29 932)

*Based on directly reported and estimated numbers.

Table III. Summary data of each recommendation: RCTs only

Recommendations	Total studies, No. (%)	RCT, No. (%)	RCTs that included at least 1 infant <25 wk,* No. (%)	RCTs including only infants <25 wk,* No. (%)	Total no. infants, No.; median per study (range of total no. infants/study)	Total no. infants <25 wk gestational age,* No. (%); median no. infants <25 wk/study (range of total no. infants/study)
ANS	139	51 (37)	18 (35.3)	0 (0)	14 303; 146 (25-2872)	179 (1.3); 0 (0-33)
Antenatal magnesium sulfate	32	15 (47)	12 (80)	0 (0)	6628; 167 (24-2418)	520 (7.8); 2, 0-153
Delayed cord clamping	57	48 (84)	31 (64.6)	0 (0)	6922; 66 (19-1566)	532 (7.7); 3, 0-142
Thermoregulation measures	43	33 (77)	24 (72.7)	1 (3)	3650; 72 (28-801)	473 (13.0); 6, 0-195
Initial oxygen concentration 21%-30%	48	20 (42)	13 (65.0)	0 (0)	2822; 74 (18-609)	186 (6.6); 4, 0-71
Early CPAP	50	43 (86)	12 (27.9)	0 (0)	7813; 87 (18-1316)	361 (4.6); 0, 0-182
Surfactant	101	95 (94.1)	67 (69.1)	0 (0)	32 620; 121 (15-6757)	3141 (9.6); 5, 0-816
Early parenteral nutrition	49	30 (61.2)	19 (63.3)	0 (0)	3567; 92 (17-1018)	481 (13.5); 6, 0-237
Total	519	335 (64.5)	196 (58.5)	1 (0.3)	78 325; 97 (15-6757)	5873 (7.5); 2 (0-816)

*Based on directly reported and estimated numbers.

international collaboration is therefore necessary in order to recruit adequate sample sizes. However, poor enrollment rates also may reflect a perception by clinicians and institutional review boards that these infants have an unacceptable high risk of morbidity and mortality, having in the past been considered "nonviable." Pavlek et al noted that only 37% of RCTs involving infants born extremely preterm even permitted infants born <24 weeks of gestation to be enrolled, potentially because of this premise. With increasing support for active care at lower gestational ages, this is no longer acceptable.[18] As more infants born at <25 weeks of gestation are offered intensive care, they must be enrolled in clinical studies to improve outcomes in this population. Future studies of infants born extremely preterm should be powered to examine the outcomes for the subgroup of infants <25 weeks of gestation. For some interventions, studies limited to this subpopulation, with its unique clinical challenges and greatest rates of adverse outcomes, may be appropriate. At a minimum, database registries should be maintained to enable collaboration and observational studies reporting key outcomes for this cohort.

The strengths of our study include the international representativeness of the clinical guidelines assessed and the large number of studies analyzed. This is the first study, to our knowledge, that has performed a systematic search of the evidence base for clinical guidelines regarding infants born at <25 weeks of gestation. There are, however, some limitations to this study. Because of a lack of data enabling estimation of the number of included infants <25 weeks of gestation, several studies were excluded. Few studies reported the exact number of infants <25 weeks of gestation, which necessitated an estimation of the numbers and proportions of these infants for majority of studies included. We took a conservative approach, using a statistical algorithm that was determined by a normal distribution of gestational age rather than the known true skewed distribution of preterm births, which ordinarily results in a greater proportion of more mature infants born preterm being recruited to trials. This process very likely resulted in an overestimate of the number of infants <25 weeks of gestation included, particularly given that the upper gestational age cut-offs used by studies varied. The included studies had different gestational age inclusion criteria, which limits our ability to estimate how many infants born <25 weeks might be expected to be enrolled overall. The inclusion criterion of <25 weeks of gestation was chosen arbitrarily to focus on the most physiologically immature subset of infants born extremely preterm, and a lower cut-off may be more applicable in the future. Although the guideline sources reviewed all describe care of infants born preterm, they differ in scope; one focusing, for example, on resuscitation, and another on respiratory support. Therefore, this study is not necessarily a comprehensive review of all common management recommendations for infants born preterm. The quality of the included studies was not assessed, in keeping with the pragmatic nature of reviewing all relevant evidence on which published guidelines were based.

