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REGULAR ARTICLE

Revisions of clinical protocols using the Plan Do Check Act cycle improved outcomes of extremely preterm infants at 2 years

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Abstract

Aim: Clinical quality improvement is often cumbersome due to established protocols. We aimed to investigate whether outcomes of preterm infants improve with protocol revisions using iteration cycles.

Methods: Preterm infants born <28 weeks gestation between January 2006 and December 2015 were retrospectively analysed. Protocols were revised using Plan Do Check Act cycle. Death and serious adverse events at term were reviewed in six-monthly quality improvement meetings. Adverse outcome of death or motor/sensory impairments at two years was compared before and after two major protocol changes, which were implemented in January 2008 and January 2012.

Results: Based on the appraisal for period 2006–2007, strategies for surfactant, narcotics, parenteral nutrition, respiratory gas humidity and prophylactic indomethacin and antibiotics were changed for period 2008–2011. For period 2012–2015, stabilisation of infants was accelerated via very early catheterisation. Of 162 infants (84 males, 25.5 ± 1.5 weeks gestation) within the whole cohort, 63 developed adverse outcomes, which were fewer for periods 2008–2011 (p = 0.013) and 2012–2015 (p = 0.035) compared with period 2006–2007 (adjusted for gestational age, Apgar scores and sex).

Conclusion: Careful bottom-up revisions of protocols using iteration cycles, accounting for local settings, successfully improved the outcomes of preterm infants.

KEYWORDS
extremely preterm infant, intact survival, neonatal intensive care, outcome and Plan Do Check Act cycle

Key Notes

- Filling gaps between the standard of care and existing protocols is challenging, which might be accelerated using iteration cycles.

Abbreviations: CI, confidence interval; NICU, neonatal intensive care unit; OR, odds ratio; PDCA, Plan Do Check Act.

- Protocols for surfactant replacement, respiratory gas humidity, indomethacin, antibiotics, narcotics, parenteral nutrition and catheterisation were revised using Plan Do Check Act cycle, which improved outcomes of extremely preterm infants at 2 years.
- Plan Do Check Act cycle may help reach a consensus when optimising clinical protocols.

1 | INTRODUCTION

In Japan, the survival rate of extremely preterm infants born at less than 28 weeks of gestation has persistently improved from approximately 80% in 2003–2010 to 93% in 2013.[1,2] However, considerable interinstitutional differences in outcomes have also been observed,[3] suggesting the need to disseminate evidence-based therapeutic regimens. However, uniform renewal of conventional regimens often encounters difficulties in institutional settings. This is partly due to their highly heterogeneous nature in terms of patient type, therapeutic options and human resources.[4,5] These factors may influence the effectiveness of implementation, and therefore, the adoption of evidence -based strategies may be needed to account for local settings.

During 2006 and 2007, the survival rate of infants born at less than 28 weeks of gestation in the neonatal intensive care unit (NICU) of Kurume University Hospital, Kurume, Fukuoka, Japan, was 58%, as opposed to the 83% in Japanese tertiary NICUs in 2005.[6] To improve the outcomes of extremely preterm infants, a local working group was formed in August 2007. Therapeutic regimens were revised to account for local settings, such as patient type, antibiogram, existing treatment protocols, medical resources, therapeutic options and workforce, using the Plan Do Check Act (PDCA) cycle. This iteration cycle is one of the quality improvement tools, consisting of clinical appraisal, literature review, strategy design and clinical practice monitoring.[7,8]

This study aimed to investigate whether evidence-based treatments were properly implemented and whether the PDCA cycle improved the outcomes in extremely preterm infants.

2 | PATIENTS AND METHODS

2.1 | Study population

Between January 2006 and December 2015, a total of 2,690 newborn infants were admitted to our NICU, which is a tertiary, referral NICU. Of these, 174 infants were born between 22 + 0 weeks and 27 + 6 weeks. All infants born at greater than 22 gestational weeks were provided with full intensive care options, whereas those born at 22 weeks of gestation were resuscitated upon request from their parents. The study cohort comprised of 162 extremely preterm infants, excluding 10 outborn infants and two infants with chromosomal abnormalities (Figure 1).

