Neonatal Intensive Care Manual for the infants born less than 28 weeks of gestation (Ver. 1.1)

Neonatal Research Network of Japan

(http://plaza.umin.ac.jp/nrndata/)

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This document reflects the consensus reached by all contributors. The contributors have exerted every effort to ensure that the information in this manual is in accordance with current recommendations and practice at the time of publication. However, the contributors are not responsible for errors or omissions or for any consequences from application of the information in this manual.

Contents

0 Introduction

0.1 Extremely preterm infants

Infants born below 28 weeks gestation are usually called “extremely preterm (EP)” or “extremely low gestational age newborn” (ELGAN) infants. The introduction of modern neonatal intensive care has improved the survival rates of these infants dramatically over the last several decades. The updated outcomes of EP infants in Japan are available on a Neonatal Research Network of Japan web site (http://plaza.umin.ac.jp/nrndata/indexe.htm). According to this database, the average survival rate of EP infants born in 2016 was more than 90% but more than 20% of survivors are left with residual disability, including cerebral palsy, suggesting that the chances of intact survival remain questionable. In addition, survival rates of infants born below 24 weeks gestation are low. Considerable efforts must therefore be made to improve both survival and outcomes of all EP infants.

0.2 Features of this manual

This is not a general manual for NICU, rather a subdivided manual for EP infants during the first several weeks in NICU as the type of care received by the infant during the first several days and weeks of life is crucial for optimum survival and neurodevelopmental outcomes. The type of management discussed in this manual may not be scientific or evidence based as NICU care is subject to center variations. However, this manual is prepared from consensus amongst practicing Japanese neonatologists and we believe that this manual can represent accept care of the EP infant in Japan.

Since this is the first version of the manual, future modifications in line with practice change are anticipated. Your opinions are therefore crucial to the development and refinement of this manual and please do not hesitate to contact us as your involvement will be crucial to improve this manual for the future.

0.3 Topics addressed by this manual:

1. Delivery room resuscitation and respiratory support
2. Respiratory care
3. Circulatory support
4. Intravenous fluid management

5. Enteral feeding
6. Infection control
7. The NICU environment

0.4 Acknowledgement

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1 Resuscitation

1.1 The clinical scenario

At birth, newborn infants are removed from the placental circulation after the umbilical cords are ligated and pulmonary respiration is established. In order to establish air breathing, the fluid that filled the lungs in-utero must be replaced with air. This instigates gas exchange within the lung. After initiation of respiration, it is important to prevent the expanded alveoli from collapsing, which establishes functional residual capacity of the lung. Pulmonary surfactant from the alveoli plays a critical role here. With breathing, alveolar oxygen partial pressure dilates pulmonary blood vessels that were contracted during the fetal period, leading to decreased pulmonary vascular resistance, increased pulmonary blood flow and further promotion of pulmonary gas exchange.

The following physical features of the EP infant must be considered when providing immediate care:

- Relatively large head compared to the body
- High position of the larynx
- Poor production of pulmonary surfactant increasing the risk of alveolar collapse
- Fragile skin susceptible to injury
- Large body surface area compared to body weight leading to hypothermia or poor control of body temperature
- Fragile germinal matrix vasculature with which postnatal stress including unstable circulation leads to intraventricular hemorrhage (IVH).

1.2 General Management

1.2.1 Prenatal counseling

Japan has one of the lowest neonatal mortality rates in the world. This is also true for EP infants. Even so, the mortality of preterm infants born at 22-23 weeks of gestation or with birth weights under 500 g are still high and their long-term neurodevelopmental outlook continues to be poor. Therefore, prenatal counseling is crucial if time allows, in order to provide information for the parents and to discuss their wishes. This is especially important if birth occurs at 22 weeks gestation because of extremely high morbidity and mortality rates. Ideally, the figures for each institution should be used for counselling but if unavailable, Japanese national data can be used.

1.2.2 Mode of delivery

There is no specific opinion as to which delivery mode (transvaginal delivery, cesarean section) is best for EP outcomes, including mortality. Policies differ from hospital to hospital. Some hospitals may advocate vaginal delivery if there are no contra-indications whilst other hospitals may preferentially choose to deliver all EP infants by cesarean section to avoid any unexpected trauma from a vaginal birth. About 75% of EP infants are delivered by cesarean section in Japan.

1.2.3 Prenatal glucocorticoid administration

Prenatal glucocorticoid administration is recommended for women below 34 weeks of gestation who are expected to deliver within a week of presentation and if active management is preferred. Prenatal glucocorticoids reduce the risk of respiratory distress syndrome (RDS), IVH, and mortality in preterm infants. There are only a few clinical trials regarding the efficacy of steroids for EP infants at 22-23 weeks of gestation but observational studies suggest that they may decrease risk of complications and death.

1.2.4 Preparation

Preparation is crucial for any preterm birth. The equipment that is required is shown in table 1. The following must be checked prior to birth:

1. Aspirator or suction device, set to below 100 mmHg [13 kPa]
2. Jackson Rees and T-piece resuscitation device
3. Laryngoscope light source.

It is important to use a check list and to obtain verbal confirmation because lack of equipment or malfunction may be fatal for the infant.

1.2.5 Umbilical cord milking

If umbilical cord milking is planned, request that the obstetrician leave at least 30 cm of cord after clamping at the placenta. Cord milking can be conducted after the infant is transferred to the radiant warmer. Umbilical cords are often twisted, so remember to untwist the cord (if needed) prior to milking it.

1.2.6 Temperature control

EP infants have a large body surface area relative to their weight and thin skin so they

are likely to lose heat energy rapidly and quickly become hypothermic. It is recommended for the resuscitation room temperature to be kept at or above 26 °C and that a radiant warmer, warm blankets, plastic wraps, a head cap, or thermal mattresses be used during the resuscitation. After the resuscitation, in order to prevent the body temperature drop during the transport to NICU, the inside temperature of the transport incubator should be maintained at 37 °C or higher. The target body temperature at reaching NICU is in the range of 36.5-37.5 °C.

1.2.7 Flow of resuscitation

Resuscitation is performed according to Neonatal Cardio-Pulmonary Resuscitation (NCPR) guidelines in Japan for both term and preterm infants, and the NCPR algorithm of Figure 1 should be observed (1).

1.2.7.1 Resuscitation personal

A primary resuscitator whose role is to focus on the respiratory management of the infant should stand at the head of the infant. The bed height should be adjusted to fit this person. Assistants stand on either side of the infant. In addition, a team leader whose role is to direct the resuscitation process as well as being additional help for the resuscitation team should be allocated.

1.2.7.2 Drying skin surface

Gentle handling is important for EP infants, especially those at 22-23 weeks of gestation. Because the skin is very fragile, it is recommended that drying be achieved by gentle wiping with warm gauze rather than by rubbing.

1.2.7.3 Probes and electrodes

One of the assistants should place ECG monitor electrodes on the infant's chest and attach an SpO2 monitor probe on the right hand immediately after birth. Gauze can be placed between the skin and the electrodes in order to prevent skin damage.

1.2.7.4 Respiratory management

The primary resuscitator evaluates the infant's condition according to the NCPR algorithm (Figure 1)(1). If required, the oropharynx should be suctioned to clear mucus and other secretions. A shoulder pillow may be placed to assist appropriate positioning of the infant's neck (sniffing position) to secure and open the airway. An under or over extended neck can both cause airway obstruction.

Then, continuous positive airway pressure (CPAP) or bag & mask ventilation should be commenced. Lung tissues of EP infants are fragile and susceptible to barotrauma, volutrauma, atelectrauma, and oxygen toxicity during CPAP and bag & mask ventilation. It is important to adjust the airway pressure and oxygen concentration according to manometer and pulse oximeter readings.

Initial oxygen concentration can start between 30 and 60% and adjusted appropriately to the target pre-ductal SpO2 cited in Figure 1 (1).

The alveoli of EP infants are easily collapsed because of pulmonary surfactant deficiency. It is therefore important to apply positive end-expiratory pressure (PEEP) of about 5 cmH2O at the expiratory phase during positive ventilation. In addition, a high airway pressure is often required at the first opening of the alveoli. Thus, positive ventilation should be initially started with an inspiratory pressure of 20-25 cmH2O, which can then be adjusted to thoracic movement and heart rate changes.

In almost all preterm infants of 22-23 weeks of gestation, assisted ventilation is ultimately required. Resuscitation with bag & mask ventilation can be used immediately after birth but after stabilization, tracheal intubation can be performed in a calm manner. If bradycardia (HR <100) continues even after appropriate bag & mask ventilation, prompt tracheal intubation is necessary.

1.2.7.5 Circulatory management

Intravenous rapid volume loading is considered a risk of IVH, so rapid volume infusions unless hypovolemia is suspected due to obvious bleeding or if the infant does not respond to initial resuscitation efforts, should be avoided.

1.2.7.6 Tracheal intubation

It is most important to keep the infant's head in the appropriate sniffing position, as shown in Figure 2 for successful tracheal intubation (1). The infant should lie in a supine position with the axes of the head and trunk maintained in a straight position. When placed in a supine position on a flat bed, the necks of EP infants may be bent due to their large heads, leading to airway obstruction. For this reason, it is important to bend the head slightly back to extend the neck and lift the mandible slightly so that there is adequate space between the mandible and the front neck (sniffing position).

The use of a shoulder pillow with hand towel (under the shoulders) makes it easy to bend the head back without undue (extension of the neck). Placing a pillow (under the head) instead of the shoulder pillow, extending the neck and lifting the head caudally forward may also be successful. Avoid hyperextension of the neck as it will obstruct the airway and block adequate view of the glottis.

Table 2 shows the reference values of tracheal tube size and length of fixing tube according to gestational age and birth weight (1). A 2.0 endotracheal tube may be used if a 2.5 tube does not pass easily into an EP infant's airway.

Laryngoscopes with a size of 00 or 0 blades must be used. In EP infants, stylets may cause tracheal injury so to avoid using stylets if at all possible.

1.2.7.7 After tracheal intubation

After tracheal intubation, the tube position should be checked using a breath CO2 detector to confirm correct placement and that the esophagus has not been intubated. Auscultation of the chest on both sides should be also performed to confirm that the endotracheal tube has not been passed into the right main bronchus.

EP infants often have RDS, and therefore, supplemental pulmonary surfactant should be promptly administered. Ideally, a diagnosis of RDS should be based on a combination of high oxygen concentration and inspiratory pressure needs, a micro bubble test, and a chest x-ray. In recent years, it has been reported that a method called Intubate-Surfactant-Extubation (INSURE), in which tracheal intubation, pulmonary surfactant administration, and immediate extubation followed by CPAP is effective in preventing chronic lung disease. However, in Japan, the INSURE method is not commonly used for EP infants, (especially around 22-24 weeks of gestation) because of the risk of IVH from unstable respiratory and circulatory dynamics. For these infants, it is recommended that they be placed on a mechanical ventilator for at least 72 hours after birth to stabilize their respiratory status and to avoid the stress of re-intubation.

1.2.7.8 Post resuscitation treatment

Avoid hypothermia after resuscitation by placing the infant as soon as possible in a closed incubator that is warmed in advance for the transport of infants to the NICU. Warm towels, plastic wrap and head caps are also effective in retaining heat.

To prevent critical hypoglycemia, blood glucose levels must be checked as soon as possible. However, regardless of this result, glucose must be infused through central venous lines (umbilical vein line or peripheral inserted central catheter [PICC]) must be started immediately after stabilization of the EP infant.

Infants requiring mechanical ventilator support must have an arterial line (umbilical artery line or peripheral artery line) for continuous blood pressure measurements and blood sampling.

References

1) The Textbook of Neonatal Cardiopulmonary Resuscitation. Based on the 2015 Guidelines of the Japan Resuscitation Council. 3rd edition. (Available from: https://www.ncpr.jp/eng/course_material.html, Accessed on Apr 13, 2019). Hosono S, editor.