In conclusion, infants born <25 weeks of gestation are not well represented in current evidence-based clinical guidelines, and further research addressing this group is needed urgently. As an example, recent data from the Australian and New Zealand Neonatal Network demonstrate that infants born <25 weeks of gestation constitute 28% of all extremely preterm births but only 4% of all preterm births <37 weeks of gestation.[19] Although there may be proportional representation of infants born <25 weeks of gestation in some studies, they still constitute a very small proportion of the study cohort. Given that this subset of infants born extremely preterm are physiologically different to more mature infants, they require a robust individual evidence base to guide their clinical management. Researchers are therefore encouraged

to consider studies that exclusively enroll infants born <25 weeks of gestation or to avoid lower gestational ages as exclusion criteria. Given that in 62% of studies the number of enrolled infants born <25 weeks was unknown, a recommendation may be made to funding agencies and journal editors that requires researchers to prespecify and report important outcomes for this greatest-risk subgroup according to each week of gestational age. Meanwhile, the application and extrapolation of existing evidence to this cohort, from clinical guidelines aimed at infants born preterm or extremely preterm, should be done very cautiously. ■

CRediT authorship contribution statement

Stacey Peart: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mia Kahvo:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tugba Alarcon-Martinez:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Kate Hodgson:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Helen S. Eger:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Susan Donath:** Writing – review & editing, Methodology. **Louise S. Owen:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Peter Graham Davis:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Charles C. Roehr:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Brett J. Manley:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Submitted for publication Jul 10, 2024; last revision received Nov 19, 2024; accepted Nov 23, 2024.

Reprint requests: Stacey Peart, MBBS, Newborn Research Department, Royal Women's Hospital, 20 Flemington Rd, Parkville, Victoria 3052, Australia. E-mail: Stacey.peart@thewomens.org.au