2.2 | Clinical strategy for quality improvement

In July 2007, a working group was formed with nine consultant neonatologists, neonatal nurse practitioners, NICU nurses and paediatric registrars to improve the outcomes in extremely preterm infants. Clinical records were reviewed every six months to inspect the relevance of therapeutic regimens during the first 28 days of life, referring to recommendations published in Cochrane Reviews (Cochrane Collaboration, London, UK) and UpToDate (UpToDate Inc), with extended searches through other search engines. Adverse events at a corrected age of 40 weeks were reviewed to identify the incidence of death, endotracheal tube reintubation, culture-positive or clinically diagnosed septicaemia, grade III/IV intraventricular

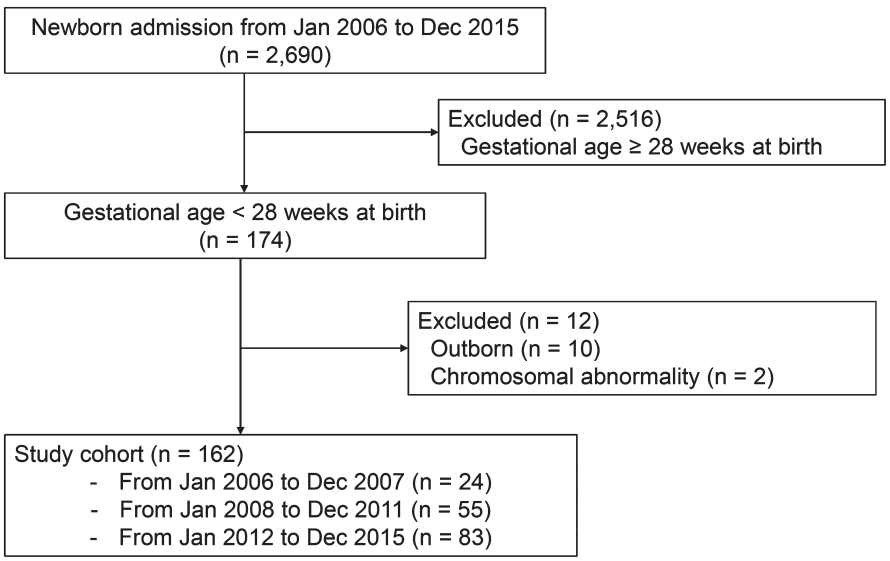

FIGURE 1 Profile of the study population

TABLE 1 Clinical characteristics of the study cohort

Variables	Period		
	2006–2007 (*n* = 24)	2008–2011 (*n* = 55)	2012–2015 (*n* = 83)
Antenatal variables			
Glucocorticoid	8 (33.3)	34 (61.8)	64 (77.1)
Intravenous ritodrine	17 (70.8)	49 (89.1)	68 (81.9)
Intravenous magnesium	14 (58.3)	31 (56.4)	55 (66.3)
Caesarean delivery	17 (70.8)	35 (63.6)	53 (63.9)
Premature rupture of membranes	5 (20.8)	23 (41.8)	25 (30.1)
Postnatal variables			
Multiple births	5 (20.8)	4 (7.2)	14 (16.9)
Male sex	9 (37.5)	27 (49.1)	48 (57.8)
Gestational age (week)	25.6 ± 1.7	25.2 ± 1.4	25.8 ± 1.5
Birth weight (g)	770 ± 256	713 ± 216	800 ± 223
Cord blood pH	7.31 ± 0.09	7.32 ± 0.12	7.36 ± 0.08
Apgar score (1 min)	4 (2 – 5)	3 (1 – 5)	4 (2 – 6)
Apgar score (5 min)	7 (6 – 7)	7 (5 – 7)	7 (5 – 8)
Respiratory distress syndrome	22 (91.7)	54 (98.2)	79 (95.2)
Surfactant replacement (min)[a]	180 (150 – 195)	15 (15 – 15)	15 (15 – 15)
Surfactant replacement <30 min	1 (4.2)	53 (96.4)	81 (97.6)
Catheterisation (min)	100 ± 38	109 ± 40	79 ± 33
Catheterisation <67 min[b]	3 (12.5)	5 (9.1)	32 (38.6)
Narcotic <24 h	10 (41.7)	46 (83.6)	67 (80.7)
Inotropes <24 h	14 (58.3)	36 (65.5)	56 (67.5)
Gentamycin <24 h	0 (0.0)	42 (76.4)	83 (100.0)
Amino acid <24 h	6 (25.0)	49 (89.1)	83 (100.0)
Indomethacin <6 h	10 (41.7)	39 (70.9)	76 (91.6)
High humidifier setting	4 (16.7)	55 (100.0)	83 (100.0)
Intravenous glucocorticoid	11 (45.8)	42 (76.4)	59 (71.1)
Inhaled glucocorticoid	0 (0.0)	6 (10.9)	15 (18.1)
Diuretics for lung disease	17 (70.8)	47 (85.5)	66 (79.5)

Note: Values are shown as number (%), mean ±standard deviation or median (quartile range).