Table 1 Tools and devices required for resuscitation of EP infants

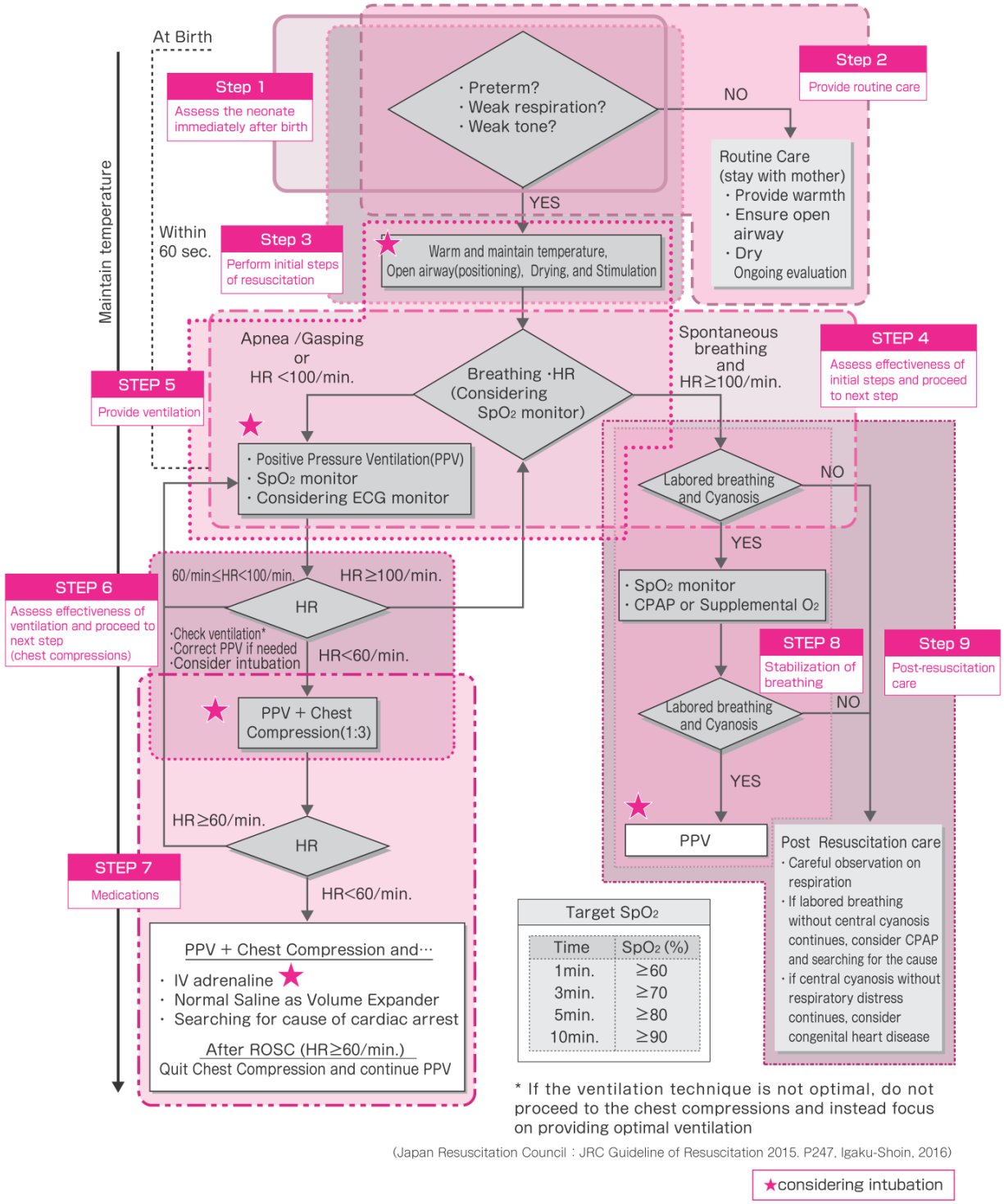
Temperature Control	Open type incubator (radiant warmer) Transport incubator (warm) Warm towels and gauze Plastic wrap (food wrap can be used)
Respiratory assist	Aspirator, suction catheter (for mouth and nose: 6-8 Fr, trachea: 5, 6 Fr) Face masks for preterm infants (different sizes) Jackson Reese (with manometer) or T-piece resuscitation device Oxygen source (with flow meter), compressed air, oxygen air blender, flow meter
Tracheal Intubation	Laryngoscope (handle, straight blade [size 00 or 0], spare battery and bulb. Make sure that the bulb is functional and not loose) Tracheal tube (inner diameter: 2 mm, 2.5 mm, 2 each), stylet Tracheal tube fixing tape Exhaled CO2 detector
Monitoring	Stethoscope Pulse oximeter (SpO2 monitor) and probe Respiratory and heart rate monitor, and electrodes
Lines	Umbilical catheter (5 Fr for veins, 3.5 Fr for arteries) Peripheral vein catheter (24G) Intravenous infusion set Injection needle (23G, 22G, 18G) Syringe (1 ml, 2.5 ml, 5 ml, 10 ml) Alcohol cotton
Drugs	Saline solution, 5% glucose solution, 10% glucose solution, adrenalin, sodium bicarbonate, calcium gluconate Pulmonary surfactant preparation
Others	Sterile gloves, gowns, masks, caps Feeding tube (3-5 Fr) Scissors

Table 2 Selection of endotracheal tube

Weight (kg)	Gestational weeks (weeks)	Tube size (mm)	Estimated insertion length up to the corner of the mouth (cm)*
＜1.0	＜28	2.0, 2.5	6.0－7.0
1.0－2.0	28－34	2.5, 3.0	7.0－8.0
2.0－3.0	34－38	3.0, 3.5	8.0－9.0
＞3.0	＞38	3.5	>9.0

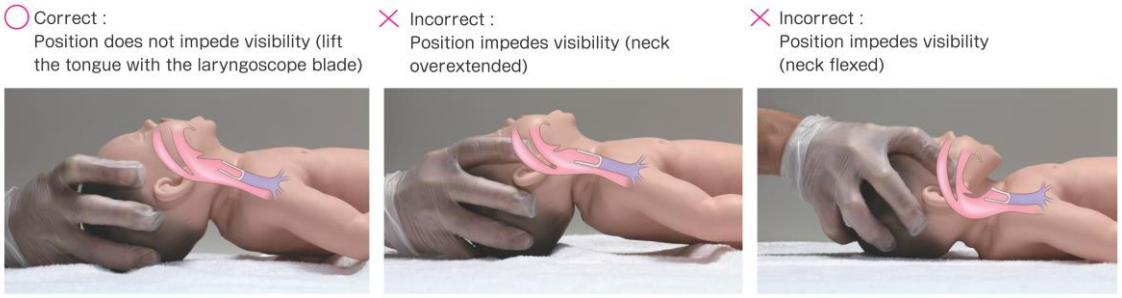
*The insertion length up to the corner of the mouth can be calculated by approximately 6 + body weight (kg) cm.

Figure 1 NCPR resuscitation algorithm



(Japan Resuscitation Council : JRC Guideline of Resuscitation 2015. P247, Igaku-Shoin, 2016)

Figure 2 Proper Sniffing position (Avoid neck hyperextension and flexion)



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2. Respiratory support

2.1 Non-invasive respiratory support and conventional mechanical ventilation

2.1.1 Clinical situation

Newborns, especially EP infants, have immature anatomical and functional respiratory systems. The smooth transition from placenta to independent air breathing is thus also frequently disrupted in EP infants, resulting in the need for respiratory support after birth in almost all infants in some way. The anatomical characteristics of the respiratory system in EP infants include a small area of gas exchange, narrow airways, and a soft and pliant chest wall. Functionally, respiratory control is immature, with the diaphragm acting as a dominant force in respiration. Breathing is predominantly nasal and there is high pulmonary vascular resistance and insufficient pulmonary surfactant secretion.

Unlike physiological respirations which is negative pressure ventilation, any kind of respiratory support is performed under positive pressure and driven externally. Lung damage is unavoidable long-term positive pressure is applied, especially on the immature developing lungs (volutrauma, barotrauma, etc.). In addition, respiratory support under tracheal intubation also increases the risk of respiratory tract infection and subglottic stenosis. Thus, non-invasive respiratory support, which is defined as respiratory support without tracheal intubation, is often preferred in order to reduce lung injury and pulmonary complications in EP infants.

2.1.2 General Management

The purpose of respiratory support is to maintain partial oxygen and carbon dioxide pressures within normal limits and to stabilize the infant's respiratory symptoms. Of course, regardless of invasive- or non-invasive respiratory support, monitoring of blood gases, including PO2 and PCO2 is essential and must be performed to prevent over or under inflation of the lungs. During respiratory support, it is also necessary to evaluate chest x-rays to ensure that lungs are not atelectatic due to alveolar collapse. Blood gas sampling is invasive especially for preterm infants. Therefore, it is recommended for non-invasive measurements to be used where available, including SpO2, transcutaneous (TC) O2 and Co2 monitoring. The values obtained from non-invasive measurements must be confirmed by a direct blood gas analysis if necessary. It should be noted that carbon dioxide partial pressure in venous blood is slightly higher than

that in arterial blood.

2.1.2.1 Methods of Non-Invasive Respiratory Support

2.1.2.1.1 Oxygen

Oxygen should be administered if there is poor oxygenation despite adequate spontaneous breathing. Both hyperoxia and hypoxemia should be avoided. FiO2 should not be initiated at 100% unless further evidence becomes available. FiO2 should be started between 30-60% and changed appropriately to target 90-95% SpO2 with a pulse oximeter (1).

2.1.2.1.2 Nasal-Continuous positive airway pressure (N-CPAP)

Spontaneously breathing infants may have respiratory distress with grunting and/or retractive breathing due to collapse of alveoli. This is seldom improved with supplemental oxygen alone and positive pressure ventilation is usually necessary to alleviate symptoms. Respiratory diseases that often affect EP infants include transient tachypnea of the newborn (TTNB), mild RDS, and obstructive apnea attacks. N-CPAP should be applied with a nasal prong closely connected with the nose and a warm and humidified source of oxygen or room air. Continuously applied positive pressure to the airway can prevent collapse of alveoli at the end of exhalation. In general, the pressure delivered should start at 3-8 cm H2O. Lung expansion increases functional residual capacity (FRC), increases gas exchange area, and improves oxygenation. It is also used for post-INSURE management for the infants with mild RDS. Reduction of early lung damage can ultimately decrease the need for mechanical ventilation.

2.1.2.1.3 Nasal-Directional positive airway pressure (N-DPAP)

The diseases indicated for N-DPAP is almost as same as N-CPAP. While N-CPAP continuously applies the same positive pressure during the both inspiratory and expiratory phases, N-DPAP can produce the different effects on inspiratory and expiratory by using jet flow. At the time of inspiration, stable positive pressure is applied by the jet stream flowing toward the infants, however, at expiration, the direction of the jet stream is converted so that the flow does not disturb infant expiration. As a result, excessive pressure is not applied to the lungs and the work of breathing is reduced with noninvasive respiratory support.

2.1.2.1.4 SiPAP

"Sigh" (deep breathing) is added to N-DPAP to enable biphasic CPAP control. In this

BiPhasic mode, pressure is generated by providing an additional flow to the baseline flow that generates low CPAP. As a result, "Sighs" are created intermittently, which expand collapsed alveoli, improve pulmonary recruitment and decrease ventilation perfusion mismatch. The duration and frequency of SiPAP pressure can be adjustable. The diseases indicated for SiPAP are almost the same as N-CPAP and N-DPAP. When used in apnea of prematurity, intermittent pressure changes may stimulate the respiratory center of the infants resulting in a reduction of the number of attacks.

2.1.2.1.5 High-flow nasal cannula (HFNC)

This is classified as oxygen therapy in respiratory management. A nasal cannula is used to provide warm and humidified oxygen at high flow rates. The high flow of gas through the nasal cavity flushes the carbon dioxide in the nasopharyngeal cavity and causes a mild PEEP to ease inspiration and lead to a reduction in work of breathing. HFNC is positioned as a form of respiratory management between oxygen administration and N-CPAP of N-DPAP. Oxygen concentration, flow rate, degree of heating and humidification can be individually set. Flow rates usually starts at 2 L/kg/min and adjusted by 1-3 L/kg/min according to the respiratory condition of the infants. Nasal prong size should not impede more than 50% of the nostril so that exhalation pathways can be maintained.

N-CPAP, N-DPAP and HFNC produce PEEP which decreases the risk of atelectasis and apnea. These modalities lead to earlier extubation practices. In EP infants, however, respiratory drive is weaker and HFNC may not provide enough PEEP to ensure stable respiratory effort. Therefore, N-CPAP or N-DPAP is preferred for this particular patient group.