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Ohuma EO, Moller AB, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. Lancet 2023;402:1261-71.
2. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008;371:261-9.
3. Patel RM, Rysavy MA, Bell EF, Tyson JE. Survival of infants born at periviable gestational ages. Clin Perinatol 2017;44:287-303.
4. Backes CH, Rivera BK, Pavlek L, Beer LJ, Ball MK, Zettler ET, et al. Proactive neonatal treatment at 22 weeks of gestation: a systematic review and meta-analysis. Am J Obstet Gynecol 2021;224:158-74.
5. Safer Care Victoria. Extreme prematurity [internet]. Victoria: Safer Care Victoria. 2020. Accessed March 15, 2024. https://www.safercare.vic.gov.au/best-practice-improvement/clinical-guidance/neonatal/extreme-prematurity
6. British Association of Perinatal Medicine. Perinatal management of extreme preterm birth before 27 weeks of gestation: a framework for practice [internet]. London (UK): British Association of Perinatal Medicine. 2019. Accessed March 15, 2024. https://www.bapm.org/resources/80-perinatal-management-of-extreme-preterm-birth-before-27-weeks-of-gestation-2019
7. Kaempf JW, Guillen U, Litt JS, Zupancic JAF, Kirpalani H. Change in neurodevelopmental outcomes for extremely premature infants over time: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2023;108:458-63.
8. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Andreias L, et al. Chronic conditions, functional limitations, and special health care needs of school aged children born with extremely low birth-weight in the 1990s. JAMA 2005;294:318-25.
9. Marlow N, Wolke D, Bracewell MA, Samara M, EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352:9-19.
10. Hille ET, den Ouden AL, Saigal S, Wolke D, Lambert M, Whitaker A, et al. Behavioral problems in children who weigh 1000g or less at birth in four countries. Lancet 2001;357:1641-3.
11. Wolke D, Meyer R. Cognitive status, language attainment, and pre reading skills of 6-year-old very preterm children and their peers: the Bavarian Longitudinal Study. Dev Med Child Neurol 1999;94:109-41.
12. Saigal S, den Ouden L, Wolke D, Hoult L, Paneth N, Streiner DL, et al. School-age outcomes in children who were extremely low birth weight from four international population-based cohorts. Pediatrics 2003;112:943-50.
13. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002;288:728-37.
14. Myrhaug HT, Brurberg KG, Hov L, Markestad T. Survival and impairment of extremely premature infants: a meta-analysis. Pediatrics 2019;143:e20180933.
15. Ding S, Lemyre B, Daboval T, Barrowman N, Moore GP. A meta-analysis of neurodevelopmental outcomes at 4–10 years in children born at 22–25 weeks gestation. Acta Paediatr 2019;108:1237-44.
16. Ishil N, Kono Y, Yonemoto N, Kusuda S, Fujimura M, Neonatal Research Network, Japan. Outcomes of infants born at 22 and 23 weeks' gestation. Pediatrics 2013;132:62-71.
17. Moore GP, Lemyre B, Barrowman N, Daboval T. Neurodevelopmental outcomes at 4 to 8 years of children born at 22 to 25 weeks' gestational age: a meta-analysis. JAMA Pediatr 2013;167:967-74.
18. Pavlek LR, Rivera BK, Smith CV, Randle J, Hanlon C, Small K, et al. Eligibility criteria and representativeness of randomized clinical trials that include infants born extremely premature: a systematic review. J Pediatr 2021;235:63-74.
19. Chow SSW, Creighton P, Holberton JR, Chambers GM, Lui K. Report of the Australian and New Zealand Neonatal Network 2021. Sydney: Australia and New Zealand Neonatal Network; 2023.
20. Rysavy MA, Mehler K, Oberthur A, Agren J, Kusuda S, McNamara PJ, et al. An immature science: intensive care for infants born at </=23 weeks of gestation. J Pediatr 2021;233:16-25.
21. Sweet DG, Carnielli VP, Greisen G, Hallman M, Klebermass-Schrehof K, Ozek E, et al. European Consensus guidelines on the management of respiratory distress syndrome: 2022 update. Neonatology 2023;120:3-23.
22. Kilpatrick SJ, Papile L, Macones GA, Watterberg KL, eds. Guidelines for perinatal care. 8th ed. Washington (DC): American Academy of Pediatrics, the American college of obstetricians and gynecologists; 2017.
23. Wyckoff MH, Wyllie J, Aziz K, Fernanda de Almeida M, Fabres J, Fawke J, et al. Neonatal life support: 2020 international consensus on

cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation 2020;142:S185-221.
24. Wyckoff MH, Singletary EM, Soar J, Olasveengen TM, Greif R, Liley HG, et al. 2021 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations: summary from the basic life support; advanced life support; neonatal life support; education, implementation, and teams; first aid task forces; and the COVID-19 working Group. Circulation 2022;145:e645-721.
25. World Bank. Accessed November 10, 2023. https://www.data.worldbank.org
26. Reilly MC, Vohra S, Rac VE, Zayack D, Wimmer J, Vincer M, et al. Parallel exploratory RCT of polyethylene wrap for heat loss prevention in infants born at less than 24 weeks' gestation. Neonatology 2019;116:37-41.
27. Ehret DE, Edwards EM, Greenberg LT, Bernstein IM, Buzas JS, Soll RF, et al. Association of antenatal steroid exposure with survival among infants receiving postnatal life support at 22 to 25 weeks' gestation. JAMA Netw Open 2018;1:e183235.
28. Kim SM, Sung JH, Kuk JY, Cha HH, Choi SJ, Oh SY, et al. Short-and long-term neonatal outcomes according to differential exposure to antenatal corticosteroid therapy in preterm births prior to 24 weeks of gestation. PLoS One 2018;13:e0198471.
29. Ochiai M, Kinjo T, Takahata Y, Iwayama M, Abe T, Ihara K, et al. Survival and neurodevelopmental outcome of preterm infants born at 22-24 weeks of gestational age. Neonatology 2014;105:79-84.
30. Hayes EJ, Paul DA, Stahl GE, Seibel-Seamon J, Dysart K, Leiby BE, et al. Effect of antenatal corticosteroids on survival for neonates born at 23 weeks of gestation. Obstet Gynecol 2008;111:921-6.
31. Kribs A, Roll C, Göpel W, Wieg C, Groneck P, Laux R, et al. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. JAMA Pediatr 2015;169:723-30.