[a]Time of surfactant replacement after birth recorded in 5 min increments.

[b]Threshold of 67 min defined as the lower quartile of all values.

haemorrhage, dependence on oxygen/respiratory support and grade III retinopathy of prematurity. Ductus arteriosus, necrotising enterocolitis and intestinal perforation requiring surgical intervention were also noted. The working group proposed a list of possible protocol changes based on the clinical appraisal and literature review. A set of major protocol revisions were chosen and agreed upon at six-monthly multidisciplinary quality improvement meetings. To avoid strategy drift, protocols were changed only when attendees of the meeting regarded the revision as relevant based on sufficient accumulated data. Short term adverse events were closely monitored to run the PDCA cycle. Subsequently, major changes in the clinical protocol were made on 1st January 2008 and 1st January 2012, which divided the study period into three periods of January 2006 to December 2007, January 2008 to December 2011 and January 2012 to December 2015.

2.3 | Clinical background variables

Clinical variables before, during and after birth were collected from patient records (Table 1).

2.4 | Data analysis

The primary outcome was assessed by death or neurological impairments, defined by Gross Motor Function Classification Score greater than II, deafness or blindness at a corrected age of two years. Death or grade III/IV intraventricular haemorrhage by a corrected age of 40 weeks and death by a corrected age of 2 years were also used as secondary outcomes. Association between the study periods and outcomes was assessed using logistic regression analysis, controlling for sex, gestational age and Apgar score at 5 min. Univariate logistic regression analysis was also performed to estimate the crude effects of clinical backgrounds on the outcome of infants.

This retrospective analysis was conducted in compliance with the Declaration of Helsinki under the approval of the Ethics Committee of the Kurume University School of Medicine. Informed consent was not required for the use of anonymised data obtained for clinical reasons.

3 | RESULTS

Values are presented as the mean ± standard deviation or median (quartile ranges) unless otherwise described. During the study period, 162 extremely preterm infants were born, with an average gestation period of 25.5 ± 1.5 weeks and an average weight of 766 ± 218 g at birth. Subsequently, all these infants, including eight infants born at 22 weeks of gestation, received standard resuscitation and survived until NICU admission. Of these, 87.7% of infants survived until discharge (Table 1 and Figure 1).

3.1 | Appraisal for period 2006–2007

Of the 24 infants born during this period, those with respiratory failure were intubated immediately after birth. Peripheral or peripherally inserted central catheters were inserted at 100 ± 38 min after birth (Table 1). Surfactant was replaced at 180 (150–195) min after birth only after confirming the depth of the endotracheal tube using a radiograph (Table 1), which was relatively later than clinically recommended.[9] Intravenous indomethacin was considered only for patients with significant ductal shunt. Prophylactic ampicillin (100 mg/kg/day) and cefotaxime (100 mg/kg/day) were administered to infants born at less than 26 weeks of gestation and those with suspicion of infection. A relatively low humidity setting was used for the ventilator circuit, with the humidifier chamber outlet temperature of 35°C and Y-piece temperature of 37°C. Nasal continuous positive airway pressure (CPAP) was routinely used at 5 cmH_2O after weaning from invasive respiratory support. We also encouraged minimum handling approach and developmental care, such as positioning of limbs, quiet environment and dim lighting.

In terms of adverse events at 40 weeks postconceptional age, eight infants died of immaturity after failing to respond to the maximum cardiac/respiratory support, each on days zero, one, two, three, three, four, 13 and 21. In addition, three infants died of septicaemia due to ampicillin/cefotaxime resistant gram-negative rods, each on days six, six and 40. Endotracheal tube reintubation was required in eight infants; tube obstruction was confirmed in four cases. None of the infants required a bowel surgery for necrotising enterocolitis or intestinal perforation. Grade III/IV intraventricular haemorrhage and dependence on oxygen/respiratory support were observed in three and 14 infants, respectively (Table 2).