2.1.2.2 Methods of Mechanical Ventilation (2)

3.1.2.2.1 Intermittent mandatory ventilation (IMV)

Respiratory support is performed with forced ventilation produced by a mechanical ventilator in IMV regardless of spontaneous breathing. Inhaled oxygen concentration, maximum inspiratory pressure, PEEP, respiratory frequency, and inspiratory time are set. Since forced ventilation is applied regardless of the spontaneous respiratory phase, fighting between spontaneous and forced ventilations may be inevitable. For example, forced ventilation may occur during the expiratory phase of the spontaneous breathing which may lead to excessive airway pressure and lung damage. Fighting does not occur in the infants without spontaneous breathing obviously or when spontaneous breathing

of the infants is suppressed with a muscle relaxant.

2.1.2.2.2 Synchronized intermittent mandatory ventilation (SIMV)
In this mode, fighting between mechanical ventilation and spontaneous breathing can be eliminated by synchronizing mechanical motions with the infants' efforts through a triggering system of inspiration. Theoretically, this can reduce lung damage. There are two ways of the inspiratory triggering: with a flow sensor or with a pressure sensor. By pre-setting the number of breaths per minute, the minimum frequency of breaths is maintained even if prolonged apneas exist or a respiratory rate is less than the pre-set frequency.

During the mechanical ventilation, the tidal volume is very important and is usually set at 4 to 6 ml/kg. Tidal volume can be controlled by the adjusting the difference between maximum inspiratory pressure and PEEP. Clinically, the setting is adjusted in consideration of a combination of chest movement, chest X-ray findings, and blood gas measurements.

2.1.2.2.3 Assist control ventilation (A/CV) or patient trigger ventilation (PTV)
Both modes are basically assisted ventilation achieved by forced mechanical ventilations synchronized with spontaneous inspiration. Oxygen concentration, peak inspiratory pressure, PEEP, and inspiratory times can be pre-set. The difference between these modes and SIMV is that the respiratory rate cannot be controlled. These modes assist all infant breaths and if spontaneous breathing rates decrease, a minimum respiratory rate cannot be guaranteed. This mode is therefore suitable for infants with weak and inadequate spontaneous breathings. If spontaneous breathing rates are too low, backup mechanical ventilation can be introduced.

In very preterm infants with unstable respiratory status and decreased spontaneous breathing efforts are usually stabilized better with SIMV modes. Once spontaneous breathing becomes more stable, A/CV can be used. After this, weaning from mechanical ventilation can be achieved by gradually decreasing peak inspiratory pressures.

2.1.2.2.4 Pressure support ventilation (PSV)
This method is characterized with a function not only to trigger the inspiration but also to terminate the expiration according to the respiratory efforts of the infants. Once a flow of expiration becomes less than a certain level compared to the peak flow of it, the

ventilator terminates inspiration and shifts to expiration. In this way, the fighting can be avoided, and the respiratory workforce can be also reduced. Inspiratory time and respiratory rates are dependent on the infant and not the ventilator. EP infants whose spontaneous breathing is already stable are candidates for this mode.

In the case of extremely premature infants who have weak spontaneous breathing and are not stable yet, forced mechanical ventilation with a fixed number of backup respirations like SIMV plus PSV is preferable and may allow more rapid weaning from mechanical ventilation.

2.1.2.2.5 Neurally adjusted ventilatory assist (NAVA)
This is a relatively new mode of mechanical ventilation. Physiologically, respiratory action is transmitted as an electrical signal from the respiratory center to the diaphragm, causing diaphragmatic contraction. This movement can create a negative pressure in thorax and expand the lungs through the air entry into airways. NAVA is designed to trigger inspiration using the electrical signal of the diaphragm. The benefit of this triggering system is that the detection of spontaneous breathing is earlier than other sensing systems e.g. SIMV to detect the changes in flow or pressure during the inspiration. Furthermore, the supportive pressure can be adjusted according to the potential of the electrical signal to diaphragm, which represents the strength of spontaneous breathings. Although this is a more physiological way to support spontaneous breathing compared to other modes, it is still difficult to apply to EP infants during the acute phase, because of the difficulty in a placement of electrodes in the esophagus of small infants and the exclusive dependency of triggering on spontaneous breathing efforts.

2.1.3 Evaluation
Generally, clinical symptoms such as grunting, tachypnea, retractive breathing, cyanosis, apnea, and wheezing, and findings from monitoring such as SpO2, TcPO2, TcPCO2, and blood gas analyses must be considered to introduce any respiratory support and for the selection of appropriate modes of respiratory support. Mechanical ventilation can be managed according to the type of respiratory failure as indicated in Table 1.

2.1.3.1 Laboratory examination
Normal value of blood gas analysis : PaO_2 50-80mmHg

$PaCO_2$	40-50mmHg
pH	7.3-7.45
HCO_3^-	20-25mEq/L

Although there is a concept that “permissive hypercapnia” with generous respiratory settings can reduce lung damage during the mechanical ventilation, hypercapnia also increases cerebral blood flow, which may increase the risk of IVH. Therefore, it is important to obtain a balance towards protecting the developing brain and towards reducing lung injury. In general, PCO2 should be maintained at 50-60 mmHg in EP infants.

References

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2) Goldsmith J, Karotkin E, Suresh G, Keszler M. Assisted Ventilation of the Neonate. 6th ed. Evidence-Based Approach to Newborn Respiratory Care Philadelphia, PA: Saunders-Elsevier; 2016.

Table 1 Type of respiratory failure and its management

	PO_2	PCO_2	Pathophysiology (disease)	Parameters to adjust
Ventilation failure (Low ventilation)	↓	↑	Upper and lower airway narrowing Central hypoventilation and apnea attacks Lung hypoplasia Pneumothorax RDS, TTNB	Respiratory Rate Tidal Volume FiO_2 PEEP
Diffusion failure	↓	→	Pulmonary hemorrhage RDS, TTNB	PEEP FiO_2
Right to left shunt	↓	→	PPHN Congenital heart diseases Atelectasis	FiO_2 Mean Airway pressure

RDS: respiratory distress syndrome, TTNB: transient tachypnea of the newborn, PPHN: persistent pulmonary hypertension of the newborn

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2.2 High -Frequency-Oscillatory Ventilation (HFOV)

2.2.1 Clinical situation

High Frequency Oscillatory Ventilation (HFOV) is a mode of mechanical ventilation that provides lung expansion with a constant mean airway pressure (MAP) to facilitate gas exchange at the airway rather than at alveolar level.

It is possible to keep alveoli constantly and persistently opened by the MAP. In addition, alveoli are expanded and deflated with a small volume that is lower than anatomical dead space if oscillation occurs at a frequency of around 15 Hz. In this way, HFOV provides efficient mechanical ventilation and simultaneously, reduces the stress of volutrauma and barotrauma (Figure 1). This minimal volume exchange at alveoli with HFOV is also maintains pulmonary surfactant function, making HFOV a preferred mode of ventilation for preterm infants immediately after birth rather than as a rescue (1,2).

2.2.2 Mechanism of HFOV

Gas exchange can be achieved by diffusion at the alveolar level by applying non-physiological oscillations with volumes below that of dead space. Gas delivered to the airways does not reach the alveoli immediately. but is subject to various physical modifications at each level of the airway and eventually reaches the alveolar level, during which inspiration and expiration are repeated within a short time period. However, the whole operating principle of HFOV is a very complicated and not fully understood (3).

The pressure waveform and the pressure change of HFOV diminishes towards the peripheral airways and becomes very tiny within the alveoli (Figure 2). Pressure differences in the Y-piece portion of the respiratory circuit are indicative of the overall pressure gradient between the inspiratory and expiratory phases. These values are dependent on respiratory settings and the tracheal tube inner diameter but are usually greater than normal mechanical ventilation. However, the pressure gradient at the distal portion of the tracheal tube is usually less than half of that at the proximal portion. The gradient further decreases with increasing airway resistance and becomes 1/10 or less of the original difference beyond the tracheal bifurcation. Even though the pressure gradient and the ventilation volume at the alveoli level is minimal, HFOV can maintain ventilation volume while maintaining the mean airway pressure because of

the high frequency of breaths.

2.2.3 General Management

2.2.3.1 Operator-selected parameters

HFOV can control oxygenation and ventilation independently, mainly by adjusting MAP and piston amplitude (Figure 1).

There are two types of HFOV, a piston type and a diaphragm type, for creating the necessary pressure gradients.

In the piston type, oscillation is produced by a piston moving at high speed, and ventilation volume increases in proportion to the amplitude (Amp) which is controlled by the stroke volume (SV). Even relatively large infants can be ventilated with this modality. The frequency is often fixed at 15 Hz. A typical brand name is the Hamming series.

In the diaphragm type, MAP and oscillation are created by the combination of high-speed valve opening and closing and a constant jet flow. The power to create oscillation is limited compared with the piston type. In order to create appropriate MAP and oscillation, it is necessary to adjust both amplitude and frequency parameters together. On the other hand, expired tidal volume (VThf) can be adjusted independently. A typical machine is the Babylog® series.

2.2.3.2 Adjustment of parameters

Regulation of oxygenation: If you want to improve oxygenation, raise FiO2 or raise MAP (Table 1).

Ventilation volume adjustment: Increase the piston amplitude if you want to lower PaCO2. By increasing the piston amplitude, the air turbulence created by pressure gradient can reach more peripheral airways and increase the diffusion of CO2. If PaCO2 does not decrease by increasing amplitude, lowering the frequency of breaths will increase volume differences within the alveoli. However, this may also increase the risk of lung injury. A frequency of less than 15Hz is not recommended for EP infants.

The Babylog® has the capacity of providing HFOV with a Volume Guarantee mode that allows automatic adjustment of the VThf constant. This function can prevent

hyperventilation and volutrauma and may be used for EP infants (4). A suggestion is to set VThf at 1 to 2 ml/kg. For some CLD infants, 2-3 ml/kg of VThf might be needed to achieve stable ventilation.

2.2.3.3 Characteristics of HFOV

Advantages

Volume change in the alveoli is very small and HFOV can reduce barotrauma and volutrauma compared to conventional mechanical ventilation.

Machine settings are easy because PaO2 and PaCO2 levels can be controlled independently.

Disadvantages

If there is an obstruction or stenosis from the tracheal tube to the peripheral airway, oscillations of HFOV will not be efficiently transmitted to the alveoli and therefore, its use in obstructive diseases such as pulmonary hemorrhage may be diminished.

High MAP causes a continuous increase in intrathoracic pressure and diminished venous return, leading to decreased blood pressure and cerebral congestion.

Application of HFOV is shown in Table 2.

2.2.3.4 Evaluation

2.2.3.4.1 MAP adjustment

MAP setting is very critical in the effectiveness of HFOV. MAP that is insufficient to maintain appropriate lung volume prevents the pressure gradient produced by HFOV from reaching the alveoli, resulting in vibration-related damage to the peripheral airways. Therefore, in order to prevent alveolar collapse, it is recommended to MAP be set by 2-5 cmH2O or 1.5 times higher than that of conventional mechanical ventilation.

Default setting: MAP 12 cm H2O for EP infants

It is necessary to adjust MAP so that the anterior surface of the diaphragm will be positioned approximately at the ninth intercostal space, as visualized on chest X-ray. During the acute phase, chest X-ray examination must be done at least once a day determine adequacy of lung inflation because of the need to apply high MAP at the

beginning of respiratory support. Thereafter, adjust MAP in accordance to CXR and clinical findings.

HFOV uses higher MAP than CMV and this may compromise venous return, leading to hypotension. In such cases, volume infusions and catecholamine support may be needed. If the infant's circulatory condition cannot be maintained despite full inotropic support, it is recommended HFOV be changed to CMV.

2.2.3.4.2 SV adjustment
Adjust SV according to target PCO2 and pH values, which should be approximately PCO2 50-60 mmHg and pH 7.3, respectively.

If the tracheal tube is bent or obstructed with secretions, HFOV may not be effective due to the failure of transmissions of oscillations to the periphery. This may be rectified with endotracheal suctioning

It is desirable to use a closed circuit aspiration catheter to prevent alveolar collapse after endotracheal aspiration.

2.2.3.4.3 Sustained inflation (SI: Sigh)
The alveoli may collapse after removal of the respiratory circuit or after endotracheal aspiration. In this state, HFOV may not be effective. If oxygenation is insufficient, SI may be necessary to recruit lung. This involves a SI breath for 5 to 10 seconds with an airway pressure 5 cm H2O higher than the current MAP. Be aware that excessive pressure and duration of SI can cause hypotension and cerebral blood flow fluctuation, so an automated and fixed interval SIs should not be used.

2.2.3.4.4 Weaning
First, lower the oxygen concentration, and decrease the MAP by every 1.0 cmH2O after FIO2 decreases to below 0.4. MAPs that are too low can cause lung collapse and lung damage, so do not lower MAPs below 6 cmH2O.
Lower the SV by 1 if PCO2 and pH are maintained at 50-60 mmHg and pH 7.3, respectively.