At the quality improvement meeting, the working group proposed early surfactant replacement and early catheterisation to promote early stabilisation of infants. High humidifier setting for the respiratory gases, prophylactic indomethacin, routine use of narcotics, early parenteral nutrition and prophylactic ampicillin/gentamicin was also proposed. Attendees of the meeting agreed that early stabilisation of infants and prevention of systemic infection and endotracheal tube blockage must be prioritised. Subsequently, protocols were changed to administer surfactant in less than 30 min after birth and use the standard humidifier setting with humidifier chamber outlet 37°C and Y-piece 40°C.[10,11] The use of prophylactic indomethacin of 0.1 mg/kg/dose,[12] ampicillin/gentamicin instead of ampicillin/cefotaxime,[13-17] continuous intravenous fentanyl of 1 μg/kg/h [18,19] and parenteral nutrition with amino acid infusion [12,20] within 24 h of birth was also implemented.

3.2 | Appraisal for period 2008–2011

For all the 55 infants born during this period, surfactant was replaced precisely at 15 min after birth (Table 1). Catheters were inserted at 109 ± 40 min after birth. Intravenous indomethacin was administered within 6 h after birth in 70.9% of the infants. The standard high humidifier setting was used for all 55 infants during the study period. Prophylactic gentamicin was administered to 76.4% of infants. From the period 2006–2007 to 2008–2011, there was an upward trend of administering narcotics and amino acid infusion within 24 h of birth (Table 1). Maternal glucocorticoid exposure also tended to increase although no protocol change was made with respect to this treatment (Table 1). No significant change was noted for the minimum handling approach, developmental care and use of CPAP devices.

Of the 55 infants born during the period 2008–2011, three died of immaturity without responding to the cardiac and respiratory support on days one, two and five. Deaths from septicaemia occurred in two infants on days one and five, respectively. Their blood cultures were positive for *Escherichia coli* and *Staphylococcus aureus*, respectively, both of which were resistant to ampicillin, cefotaxime and gentamicin. Deaths due to necrotising enterocolitis and bronchopulmonary dysplasia were also noted in one each infant on days eight and 35, respectively. Endotracheal tube reintubation was required in 13 infants; tube obstruction was confirmed in two infants. Bowel surgery for necrotising enterocolitis or intestinal perforation, grade III/IV intraventricular haemorrhage and dependence on oxygen/respiratory support were observed in two, 13 and 49 infants, respectively (Table 2).

The working group proposed to speed-up the administration of prophylactic indomethacin and commencement of narcotics and parenteral nutrition via very early insertion of vascular catheters. Attendees of the quality improvement meeting agreed that the incidence of intraventricular haemorrhage should be reduced via an even earlier stabilisation of infants. Protocols were changed to encourage very early completion of catheterisation within 1 h after birth using umbilical catheters. The catheters were used to administer indomethacin within 6 h of birth, and subsequently, administration of narcotics and parental nutrition was also initiated.

3.3 | Appraisal for period 2012–2015

For 83 infants born during this period, surfactant was replaced precisely at 15 min after birth (Table 1). The standard humidifier settings and prophylactic gentamicin were used in all infants. Catheterisation was completed at 79 ± 33 min after birth. Intravenous indomethacin was administered within 6 h after birth in 91.6% of the infants. Between periods 2008–2011 and 2012–2015, there was a trend towards increased maternal glucocorticoid exposure. However, no marked changes were observed in the use of narcotics and amino acid infusion within 24 h of birth and the minimum handling approach, developmental care and use of CPAP devices (Table 1).

Of the 83 infants born during this period, one infant born at 23.3 weeks of gestation died on day zero because of immaturity after failing to respond to the cardiac/respiratory support.

TABLE 2 Outcome of the study cohort

Variables	Period 2006–2007 (*n* = 24)	2008–2011 (*n* = 55)	2012–2015 (*n* = 83)
40 weeks corrected age			
Death	11 (45.8)	7 (12.7)	1 (1.2)
Endotracheal tube reintubation	8 (33.3)	13 (23.6)	13 (15.7)
Endotracheal tube blockade	4 (16.7)	2 (3.6)	0 (0.0)
Enteral feeding 100 ml/kg >day 17[a]	12 (50.0)	19 (34.5)	15 (18.1)
Necrotising enterocolitis or intestinal perforation	0 (0.0)	2 (3.6)	3 (3.6)
Symptomatic patent ductus arteriosus[b]	5 (20.8)	10 (18.2)	7 (8.4)
Surgical ductus closure	5 (20.8)	10 (18.2)	7 (8.4)
Antibiotic for systemic infection	20 (83.3)	50 (90.9)	55 (66.3)
Intraventricular haemorrhage III/IV	3 (12.5)	13 (23.6)	11 (13.3)
Intraventricular haemorrhage III/IV or death	11 (45.8)	16 (29.1)	11 (13.3)
Periventricular leukomalacia	0 (0.0)	0 (0.0)	0 (0.0)
Chronic lung disease[c]	14 (58.3)	49 (89.1)	64 (77.1)
Grade III retinopathy of prematurity	8 (33.3)	36 (65.5)	21 (25.3)
48 weeks corrected age			
Death	11 (45.8)	7 (12.7)	1 (1.2)
Respiratory support[d]	1 (4.2)	6 (10.9)	20 (24.1)
Respiratory support[d] or death	12 (50.0)	13 (23.6)	21 (25.3)
2 years corrected age			
Death	11 (45.8)	7 (12.7)	2 (2.4)
Tube feeding	1 (4.2)	1 (1.8)	5 (6.0)
Tube feeding or death	12 (50.0)	8 (14.5)	7 (8.4)
Respiratory support[d]	1 (4.2)	2 (3.6)	6 (7.2)
Respiratory support[d] or death	12 (50.0)	9 (16.4)	8 (9.6)
Deafness and/or blindness	1 (4.2)	8 (14.5)	7 (8.4)
Deafness, blindness or death	12 (50.0)	15 (27.3)	9 (10.8)
Cerebral palsy	1 (4.2)	10 (18.2)	24 (28.9)
Cerebral palsy or death	12 (50.0)	17 (30.9)	26 (31.3)
Epilepsy	1 (4.2)	5 (9.1)	4 (4.8)
Epilepsy or death	12 (50.0)	12 (21.8)	6 (7.2)
Language disability	0 (0.0)	11 (20.0)	22 (26.5)
Language disability or death	11 (45.8)	18 (32.7)	24 (28.9)
Cerebral palsy, deafness or blindness	2 (8.3)	13 (23.6)	28 (33.7)
Cerebral palsy, deafness, blindness or death	13 (54.2)	20 (36.4)	30 (36.1)

Note: Values are shown as number (%).

[a]Threshold of 17 days defined as the upper quartile of all values.

[b]Haemodynamically significant ductus arteriosus requiring intravenous indomethacin (excluding prophylactic treatment) and/or surgical closure.

[c]Defined as need for supplemental oxygen at 36 weeks of postconceptional age.

[d]Including supplemental oxygen and other invasive/non-invasive respiratory support.

Thirteen infants required endotracheal tube reintubation, none of which was confirmed as tube obstruction. Bowel surgery, grade III/IV intraventricular haemorrhage and dependence on oxygen/respiratory support were seen in three, 11 and 64 infants, respectively (Table 2).

3.4 | Independent variables of the primary outcome

At a corrected age of two years, 20 infants died, 35 developed cerebral palsy and 16 were diagnosed as deaf or blind (Table 2). Univariate analysis revealed that death or neurological impairments were associated with gestational age, birth weight, Apgar scores at 1 and 5 min, the requirement for inotropes on day zero, surgical ductus closure and delayed establishment of enteral feeding ($p < 0.001$,

TABLE 3 Independent variables of death or neurological impairments at 2 years corrected age