2.2.3.4.5 Timing of extubation
It is possible to extubate directly from HFOV.

If MAP is between 7-8 cmH2o and FiO2 <0.3, consider extubation.
Lowering the MAP too much may cause obstruction of the peripheral airways, resulting in atelectrauma. In addition, spontaneous breathing is difficult with low MAP and a narrow tracheal tube. For the same reason, it is not recommended to shift to a CPAP mode before extubation.

SpO2 levels may sometimes decline because of apnea attacks during the weaning process. In this case, caffeine citrate administration may be considered, with a loading dose of 20mg/kg, followed 24 hours later with a daily maintenance dose of 5-10mg/kg/d (5).

2.2.3.5 Note
The results of a study that examined the respiratory function of preterm infants born less than 29 weeks of gestation at 11-14 years of age who were randomized to either HFOV or CMV in NICU found significantly better respiratory function parameters in the HFOV group, suggesting that HFOV at birth may have long-term respiratory benefits even until adolescence (6).

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Table 1 How to change HFOV settings

	Purpose	Action
Oxygenation	PaO2 ↑	Increase MAP Increase FiO2
	PaO2 ↓	Decrease MAP Decrease FiO2
Ventilation	PaCO2 ↑	Decrease SV Increase Hz
	PaCO2 ↓	Increases SV Decreases Hz

Table 2 Indications of HFOVV

(Effective)	(Not effective)
■ RDS ■ Air leak syndrome ■ Lung hypoplasia ■ CLD ■ MAS (Oscillation might be useful for excretion of airway secretion) ■ PPHN (with iNO)	■ Airway obstruction □ Upper airway stenosis □ MAS □ Lung hemorrhage □ Use thin endotracheal tube □ Thick respiratory secretion ■ After surfactant administration ■ Cardiac dysfunction ■ Intraventricular hemorrhage ■ Brain edema

Figure 1 Parameters in HFOVV

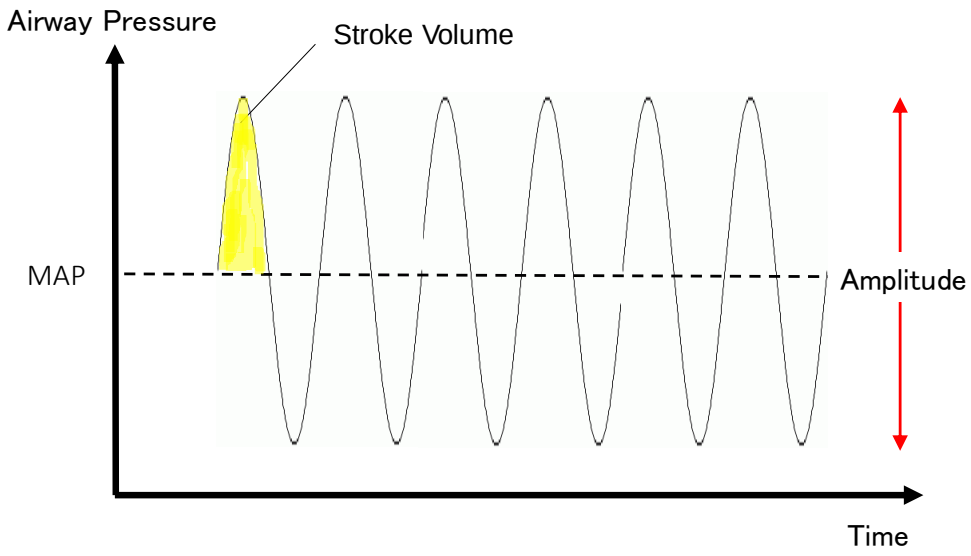
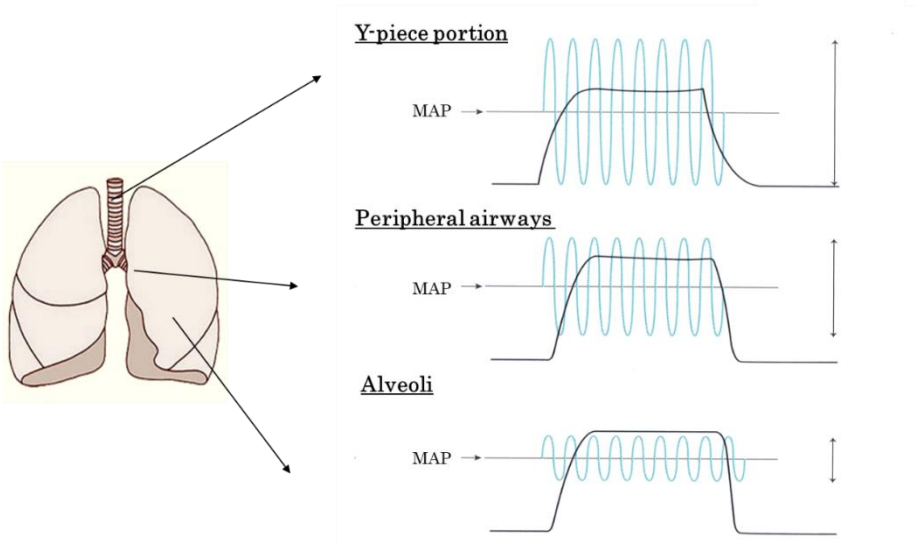


Figure 2 Airway pressure waveforms during HFOV



(Contributor: Hidehiko Nakanishi, Audit: Tomohiko Nakamura)

2.3 Prevention of CLD

2.3.1 Clinical situation

2.3.1.1 Pathogenesis

The pathogenesis of CLD is multifactorial and the result of lung immaturity. The process is initiated by activation of inflammatory cells such as alveolar macrophages and multinucleated leukocytes induced either by intrauterine inflammation such as chorioamnionitis (CAM) and/or postnatal inflammatory damages (biotrauma). In addition to inflammatory damages, mechanical injuries to terminal bronchioles that are adjacent to alveoli can be caused by atelectasis (atelectrauma) secondary to surfactant deficiency and ventilator induced lung injury (VILI). In recent years, environmental factors such as genetic predisposition and maternal smoking have also been strongly implicated in the pathogenesis of CLD (Figure 1).

Furthermore, hyperinflation secondary to excessive mechanical ventilation can also compress pulmonary blood vessels and increase pulmonary vascular resistance. Hypoxemia and hypoventilation lead to pulmonary hypertension (Figure 1), which complicates the long-term prognosis of EP respiratory distress and CLD.

2.3.1.2 Physical examination

Respiratory failure with hypoxemia, necessitating the need of supplemental oxygen and ventilatory support are the hallmarks of CLD. Lung damage may be compounded by expiratory difficulties caused by narrowing of the peripheral airways and a bulging thoracic cavity, due to chronic emphysema. Attention should also be paid to the signs of right heart failure due to pulmonary hypertension.

2.3.1.3 Diagnosis

2.3.1.3.1 Japanese criteria

In Japan, CLD is classified into seven disease types according to the predisposing pathological condition (RDS or CAM) and chest X-ray findings (foamy or emphysematous shadows (Table 1)(1).

The diagnostic criteria of the National Institute of Child Health and Human Development (NICHD), which is regarded as the standard diagnostic method for bronchopulmonary dysplasia (BPD) worldwide, are shown in (Table 2)(2). However, there is no consensus on the treatment of BPD with HFNC, which was recently introduced and disseminated.

Note that the need for oxygen supplementation and/or respiratory support at 36 weeks of corrected age is critical for the diagnosis of CLD but this may be modified arbitrarily by attending physicians.

2.3.1.3.2 Objective Diagnosis

The diagnosis of CLD is determined by the need for supplemental oxygen and/or respiratory support but this may be subjective and dependent on the judgement of the attending physician. Oxygen, for example, may be used for other conditions other such as apnea. There is thus a concern that that the diagnosis and rates of CLD may be influenced by the facility or the attending physician. In order to standardize the diagnosis of CLD, the oxygen reduction test (ORT) at 36 weeks of corrected age has been implemented in Japanese NICUs (3). This test determines the need for oxygen by infants born below 35 weeks gestation and involves evaluation of the infant's physical condition for 30 minutes after oxygen supplementation is ceased. The diagnostic flow chart and test methodology are shown in Figure 2 and Table 4.

2.3.1.3.4 Optional diagnosis

Compared with CLD diagnosed at 28 days of age, the diagnosis at 36 or 40 weeks of corrected age correlated better with future neurological outcomes (4). Furthermore, the CLD working group of International Neonatal Consortium (INC) has proposed a respiration assessment method called Premature Infant Respiratory Status (PIRS) (Table 5). This diagnosis correlates well with the long term outcomes but is difficult to interpret early on in life.

2.3.2 General management

2.3.2.1 Daily management

CLD is an independent predictor of future neurodevelopment and therefore, all efforts should be made to 1. Prevent and 2. Ameliorate its severity. For example, attempts must be made to minimize or avoid intrauterine inflammation or minimize lung damage from mechanical ventilation.

Table 4 shows preventative and therapeutic strategies that are available in Japan. There is no one best and established method, probably because of the multifactorial nature of the disease. There are, however, some therapies with weak benefits. At the moment, the combination of prenatal glucocorticoid and postnatal inhaled corticosteroids appear beneficial in minimizing the need for mechanical ventilation, even in infants born at 24-26 weeks gestation. Indeed, it may even reduce the severity of CLD and the need for home oxygen in this gestation group (5).

2.3.2.2 Optional treatment

Infants dependent on mechanical ventilation for severe CLD are managed by different policies at each facility. For example, the types of ventilators may be different, as may be the ventilator settings. In Japan, may facilities use HFOV. CLD is a particularly difficult disease to manage as any lung will have a combination of normal, hyper and hypo inflated areas. Adequate PEEP is vital to open atelectatic areas, as is sufficient expiratory time (to avoid hyperinflation). Increased respiratory rates are usually not warranted. In severe cases, tracheostomy may be needed to promote quality of life for the infant, by allowing neurodevelopmental care that would otherwise be restricted in the intubated patient.

In severe CLD, there may be concurrent pulmonary hypertension. In these cases, pulmonary vasodilators and regular evaluation with echocardiography and the pulmonary hypertension score (PH score) is necessary to detect pulmonary hypertensive crises (PH crisis). This may be fatal. Once the infants are discharged from NICU, it is recommended that continued care be closely monitored by local primary care physicians and PICU specialists.

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Table 1 Classification of chronic lung diseases (Japan) (Reference 1)

Type	RDS	Intra uterine inflammation (Elevated serum Ig M, Chorioaminionitis)	Foamy or emphysematous shadows on X-ray
Ⅰ	+	-	+
Ⅱ	+	-	-
Ⅲ	-	+	+
Ⅲ'	-	+	-
Ⅳ	-	suspected	+
Ⅴ	-	-	-
Ⅵ		Un classification case	

Table 2　Definition of CLD and BPD

Treatment with > 21% oxygen for at least 28 d plus

		CLD （japan）	BPD （NICHD）	
Gestation Age		All wk	< 32 wk	≧ 32 GW
Tim point of assessment		36 wk PMA	36 wk or discharge to home, whichever comes first	>28 d but < 56 d postnatal age or discharge to home, whichever comes first
Severity	Mild		Breathing room air	
	Moderate		Need for < 30% oxygen	
	Severe	Need for > 21% oxygen	Need for ≧30% oxygen and/or positive pressure (PPV or NCPAP)	

Table 3 Prevention and treatment of CLD

Procedure and Treatment	Effectiveness	Comment
Resuscitation	○	Limited use of oxygen after birth
Oxygen use at chronic phase	○	Keep SpO2 upper limit at 95% or less
Surfactant administration	○	
Early prophylactic administration of surfactant	○	Within 30 minutes after birth
HFOV	△	HFOV is preferred in Japan but there is no evidence for its use in CLD outside of Japan
nCPAP	○	To avoid tracheal intubation
NO inhalation	△	Variable effect
Systemic steroid administration	○	Effective but serious adverse events are concerned
Inhaled steroid	○	Effective to reduce severity
Caffeine administration	○	Effective to reduce severity, especially when used early
Diuretic administration	△	
Bronchodilator ß2 stimulant	×	
Vitamin A, vitamin E administration	×	
Stem cell therapy	?	Waiting clinical application

Table 4 Method of ORT (Oxygen Reduction Test)

① Check for the adverse events 1 hour before the reduction of nasal cannula oxygen administration*

② Nasal canula supply reduced gradually

・Start at resting time of the infant and at least 30 minutes after the nutrition.

・Decrease flow rate gradually without changing the oxygen concentration and finally stop it

Flow rate 1.0-2.0 L/min: Decrease by 0.5 L/min. Every 5 minutes
Flow rate <1.0 L/min: Decrease by 0.1 L/min. At 1 minute intervals

③ Tolerance test

・Continue 30 minute observation. Check if the following failure criteria are not met or there are no adverse events

・The oxygen delivery device should be removed from the infant.

・If SpO2 is maintained at greater than 95% in the first 15 minutes, it is judged that there is no CLD 36 and the test is completed (Rapid-pass criteria)

④ Failure criteria

The diagnosis of CLD36 was made when the following conditions were met, and the test must be completed promptly.

SpO2 80-89% is more than 5 minutes
SpO2 less than 80% is more than 15 seconds
Examiner decides that discontinuation is necessary, such as frequent occurrence of apnea

If it does not meet the failure criteria, it is judged that there is no CLD 36.

⑤ Resume the original oxygen administration promptly after the test.
Check for the presence of adverse events for 1 hour after completion*

※Adverse event

This must be observed from 1 hour before the test through 1 hour after.

・Apnea (respiratory arrest> 20 seconds or need of stimulation to recover)
・Bradycardia (less than 80 HR> 10 seconds or need of stimulation to recover)
・Need of FiO2 increases 5% or more within 1 hour after completion

Table 5 Premature Infant Respiratory Status (PIRS)

Evaluate according to following categories at 40 weeks of corrected age or at the time of discharge if discharge earlier,

(1) Do not require oxygen or respiratory assistance more than last 7 days

(2) Do not require oxygen and respiratory support for the last 7 days, but require medications

(3) Oxygen and/or respiratory support were stopped within last 7 days

(4) Oxygen supplementation with low flow nasal canula (flow≤ 1 L/m)

(5) Oxygen administration exceeding 1 L/min or respiratory support

(6) Death due to respiratory failure from 2 weeks after birth through 40 weeks of corrected age

Respiratory support: Regardless of oxygen use, any respiratory supports including HFNC, CPAP, tracheal intubation

Medications: diuretics, bronchodilators, steroids, caffeine, vasodilators

Figure 1 Pathogenesis of CLD

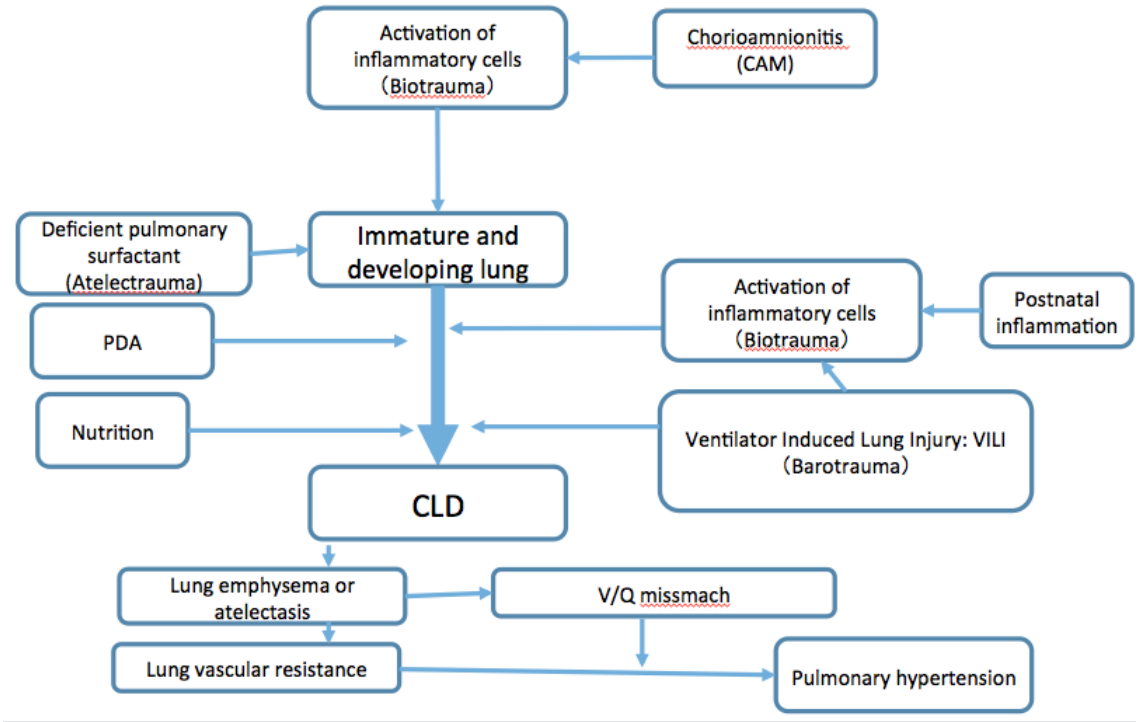


Figure 2 Criteria of Oxygen reduction test (ORT)

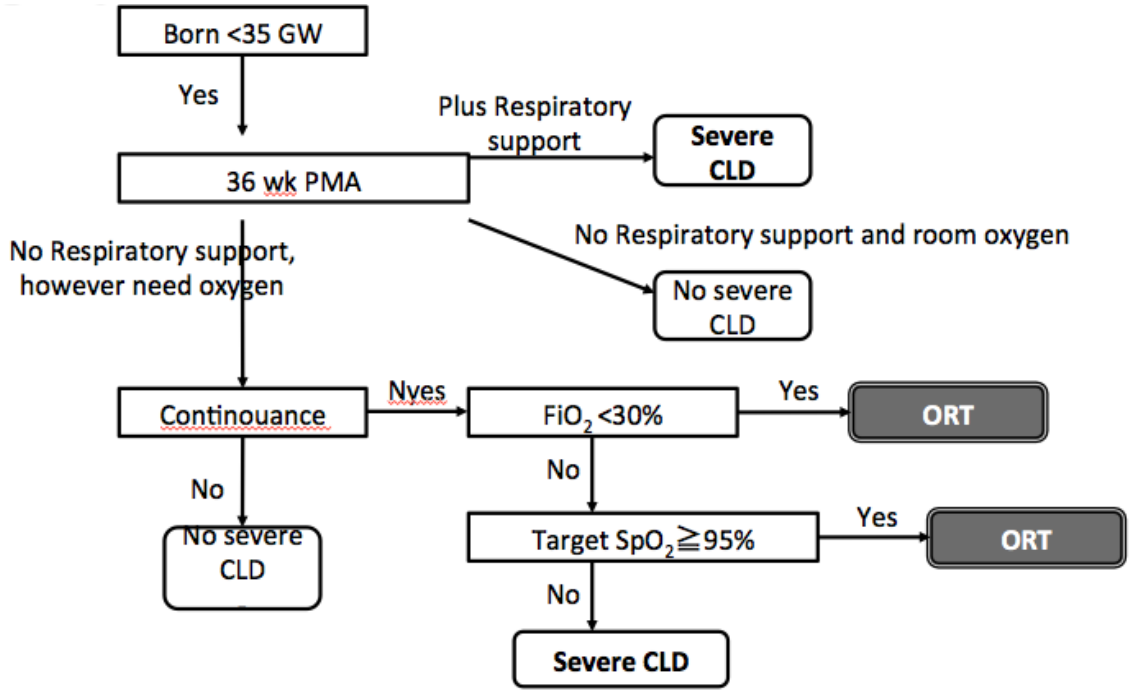
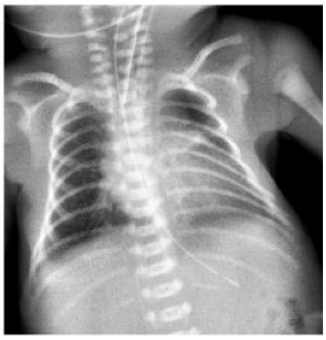
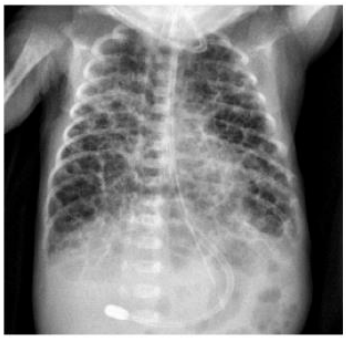
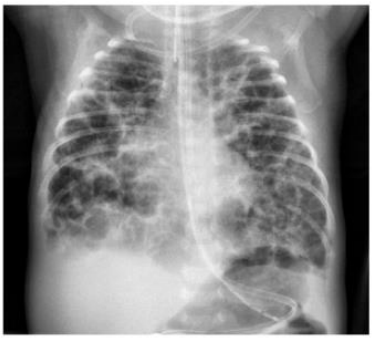


Figure 3 Chest X-ray findings of severe CLD







Day 1

Born at 24 GW

Day 28

28 wk PMA

Foamy and emphysematous shadows on X-ray

Need ≧30% oxygen and positive pressure ventilation

Day 90

36 wk PMA

Foamy, emphysematous shadows and atelectasis on X-ray

Need ≧30% oxygen and positive pressure ventilation

（Contributor: Tomohiko Nakamura, Audit: Hidehiko Nakanishi）

3 Circulatory support

3.1 General support

3.1.1 Clinical situation

3.1.1.1 Characteristics of cardiovascular system in preterm infant after birth

3.1.1.2 Transition from fetal circulation

Immediately after birth, the transition from fetal to neonatal circulation occurs as follows: Firstly, an increase in systemic vascular resistance occurs after separation of placenta the placenta from the infant. The placenta has low vascular resistance and this leads to a decrease in pulmonary vascular resistance due to pulmonary expansion after the start of breathing. Thereafter, the closure of the ductus arteriosus and foramen ovale occurs and the transition from fetal to independent circulation is complete to allow blood flow from both ventricles to whole body (1). Because this transition is a dramatic change for the infants, it is sometimes difficult for EP infants to adapt correctly.

3.1.1.3 Cardiac function

EP infants have fewer myocardial fibers, contractility, lower catecholamine levels and less cardiac reactivity. In addition, the ventricular compliance is low, in both systole and diastole and the EP heart is limited in its capacity for extra work. Therefore, it is sometimes difficult for the cardiac function of EP infants, characterized by poor contractility and low cardiac reserve, to confront any increase in after load. This leads eventually to poor performance (2). The other characteristic of cardiac function is that the cardiac output from left ventricle is maintained by increased heart rate, demonstrating a lack of adaptability when compared with an older child and an adult. Any volume load due to a patent ductus arteriosus (PDA) or bradycardia will directly lead to decreased cardiac function (3).

3.1.1.4 Adrenal function

The adrenal grand grows throughout fetal life through the actions of the corticotropin-releasing hormone (CRH) or estrogen from the placenta. Progesterone, a substrate for cortisol production, is also supplied by the placenta. The adrenal grand is not fully developed in the preterm infant and placental supply of adrenal hormones e.g. cortisol will stop suddenly at birth. EP infants are also exposed to many stresses before and after birth and cortisol production is rarely adequate in this situation, leading to unstable hemodynamics due to lack of vasoconstrictive and sodium retention properties

of cortisol.

3.1.2 General Management

3.1.2.1 First 24 hours after birth

The first 24 hours after birth is an extraordinarily acute phase characterized by dramatic transition from fetal to neonatal circulation, relative adrenal insufficiency due to inadequate cortisol production under stress before and after birth, hypercytokinemia due to intrauterine inflammation causing preterm delivery, and extravasation, especially antenatal steroids were not given. Maternal glucocorticoid administration not only promotes maturation of lungs and surfactant production but also promotes maturation of vasculature and digestive tract mucosa. Together with increased insensible water loss through immature skin, all these conditions promote intravascular dehydration and edema. Absolute insufficient intravascular water content eventually leads to hypotension.

The following management is important to maintain circulatory blood volume.

3.1.2.1.1 Water quantity

Water intake usually starts at 60-80 ml/kg /d. However, EP infants are prone to dehydration as mentioned above and 80-100 ml/ kg/d, or even more is sometimes required. In order to prevent overhydration, which increases cardiac load, the humidity in the incubator should be maintained as close to 100% so as to minimize the insensible water loss.