	Death or neurological impairments			
	No	Yes	Odds ratio	
Variables	**(*n* = 99)**	**(*n* = 63)**	**Mean (95% CI)**	***p***
Univariate analysis				
Period				
2006–2007	11 (45.8)	13 (54.2)	Reference	
2008–2011	35 (63.6)	20 (36.4)	0.484 (0.183 – 1.279)	0.143
2012–2015	53 (63.9)	30 (36.1)	0.479 (0.191 – 1.201)	0.117
Antenatal glucocorticoid				
No	30 (53.6)	26 (46.4)	Reference	
Yes	69 (65.1)	37 (34.9)	0.619 (0.32 – 1.197)	0.154
Intravenous ritodrine				
No	18 (64.3)	10 (35.7)	Reference	
Yes	81 (60.4)	53 (39.6)	1.178 (0.505 – 2.747)	0.705
Intravenous magnesium				
No	39 (62.9)	23 (37.1)	Reference	
Yes	60 (60.0)	40 (40.0)	1.130 (0.589 – 2.171)	0.713
Caesarean delivery				
No	29 (50.9)	28 (49.1)	Reference	
Yes	70 (66.7)	35 (33.3)	0.518 (0.268 – 1.001)	0.050
PROM				
No	64 (58.7)	45 (41.3)	Reference	
Yes	35 (66.0)	18 (34.0)	0.731 (0.369 – 1.450)	0.371
Multiple births				
No	87 (61.7)	54 (38.3)	Reference	
Yes	12 (57.1)	9 (42.9)	1.208 (0.477 – 3.058)	0.690
Sex				
Female	53 (67.9)	25 (32.1)	Reference	
Male	46 (54.8)	38 (45.2)	1.751 (0.923 – 3.324)	0.087
Gestational age (week)	26.0 ± 1.3	24.9 ± 1.5	0.599 (0.473 – 0.758)	<0.001
Birth weight (per 100 g)	8.05 ± 2.12	7.06 ± 2.17	0.795 (0.675 – 0.936)	0.006
Cord blood pH	7.34 ± 0.08	7.33 ± 0.13	0.27 (0.011 – 6.524)	0.420
Apgar score (1 min)	4 (4 – 5)	4 (4 – 5)	0.718 (0.603 – 0.855)	<0.001
Apgar score (5 min)	7 (7 – 7)	6 (6 – 8)	0.709 (0.594 – 0.847)	<0.001
Respiratory distress syndrome requiring surfactant replacement				
No	7 (100.0)	0 (0.0)	Not applicable[a]	
Yes	92 (59.4)	63 (40.6)		
Surfactant replacement				
≥30 min	14 (51.9)	13 (48.1)	Reference	
<30 min	85 (63.0)	50 (37.0)	0.633 (0.276 – 1.455)	0.282
Catheterisation <67 min*				
No	77 (63.1)	45 (36.9)	Reference	
Yes	22 (55.0)	18 (45.0)	1.400 (0.679 – 2.886)	0.362
Inotropes on day 0				
No	42 (79.2)	11 (20.8)	Reference	
Yes	57 (52.3)	52 (47.7)	3.483 (1.624 – 7.469)	0.001

(Continues)

TABLE 3 (Continued)

Variables	Death or neurological impairments: No (*n* = 99)	Death or neurological impairments: Yes (*n* = 63)	Odds ratio: Mean (95% CI)	*p*
Prophylactic gentamycin on day 0				
No	21 (56.8)	16 (43.2)	Reference	
Yes	78 (62.4)	47 (37.6)	0.791 (0.376 – 1.665)	0.537
Prophylactic indomethacin <6 h				
No	50 (57.5)	37 (42.5)	Reference	
Yes	49 (65.3)	26 (34.7)	0.717 (0.379 – 1.357)	0.307
Surgical ductus closure				
No	81 (57.9)	59 (42.1)	Reference	
Yes	18 (81.8)	4 (18.2)	0.305 (0.098 – 0.948)	0.040
High humidifier setting of respiratory gases				
No	9 (45.0)	11 (55.0)	Reference	
Yes	90 (63.4)	52 (36.6)	0.473 (0.184 – 1.216)	0.120
NEC or intestinal perforation				
No	97 (61.8)	60 (38.2)	Reference	
Yes	2 (40.0)	3 (60.0)	2.425 (0.394 – 14.936)	0.340
Establishment of enteral feeding 100 ml/kg				
day 17**	85 (73.3)	31 (26.7)	Reference	
≥day 17	14 (30.4)	32 (69.6)	6.267 (2.958 – 13.277)	<0.001
Postnatal administration of intravenous glucocorticoid				
No	32 (69.6)	14 (30.4)	Reference	
Yes	67 (57.8)	49 (42.2)	1.672 (0.807 – 3.462)	0.167
Multivariate model				
Period 2008–2011 (vs. 2006–2007)			0.233 (0.074 – 0.733)	0.013
Period 2012–2015 (vs. 2006–2007)			0.318 (0.109 – 0.923)	0.035
Gestational age (week)			0.619 (0.472 – 0.811)	0.001
Apgar score (5 min)			0.759 (0.621 – 0.927)	0.007
Male sex			2.049 (0.978 – 4.292)	0.057

Note: Values are shown as mean ± standard deviation, median (quartile range) or incidence (%). Neurological impairments are defined as the Gross Motor Function Classification Score of III–V, deafness or blindness at two years corrected age. Thresholds of 67 min and 17 days are defined as lower* and upper** quartiles of all values, respectively.