3.1.2.1.2 Dehydration after birth

Markers of hypotension due to dehydration are as follows; tachycardia without hyperthermia, oliguria, a progression of metabolic acidosis, lactic acidosis, increasing hematocrit and hypernatremia. Additionally, a low left atrium and aorta ratio (LA/Ao), a low left ventricular internal diameter diastolic (LVIDd), inferior vena cava collapse on echocardiography, decreased cerebral and other organ flows on ultrasound, and a decreased cardio thoracic ratio (CTR) on chest X-ray can be used to evaluate dehydration. However, a continuous and comprehensive assessment using all of these parameters are often required. Do not correct dehydration too rapidly as this increases the risk of IVH.

Hydration or volume loading

・5% albumin
・FFP (especially for infants born at 22-24 weeks)
・Saline
Administer 10-20 ml/kg over 1-3 hours depending on the condition
・Red blood cell transfusion
If anemia is present (Hb <12 g/dl), this must be first line treatment.
Administer 10-15 ml/kg of packed blood over several hours to 6 hours.

3.1.2.1.3 Relative adrenal insufficiency

It should be recognized that EP infants are basically in the condition of relative adrenal insufficiency and has impaired cortisol secretion in response to stressors. In order to supplement impaired adrenal function, a single dose of intravenous hydrocortisone at 1-2 mg/kg is usually effective (4,5). Cytokine-mediated vascular permeability is suppressed, resulting in decreased water leakage outside blood vessels and need for fluid infusions. If not effective, the second dose should be considered based on the following conditions; a degree of immaturity of the infants, a history of maternal glucocorticoid treatment, the severity of edema, and the presence of hypotension.

3.1.2.1.4 Inotropes

If hypotension and oliguria are present with insufficient cardiac contractility despite echocardiographic signs of appropriate intracardiac volume, cardiac function may be impaired. If worsening, Additionally, inotropic agents as dobutamine (1-5 μg/kg/m), and dopamine (1-3 μg/kg/min) along with correction of acidosis may be needed. (Refer to the section on Cardiovascular agents)

3.1.2.2 24 to 72 hours after birth

During this time, fluid that initially leaked out of blood vessels may return, leading to increased blood pressure. At this time, it may be necessary to increase water content by 10-20 ml/kg per day if the infant is stable. Calcium is added to glucose in the first few days but additional sodium may be needed once serum sodium starts to decrease.

3.1.2.2.1 Adjustment of intravascular volume

Venous congestion due to the increased intrathoracic pressure associated with invasive procedures and any changes of respirator setting leading to increased MAP must be avoided. It should be also considered that during this period, an afterload mismatch due to increased blood pressure and afterload with a decreased cardiac contractility

which is typically observed as cardiac dilation can frequently occurs. The afterload mismatch can be assessed with a heart rate corrected mean velocity of circumferential fiber shortening (mVcfc) as an index of left heart pump function and an endsystolic wall stress (ESWS) as an index of afterload (3,6).

A comprehensive evaluation according to parameters such as heart rate, urine output, blood test findings, cranial echography, and echocardiography is required for an appropriate circulatory care. During the acute phase, rapid blood pressure changes must be avoided to decrease risk of IVH (4).

If water overload is suspected, use diuretics, e.g. intravenous injection of furosemide at a dose of 0.5-1 mg/kg

If afterload mismatch is suspected, use a vasodilator, e.g. continuous intravenous administration of nitroglycerin at 0.3-1.5 μg/kg/min

3.1.2.3 More than 72 hours after birth

Blood pressure and hemodynamics become relatively stable, and the risk of IVH also decreases. However, for EP INFANTS at a gestational age of 22-23 weeks or of birth weight less than 500 g, it is sometimes necessary to continue the same care as during the acute phase depending on the condition of the infant.

Once vital signs are stable, the arterial line should be removed. However, it is necessary to continue evaluating vital signs and urine volume, and to perform cranial ultrasound, echocardiography and blood laboratory tests as appropriate.

Sodium intake may need to be increased if serum sodium drops further due to improving renal function. The intravascular volume and organ blood flows should be assessed with echography when necessary. It should be decided whether PDA is symptomatic or not with echocardiography. Once the infants become more than one week old, regardless of the gestational age at birth, the systolic blood pressure must be maintained over 40 mmHg. Hypotensive treatment must be instituted if systolic blood pressure decreases below this.

PDA care is described in detail in the session of “PDA Management”.

3.1.2.4 Late onset adrenal insufficiency

The pathogenesis of this condition is not yet fully understood, but 10-20% of EP infants, according to the Neonatal Research Network of Japan database, may develop late onset adrenal insufficiency (7,8). Symptoms include sudden hypotension, oliguria, edema, hyponatremia, hyperkalemia, and worsening respiratory status but the only sign during the early stages may only be a decrease in urine output. When this disease is noted, other causes such as dehydration, sepsis, PDA, etc. must be excluded first. If symptoms such as hypotension do not improve, intravenous hydrocortisone of 1-2 mg/kg/dose should be given. In many cases, symptom disappears with a single dose of hydrocortisone within 30 minutes. If no response is observed after the first dose, hydrocortisone may be repeated. However, symptoms are refractory and severe, vasopressin 0.2-1 mU/kg/min may be considered. Although this condition naturally resolves as the EP matures, it may recur until around 32 weeks of corrected age. PVL may ensue after such events, so early detection of symptoms and early administration of hydrocortisone are crucial (9).

3.1.3. Evaluation

3.1.3.1 Blood pressure monitoring

In order to evaluate the hemodynamics of EP infants, arterial blood (peripheral artery or umbilical artery) monitoring is preferable. This is also necessary for appropriate and timely interventions. However, this is not mandatory and placement depends on the condition and needs of the infant.

Optimal blood pressure in EP infants is not clear, but during the acute phase, the average blood pressure should be maintained over the value of gestational age in mmHg (for example, 27 mmHg for 27 weeks gestation).

3.1.3.2 Echocardiography

Repeated echocardiography performed at bedside by neonatologists is routine procedure in Japan. It is not invasive and can be done several times a day during the acute phase. Since the purpose of repeated echocardiography is to evaluate cardiac functions of the infants, it is possible to carry out tailor-made circulatory management for each infant according to the echocardiographic measurements combined with other parameters such as heart rate, urine volume, lactic acid concentration, and electrolyte values.

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（Contributor: Hiroko Iwami, Audit: Masahiro Hayakawa）

3.2 Cardiovascular agonists

3.2.1 Clinical situation

Since EP infants are more likely to develop heart failure compared with term infants because of underdeveloped myocardial function, several cardiovascular agonists may need to be used.

Heart failure will lead to impaired oxygen supply to body tissues despite increased demands from increased venous pressure and decreased cardiac output from myocardial dysfunction. Cardiac output is defined by a series of cardiac indices; diastolic capacity, preload, systolic capacity, afterload, and heart rats (1). Therefore, it is important to use suitable agonists according to the cause of heart failure. Furthermore, because the sudden transition from fetal to neonatal circulation is always in the background of heart failure in those EP infants, the complete understanding of basic physiology is essential for the treatment during the acute phase.

Generally, left ventricular ejection fraction (LVEF) in preterm infants temporarily declines after birth and then rises during the next 12-24 hours after birth, and the left ventricular outflow velocity (LVO) also changes in a same fashion. However, EP infants especially less than 25 weeks of gestation may not be capable of this adaptation. Therefore, volume loading, which is often necessary during the acute phase, can cause heart failure easily. This is also explained by the characteristic of myocardial function of EP infants. According to Frank-Starling's law, if left ventricular preload (water content) is increased, the left ventricular myocardial contraction force is increased, and the left ventricular stroke volume and cardiac output are also increased (2). However, this phenomenon cannot be expected in EP infants because of immature myocardial function. Therefore, attention must be paid if the preload is increased especially when the myocardial contraction force is not enough. Thus, it is important to assess myocardial function and cardiac output properly with echocardiography in order to provide appropriate supports.

3.2.1.1 Causes of cardiac failure

Immaturity

Severe asphyxia

Twin to twin transfusion syndrome（TTTS）

Maternal drug effect (such as Ritodrine)
Myocarditis, cardiomyopathy, transient myocardial ischemia
Severe respiratory failure/PPHN (right heart failure)
Acidosis, hyperkalemia, hypocalcemia, hypoglycemia
PDA
Hypothermia
Sepsis
Arrhythmia

3.2.1.2 Symptom (1,3)

Decreased cardiac output: poor skin color, cold extremities, tachycardia, decreased blood pressure, decreased urine output, reduced intestinal motility, abdominal distension

Pulmonary congestion (left heart failure): tachypnea, retractive breathing, apnea, wheezing, wet rales, poor oxygenation

Systemic congestion (right heart failure): edema, ascites, hepatomegaly, decreased urine volume

3.2.1.3 Diagnosis

Chest X-ray: cardiomegaly (preload assessment), with or without pulmonary congestion

ECG: presence or absence of arrhythmia or myocardial damage

Laboratory test: CBC, biochemistry, blood gas analysis (gas exchange, acidosis), lactic acid (marker for organ blood flow), brain natriureteric peptide (BNP), creatinine kinase-muscle/brain (CK-MB), troponin T (if you suspect myocardial damage)

Echocardiography:

Evaluation of preload (2,4,5):

Left ventricular end diastolic dimension (LVDd) (reference range: ELBW 8-10 mm, VLBW 10-12 mm, depends on BW, GA and time after birth)

LA/Ao (reference range 0.8-1.2)

Dimension of inferior vena cava (respiratory sift)

Left ventricular cardiac output (LVCO) (reference range 190-310 ml/kg/min)

Evaluation of afterload :

end systolic wall stress (ESWS) reference range <40 g/cm^2

Evaluation of contractility:

Ejection fraction (EF) reference range >50 %

Fractional shortening (FS) reference range >30 %

mVcfc reference range >0.8 circ/s

Evaluation of diastolic ability:

Left ventricular inflow blood flow waveform

Peak velocity of early diastolic mitral annulus motion (E') (reference range depends on BW, GA and time after birth)

3.2.2 General Management

The general concept of treating heart failure is to increase oxygen supply and to reduce oxygen and energy demand of body tissues and the etiology of the condition.

3.2.2.1 Respiratory support

Since respiratory effort increases oxygen consumption, positive pressure respiratory support is effective especially for the heart failure complicated with pulmonary congestion and respiratory failure. Respiratory support usually increases intrathoracic pressure which results in reducing venous return and preload. Thus, the cardiac output depends on afterload. However, if the cardiac output is already dependent on preload such as hypovolemia, it should be recognized that the increased intrathoracic pressure decreases the cardiac output. If severe oxygen diffusion failure and/or pulmonary hypertension are observed, inhaled NO is recommended. Although sedation has the effect to reduce the oxygen demand, it should be used with a caution because it can cause hypotension due to the decreased intrinsic catecholamine production and the vasodilate action.

3.2.2.2 Circulatory approach based on the etiology

Preloading

It is usually difficult to improve diastolic function, so excessive preload can be treated with water restriction and/or diuretics. In the case of insufficient preload, volume loading is performed with saline or blood infusion.

Contraction

Catecholamines such as dopamine (DOA) and dobutamine (DOB) can be administered. Milrinone can enhance cardiac contraction but has also a vasodilator action. So, pay attention to this side effect.

Afterload

If cardiac contraction is relatively poor and blood pressure is high, there is a possibility of increased afterload and milrinone is preferable. It should be noted that afterload can be increased a few hours after birth in EP infants as already mentioned. Conversely, sepsis and late circulatory collapse due to adrenal failure cause high cardiac output heart failure with decreased afterload. Maintenance of afterload with administration of catecholamine and vasopressin may be needed.

3.2.2.3 Agonist

Cardiovascular agonists have their own specific receptors. For example, adrenergic receptors include α1 (vasoconstriction), ß1 (enhancing cardiac contractility and increasing heart rate), and ß2 (vasodilatation and bronchial dilation). Dopamine receptors (DR) can dilate renal arteries. On the other hand, phosphodiesterase-lll (PDElll) inhibitors (milrinone, olprinone) can enhance vasodilatation and cardiac contraction through metabolic actions.

3.2.3.1 Catecholamine (1,6,7,8,9)

Dopamine hydrochloride

This is mainly ß-acting, but exerts different pharmacological effects depending on blood concentration.

0.5-3.0 μg/kg/min (ß1> ß2, DA> α1) diuretic effect, cardiac contraction enhancement

3-10 μg/kg/min (ß1> ß2, α1, DA) both heart rate and blood pressure increase as cardio tonic agent

10-20 μg/kg/min (α1 >> DA, ß) risk of side effects such as increase in pulmonary capillary pressure, contraction of peripheral blood vessels, renal artery vasoconstriction, tachycardia and arrhythmia

Dobutamine hydrochloride

Strong ß1 action and weak α and ß2 action

No noradrenaline release effect, rarely causes tachycardia compared with dopamine

Selectively enhances cardiac contractility without increasing cardiac oxygen consumption.

1-10 μg/kg/min recommended

High doses increase the risk of tachycardia and arrhythmia.

No significant difference between DOA and DOB in neonatal death, periventricular leukomalacia (PVL), and IVH incidence

DOA and DOB are often combined in a 1:1-2.

Isoproterenol
Powerful β1 and β2 action
Because of side effect of tachycardia, difficult to use for EP infants, who are already tachycardic
Sometimes causes hypotension due to vasodilation
0.01-0.2 μg/kg/min for shock, bradycardia, and atrioventricular block.

Adrenaline
Most potent endogenous catecholamine
Heart rate increased along with increased cardiac contraction and cardiac output
Although considered if DOA and DOB are not effective to maintain blood pressure in neonatal resuscitation, no scientific evidence of benefit is established
0.01 μg/kg/min as a stating dose, then increase to 0.2 μg/kg/min if necessary.

3.2.3.2 Glucocorticoids (2,7,9)
Prevention of edema, maintaining circulating blood volume, increase preload, prevention of excessive reduction in afterload, and enhancement of cardiac contractility
Genomic effect to enhances the reactivity to endogenous and exogenous catecholamines
Effective for circulatory failure due to relative renal failure with edema, hyponatremia, and poor organ blood flow, if volume loading and catecholamine failed to improve.
Hydrocortisone 1-5 mg/kg
Adverse events include the risk of hyperglycemia and gastrointestinal perforation.

3.2.3.3 Diuretic
Furosemide
Effective to relieve heart pump failure and lung congestion due to excessive preload associated with cardiac dilation and atrioventricular valve regurgitation.
Immediate action and strong diuretic action.
Half-life is about 20 hours in EP infants due to poor renal clearance.
0.5-1 mg/kg every 6-12 hours (7)

3.2.3.4 Vasodilators (1,6,7)
3.2.3.4.1 Phosphodiesterase-lll (PDElll) inhibitor
Inodilator with cardiotonic and vasodilator actions

Has weaker action than in adults because of poor expression of PDEIIII in the myocardium of EP infants
0.1-0.3 μ/kg/min
Use in low doses to avoid exacerbating PDA

3.2.3.4.2 Nitroglycerin
Antidepressant for heart failure
Low dose dilates venous vessels and reduces preload
High dose dilates arteries and reduce afterload
In EP infants, even low dose dilates arteries
In addition, dilate the coronary artery and increases oxygen supply to myocardium
0.3-2 μg/kg/min
Increased incidence of PDA

3.2.3.4.3 Inhaled Nitric Oxide（iNO）
More than 70% of perinatal centers use iNO as treatment for PPHN in very premature infants in Japan (10).
Echocardiographic diagnosis
10 ppm as a stating dose
Cardiac function and pulmonary hypertension evaluated every 8 hours by echocardiography
Use SpO2 for weaning
No noticeable side effects reported by evaluating hemodynamics appropriately with echocardiography

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3.3 Management of PDA

3.3.1 Clinical situation

Delayed physiological closure of ductus arteriosus in preterm infants is termed PDA. A PDA with hemodynamically significant symptoms is defined as a symptomatic PDA. According to the Neonatal Research Network of Japan database (2003-2014), the incidence of symptomatic PDA among extremely low birth weight infants is approximately 58% at 24 weeks of gestation and approximately 38% at 28 weeks of gestation. PDA is common among EP infants and daily, even multiple examinations with echocardiography on the bedside to evaluate the presence of a PDA and associated hemodynamic effects are recommended during the acute phase.

3.3.1.1 Pathogenesis

With gestational maturity, the intimal wall of the fetal ductus arteriosus thickens to allow closure after birth. However, this may be insufficient in EP infants, as the response of the ductus arteriosus to oxygen-induced closure is weak. Physiologically, there are persistently high levels of active substances that dilate the ductus arteriosus such as prostaglandin E (PGE), nitric oxide (NO) and cytokines induced by inflammation such as inducible nitric oxide synthase (iNOS) and tumor necrosis factor–α (TNF-α). These work together to delay ductal closure. Therefore, intrauterine infection and neonatal infection like sepsis are risk factors for PDA, resulting in dramatic increase in blood flow though the PDA when pulmonary vascular resistance falls after birth.

3.3.1.2 Pathophysiology

Adverse effects of PDA are as follows;

① Pulmonary congestion
tachypnea, respiratory distress, apnoea, heart murmurs, pulmonary hemorrhage, and exacerbation of CLD

② Decreased systemic organ blood flow by the steal effect through PDA resulting in increased pulse pressure (diastole <systole/2), decreased urine output, prerenal renal failure, peripheral coldness, poor skin color, reduced intestinal movement, necrotizing enteritis, gastrointestinal perforation, and PVL

③ Left ventricular heart failure associated with increased preload
If the diastolic function maintained: left ventricular hypercontractility, tachycardia, increased pulse pressure, hyperactive precordium.

If diastolic function is impaired: decreased left ventricular contraction, afterload mismatch, pulmonary hemorrhage, IVH

3.3.1.3 Diagnosis

3.3.1.3.1 Chest x-ray

Pulmonary congestion, cardiac enlargement.

3.3.1.3.2 Echocardiography

The ductus arteriosus tends to narrow from the side of the pulmonary artery but sometimes, closure from the aortic side may be noted on echocardiography. Therefore, both the short axis aortic view, which is a routine view, and the ductal view should be checked. Measurement of the following indices are recommended:

- Minimum ductus arteriosus diameter: Always measured in B mode. If measured with color Doppler, it is likely to be overestimated.
- Ductus arteriosus blood flow: Use color Doppler to determine the direction of flow. Soon after birth, because of the high pulmonary vascular resistance, right-to-left or two-way blood flows can be seen. Check the blood flow pattern by pulse Doppler. If the pattern is single peak and pulsatile with a low maximum blood flow velocity, the shunt flow is large, and PDA does not tend to close.
- Left pulmonary artery blood flow velocity: Use pulse Doppler. The left pulmonary arterial endo-diastolic velocity (LPAedv) or diastolic/systolic blood flow velocity ratio is proportional to the shunt blood flow.
- Left arterial-to-aoritic root diameter ratio (LA/Ao) : Indicates left atrial volume overload
- Left ventricular and-diatstric diameter (LVDd) : Indicates left ventricular volume overload
- Ejection fraction (EF) : Indicates left ventricular contraction capacity

＊PDA dependent congenital heart diseases such as Coarctation of the Aorta must be ruled out.

One of following findings generally indicates a hemodynamically significant PDA; arterial duct diameter> 1.5 mm, LPAedv> 0.2 m/s, LA/Ao> 1.4. However, the necessity of treatment should be determined based on not only echocardiographic findings but also on other ultrasound findings such as organ blood flow and clinical symptoms.

Echocardiography findings of GA 27wk infant with PDA on Day 0 (Figures 1, 2, 3)

3.3.1.3.4 Cranial and abdominal echography

The influence of impaired organ flows due to PDA can be assessed by measuring the resistance index (RI) of anterior and middle cerebral arteries, celiac artery, superior mesenteric artery and renal artery. Normal range is usually 0.6-0.7. The higher RI indicates the increased PDA shunt flow. In the severe case, the discontinuation or reversal of diastolic blood flow can be seen.

3.3.1.3.5 Laboratory blood test

Lactic acid levels, renal function, and natriuretic peptide levels are useful indicators of volume loading. Natriuretic peptides such as brain natriuretic peptide (BNP) and N-terminal pro b-type (NT-proBNP) are useful indicators of illness severity as levels increase with worsening PDA.

3.3.2 Management

3.3.2.1 Supportive management

- Since excessive volume load worsens PDA symptoms such as pulmonary congestion, careful fluid management is essential. However, it should be also understood that excess fluid restriction and diuretics use can also cause intravascular dehydration and impairment of blood flow to essential organs.
- If there is pulmonary edema, respiratory management with high PEEP and MAP is recommended. In this care, permissive hypercapnia is also preferable because of its vasoconstrictive action on pulmonary arteries.
- Keep Hgb more than 12 g/dl. Blood transfusion is necessary if anemic.
- Avoid other aggregating factors such as infection.

3.3.2.2 Medication

The decision to use medications to treat a PDA can be based on combination of clinical symptoms, echocardiographic findings including, blood flow to other organs, as well as laboratory blood tests. Although there is a guideline for PDA treatment in Japan, each hospital must still have its own policy for treatment. The majority of hospitals will treat if the PDA is hemodynamically significant by echocardiography even before the infant is symptomatic. In addition, over half of hospitals use prophylactic indomethacin to prevent symptomatic PDA and IVH in EP infants.

3.3.2.2.1 Indomethacin

・This is a prostaglandin synthesis inhibitor
・Most Japanese hospitals modify the dose according to the gestational age as shown in Table 1 because of side effects (Table 2) [2]. The doses are basically reduced, and the intervals are prolonged for more premature infants with a course of 3 doses.
・Withholding of enteral feeding is not recommended unless there is a special reason.
・Prior to the second and third administration, echocardiography is mandatory. If PDA is already closed, additional doses are not necessary. Based on echocardiographic findings, including left ventricular overload and urine volumes as indicators of adverse effects, subsequent doses may be delayed or skipped.
・Since the incidence of symptomatic PDA among EP infants is high, some hospitals start treatment if PDA is present beyond the first day of life even if the infant is asymptomatic.

3.3.2.2.2 Ibuprofen
・This is a prostaglandin synthesis inhibitor
・Approved for use in Japan in 2018.
・Less side effects (e.g. renal) than indomethacin and has similar efficacy.
・Three doses for the first course: 10 mg/kg for the first time, 5 mg/kg for the second and the third doses in 24 hour intervals.
・Between each dose, like indomethacin, echocardiography is mandatory. The next dose can then be delayed/skipped depending on findings.

3.3.2.3 Surgical ligation
3.3.2.3.1 Indications
If the PDA remains symptomatic despite medication or if the infant has complications from medications, consider surgical ligation. This includes:
・Unlikeliness of PDA closing even after maximum medical treatment has been completed
・PDA has reopened and there is low possibility of closure with repeated medical treatment
・Additional medical treatment is contraindicated due to severe complications and side effects
・No time allowance for medical treatment to take effect due to imminent heart failure

3.3.2.3.2 Complications of surgical ligation

・Bleeding, infection, hypothermia during surgery, recurrent nerve paralysis (hoarseness, aspiration), phrenic nerve paralysis (eventration of diaphragm), chylothorax, pneumothorax, surgical wound infection.

3.3.2.3.3 Postoperative management

Blood pressure always rises immediately after ligation. Monitoring of arterial blood pressure is recommended to prevent IVH due to hemodynamic changes. Echocardiography is also recommended to evaluate hemodynamics. If there was severe and persistent heart failure before ligation, left ventricular dilatation must be evaluated post-operatively with echocardiography. If this is present, the infant may be at risk of post-operative heart failure, which is characterized with afterload mismatch secondary to rapid cardiac load change. In this instance, support with vasodilators is indicated. However, if hypovolemia is also present, hypotension is likely to occur. Once hypotension is observed, it is usually catecholamine refractory and glucocorticoids are needed.