Abbreviations: CI, confidence interval; NEC, necrotising enterocolitis; PROM, premature rupture of the membranes.

[a]Logistic regression analysis not performed due to complete separation of independent variables into a particular outcome status.

$p = 0.006$, $p < 0.001$, $p < 0.001$, $p = 0.001$, $p = 0.040$ and $p < 0.001$, respectively) (Table 3). Reduction in death or neurological impairments was associated with the therapeutic regimen for periods 2008–2011 and 2012–2015 even after adjusting for gestational age, Apgar scores at 5 min and sex (vs. period 2006–2007; $p = 0.013$ and 0.035, respectively) (Table 1).

3.5 | Independent variables of the secondary outcomes

At a corrected age of 40 weeks, death ($n = 19$) or survival with intraventricular haemorrhage ($n = 19$) was associated with period 2012–2015 (vs. period 2006–2007; $p = 0.001$), antenatal glucocorticoid ($p = 0.003$), gestational age ($p < 0.001$), birth weight ($p = 0.002$), Apgar scores at 1 and 5 min (both $p < 0.001$), surfactant replacement within 30 min after birth ($p = 0.024$), requirement for inotropes on day zero ($p = 0.005$), indomethacin administration within 6 h after birth ($p = 0.001$), high humidifier setting ($p = 0.019$) and delayed establishment of enteral feeding ($p < 0.001$) (Table S1). In the multivariate model, death or survival with intraventricular haemorrhage was associated with the therapeutic regimen for periods 2008–2011 and 2012–2015, even after adjusting for gestational age, Apgar scores at 5 min and sex (vs. period 2006–2007, $p = 0.009$ and $p < 0.001$, respectively) (Table 4A).

Death before a corrected age of 2 years was associated with periods 2008–2011 and 2012–2015 (vs. period 2006–2007, $p = 0.002$

TABLE 4 Independent variables of secondary outcomes: Multivariate models

A: Grade III/IV intraventricular haemorrhage or death at 40 weeks corrected age as a secondary outcome				
	Death or haemorrhage			
	No	Yes	Odds ratio	
Variables	(*n* = 124)	(*n* = 38)	Mean (95% CI)	*p*
Period				
2006–2007	13 (54.2)	11 (45.8)	Reference	
2008–2011	39 (70.9)	16 (29.1)	0.177 (0.049 – 0.647)	0.009
2012–2015	72 (86.7)	11 (13.3)	0.072 (0.018 – 0.285)	<0.001
Gestational age (week)	25.9 ± 1.3	24.3 ± 1.4	0.499 (0.356 – 0.700)	<0.001
Apgar score at 5 min of birth	7 (7 – 8)	6 (6 – 6)	0.726 (0.567 – 0.929)	0.011
Male sex	61 (72.6)	23 (27.4)	2.281 (0.900 – 5.776)	0.082
B: Death by two years corrected age as a secondary outcome				
	Death			
	No	Yes	Odds ratio	
Variables	(*n* = 142)	(*n* = 20)	Mean (95% CI)	*p*
Period				
2006–2007	13 (54.2)	11 (45.8)	Reference	
2008–2011	48 (87.3)	7 (12.7)	0.033 (0.006 – 0.185)	<0.001
2012–2015	81 (97.6)	2 (2.4)	0.005 (0.000 – 0.053)	<0.001
Gestational age (week)	25.7 ± 1.4	24.2 ± 1.7	0.533 (0.332 – 0.854)	0.009
Apgar score at 5 min of birth	7 (7 – 8)	6 (6 – 7)	0.601 (0.410 – 0.882)	0.009
Male sex	73 (86.9)	11 (13.1)	1.937 (0.518 – 7.251)	0.326

Note: Values are shown as mean ±standard deviation, median (quartile range) or incidence (%).
Abbreviation: CI, confidence interval.

and $p < 0.001$, respectively), antenatal glucocorticoid ($p = 0.004$), gestational age ($p < 0.001$), birth weight ($p = 0.008$), Apgar scores at 1 and 5 min ($p = 0.005$ and $p = 0.003$, respectively), early surfactant replacement ($p < 0.001$), the requirement for inotropes on day zero ($p = 0.049$), high humidifier setting ($p < 0.001$), necrotising enterocolitis or intestinal perforation ($p = 0.002$), use of gentamicin (vs. cefotaxime, $p = 0.004$) and early commencement of parenteral nutrition ($p < 0.001$, Fisher's exact test) (Table S2). In the multivariate model, death was dependent on the therapeutic regimen for periods 2008–2011 and 2012–2015 even after adjusting for gestational age, Apgar scores at 5 min and male sex (vs. period 2006–2007, both $p < 0.001$) (Table 4B).

4 | DISCUSSION

Accumulating clinical evidence in neonatal medicine has contributed to improve therapeutic strategies for preterm infants.[21,22] However, individual centres often find it difficult to adopt new therapeutic regimens, and empiric therapies may remain without being updated because of considerable variations in the patient backgrounds and availability of medical resources at each centre. During the period 2006–2007 of our study, surfactant replacement was performed only after radiographic confirmation of the depth of the endotracheal tube, based on the prior experience in a caesarean-born infant. Shortly after surfactant replacement, this infant developed right-sided pneumothorax, whose endotracheal tube was discovered to be within the right main bronchus on the first radiograph. On another occasion, NICU nurses had trouble with excessive condensation within the ventilator circuit, which led to a de-escalation of the humidifier setting to a lower than the standard level.

We believe that these outdated regimens may have been responsible for some of the adverse events. Considering the clinical staff's anticipation towards introducing dramatic changes to the protocol, the working group decided to promote bottom-up discussions within the clinical staff regarding the priority, scientific basis and potential risk/benefits of newly introduced therapeutic regimens. Guided by regular appraisals of clinical practice and literature review, two sets of interventions were implemented. These included early stabilisation of infants with immediate surfactant replacement,[9] swift vascular catheterisation and early prophylactic indomethacin therapy,[12] early administration of narcotics [18] and parenteral nutrition,[20] as well as culture adjusted routine antibiotics and standard high humidity of respiratory gases.[10] These interventions led to a significant improvement in infant outcomes.

Even for the revision of outdated regimes, attempts to change clinical protocols are often met with resistance and obstacles. A bottom-up approach and transparent process with careful appraisal of the clinical practice may help yield a consensus while maintaining a team solidarity.

The PDCA cycle is a quality improvement tool developed for the manufacturing industry [23] and has been increasingly used in the healthcare sector.[7,8] Unlike other quality improvement tools,[24] the PDCA cycle repeatedly requires time-consuming processes in exchange for its simplicity and nature to provide continuous improvement of the system. Although publications of clinical projects using the PDCA cycle are still limited in Japan, this tool is increasingly used in quality improvement of nursing, and the application of which is now recommended by the Japan Nursing Society.[25] In our current project, the quality improvement process using the PDCA cycle was well accepted by the multidisciplinary team, through which physicians, nurses and other members were able to contribute equally to the project. Considering the time required to accumulate cases for the appraisal of clinical practice, the PDCA cycle's time-consuming nature is unlikely to be a critical disadvantage in quality improvement projects. Therefore, iteration cycles, such as the PDCA cycle, might be one option when revising outdated clinical protocols without major conflict with existing therapeutic regimes.

Our study assessed the relationship between clinical outcomes and the sets of therapeutic regimens represented by the study periods, rather than each specific procedure. However, findings from the univariate analysis highlighted several potential variables associated with infant survival, such as respiratory gas humidity and the choice of antibiotics. Further studies are needed to assess the impact of these variables on the outcome.

There were several limitations to our study. First, although we observed a temporal improvement of the outcome in our study cohort, the number of infants, who developed cerebral palsy and/or neurosensory impairments, appeared to increase with time (Table 2). It was possible that a considerable fraction of infants, who survived in relationship with the revision of clinical protocols, developed neurological impairments. Second, this study was not powered to identify specific procedures associated with improved outcomes in infants. Therefore, several procedures enforced during periods 2008–2011 and 2012–2015 may be unrelated to the outcomes. Third, the cohort size was small and heterogeneous among the three observational periods. Finally, the difference in the outcomes observed among the study periods might have been due to temporal improvement of practice and unintended protocol changes, as seen in the increased administration of antenatal glucocorticoid.

5 | CONCLUSIONS

The use of PDCA cycle, which consists of review of clinical practice, short term outcome and latest clinical evidence, followed by the protocol revision and reappraisal, was associated with improved long-term outcomes in extremely preterm infants. Our bottom-up approach in adopting standard treatments accounting for the local environment may help fill the gap between the standard of care and ongoing clinical practice.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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