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Table 1 Doses of indomethacin for EP infants

Age	First dose(mg/kg)	Second dose (mg/kg)	Third dose (mg/kg)
Within 48 hours	0.2	0.1	0.1
Age 2-7 days	0.2	0.2	0.2
Age 7 days or more	0.25	0.25	0.25

(Modified from reference 2)

Table 2 Adverse effects of indomethacin

Symptoms	Clinical findings
Renal disorder	Decreased urine output, progress of edema
Intestinal perforation, necrotic enterocolitis	Increased gastric residues, bile/bloody gastric aspirates, bloody stool, abdominal color change, abdominal distension
Hypoglycemia	Apnea, irritability, convulsion, sometimes asymptomatic
Thrombocytopenia	Umbilical bleeding, bleeding at a needle insertion site, abnormal hemostasis at a blood sampling site

(Modified from reference 2)

Figure. 1 Arterial duct patency, 2D short-axis image and short-axis Doppler image: PDA diameter 1.6mm

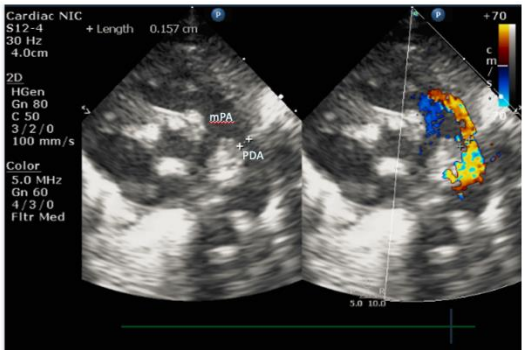


Figure.2　PDA flow velocity: Left to Right shunt, continuous wave pattern

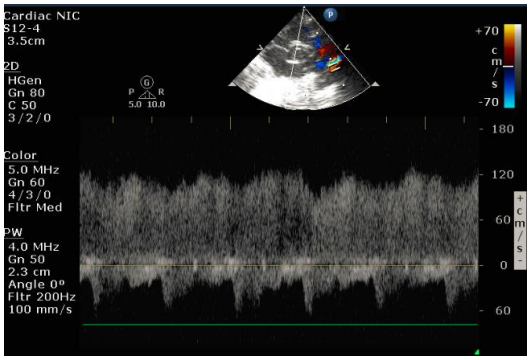
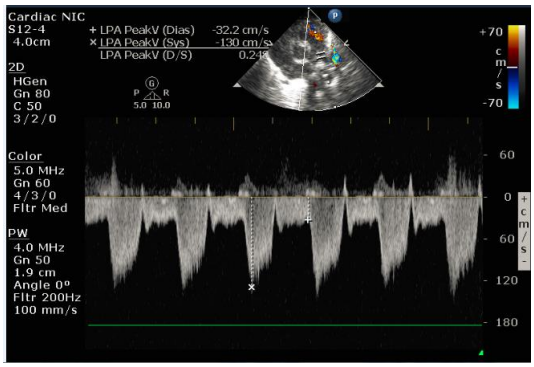


Figure 3　Left PA flow velocity: LtPA end diastolic velocity 0.32m/s



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3.4 Prevention of IVH

3.4.1 Clinical situations.

IVH in EP infants is the result of ventricular extension of subependymal hemorrhage from immature vessels. The incidence of IVH among extremely low birth weight infants is reported to be 12.8% overall and 4.6% for severe IVH in Japan (born 2003 to 2012) (1).

The pathogenesis of IVH involves anatomical and physiological immaturity. The supraventricular subependymal layer surrounds the lateral ventricles and is most prominent between the caudate nucleus to the thalamus. The size of the subependymal layer increases until around 26 weeks of gestation, and gradually involutes thereafter. This structure is crucial for fetal brain development, containing many cellular components from which neurons and glial cells are generated. The walls of these vessels are thin and very fragile and the vessels feeding to this area is the so-called arterial border zone, consisting of peripheral branches of the medial striatum artery and the lateral striatum artery which are greatly susceptible to hypoxic tissue damage.

The cranial veins are perfused from the cerebral medullary vein, through the epididymal region of the ventricle, and finally drains into the terminal vein and the internal cerebral veins. Therefore, any increase in cerebral blood flow will increase the likelihood of congestion at the lower ependymal region. There is no vessel valve between the superior vena cava and the main cerebral veins, so right atrial pressure directly impacts on cerebral venous pressure. In cases of cardiac dysfunction, pulmonary hypertension and increased intrathoracic pressure, the pressure of cerebral venous perfusion pressure may increase due to the increased right atrial pressure. Since the autoregulation of cerebral blood flow in EP infants is immature and limited, the changes in blood pressure can directly cause cerebral blood flow fluctuation. Cerebral autoregulation is particularly impaired in sepsis, acidosis and hypotension. Hypercapnia, seizures, crying, intratracheal suctioning, administration of inotropic agents, and a rapid administration of hypertonic solutions can also increase systemic and cerebral pressures, increasing the risk of IVH. Intraparenchymal hemorrhage associated with IVH is considered to be a venous hemorrhagic infarction resulting from congestion in the cerebral parenchyma and is a result of impaired intrathecal venous perfusion due to hemorrhage in the lower ependymal region of the ventricle.

Post hemorrhagic hydrocephalus may occur due to the obstruction of cerebrospinal fluid flow and absorption route due to hemorrhagic clots or decreased cerebrospinal fluid absorption due to chronic arachnoiditis. Risk is increased with severity of IVH. Once hydrocephalus occurs, brain growth is impaired due to the increased intracranial pressure from ventricular dilatation. This may then progress on to white matter damage over several months due to free radicals released from the lysis of hemoglobin.

The prognosis of IVH depends on the severity and the presence or absence of brain parenchymal lesions. The mortality, the incidence of hydrocephalus, and neurological sequalae are higher amongst infants with severe IVH group (Grade III or IV in the classification of Papile or Grade III plus intraparenchymal hemorrhage in the classification of Volpe (Table 1 and 2)(2,3). Among extremely low birth weight infants born between 2003 and 2004 in Japan, NICU mortality rate is 4.4% without IVH, 11.6% in the mild IVH group (Grade I + Grade II according to Papile classification), and 44.5% in the severe IVH group. However, post-discharge mortality rate was not different (0.6 and 0.7%, respectively). At 3 years of age, cerebral palsy was 6.9% in the group without IVH, 12.6% in the mild IVH group, and 39.7% in the severe IVH group. Visual disorders (unilateral and bilateral) occurred 0.9% in the group without IVH, 3.6% in the mild IVH group, 6.8% in the severe IVH group. Neurodevelopmental delay was observed 15.5% in the group without IVH, 19.7% in the mild IVH group, 41.2% in the severe IVH group.

3.4.1.1 Diagnosis

Cranial echography is simple and useful for diagnosing IVH (Figure 1 and Table 1). However, due to impairment of ultrasound imaging by bony windows, the diagnosis of hemorrhages other than IVH such as subdural hemorrhage and epidural hemorrhage is often difficult. Head CT and MRI are useful for these. Follow-up scans to gauge the progress of IVH is necessary.

3.4.2 General Management

Clinical symptoms of intracranial hemorrhage include neonatal seizures, apnea attack, fever, hypotension, anemia, shock, jaundice. Infants may also be asymptomatic. The Papile classification is widely used as a classification of severity of IVH (2). This classification is based on CT findings, but it is also used as a classification of echography. 50% of IVH occurs within 24 hours after birth, 25% on day 1 and 15% on day 2 i.e. 90% of IVH develops within 72 hours of birth. Therefore, close observation

over this time period is particularly important.

3.4.2.1 Treatment

There is no direct and effective treatment for IVH. Treatment is supportive. Circulatory and respiratory support is necessary for infants in shock and/or acidosis. Blood transfusion is needed for the infants with anemia and/or coagulation disorders. There is currently no effective intervention to prevent post IVH hydrocephalus in terms of timing and procedures. Acetazolamide and furosemide are not recommended, because they do not reduce the need of ventriculoperitoneal shunt (VP shunt), but increase mortality, the incidence of neurological damages, and the risk of kidney calcification. Repeated lumbar puncture has been reported to be effective, but it is not recommended because of the risk of central nervous system infection in EP infants. If hydrocephalus progresses, a VP shunt is indicated. However, if infant is too sick or small, a reservoir under the scalp to allow easy access for repeated ventricular puncture may be used as an alternative. Early intervention improves mortality, VP shunt avoidance, and neurological prognosis.

3.4.2.2 Prevention

Prevention is most important because IVH has a serious negative effect on prognosis.

3.4.2.2.1 Prenatal prevention

・Maternal transport to tertiary centers

The rate of severe IVH in outborn EP infants is higher than inborn infants.

・Maternal glucocorticoid administration (4)

Maternal steroid administration reduces both RDS and IVH.

3.4.2.2.2 Postnatal prevention

・Professional management and minimal handling

IVH can be induced by routine cares such as tracheal aspiration. Therefore, management by trained nurses and neonatologists is important.

・Indomethacin

Prophylactic indomethacin (0.1 mg/kg/6 hour continuous infusion, 3 days) significantly reduces the risk of grade III or IV IVH (5,6)

・Sedation

Stabilizes hemodynamic changes

Morphine hydrochloride (100-200 μg/kg i.v., 10-50 μg/kg/hour div.)

Fentanyl (1-4 μg/kg i.v., 0.5-1.0 μg/kg/hour div.)

3.4.3 Evaluation

3.4.3.1 Laboratory test

Hematology, biochemistry, coagulation tests, blood gas analysis are conducted to identify the cause of IVH and to evaluate the influence of bleeding. Hemorrhage may result in neonatal seizures and suppression of brain function, so continuous EEG monitoring is also recommended.

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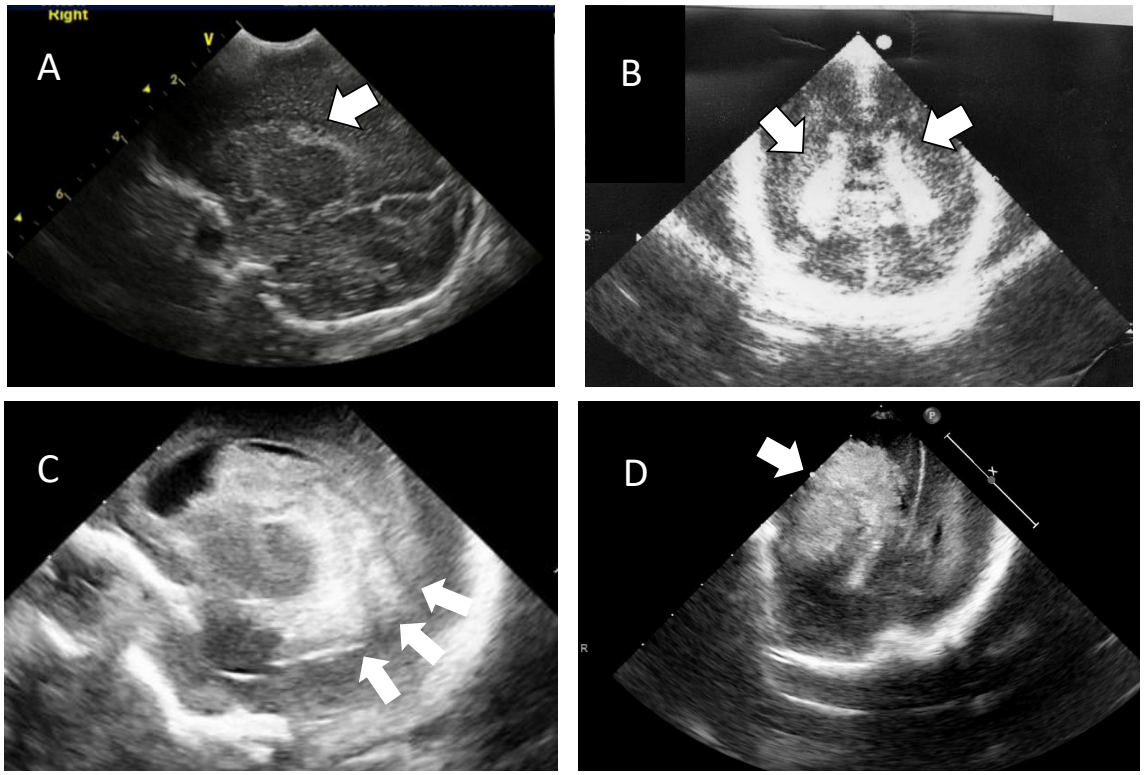
Table 1 Classification of intraventricular hemorrhage by Papile (Reference 2)

Grade Ⅰ	Subependymal hemorrhage only
Grade Ⅱ	Intraventricular hemorrhage without ventricular enlargement
Grade Ⅲ	Intraventricular hemorrhage with ventricular enlargement
Grade Ⅳ	Intraventricular hemorrhage with intraparenchymal hemorrhage

Table 2 Classification of intraventricular hemorrhage by Volpe (Reference 3)

Grade Ⅰ	Subventricular hemorrhage ± mild intraventricular hemorrhage (less than 10% of the ventricular area in parasagittal view)
Grade Ⅱ	Intraventricular hemorrhage without ventricular enlargement (10-50% of the ventricle are in parasagittal view)
Grade Ⅲ	Intraventricular hemorrhage with ventricular enlargement (greater than 50% of the ventricular area in parasagittal view)

Figure 1 Echographic diagnosis of IVH- Classification of severity



A: Papile grade I, B: Papile grade II, C: Papile grade III, D: Papile grade VI

(Contributor: Masahiro Hayakawa, Audit: Hiroko Iwami)

4 Intravenous fluid management

4.1 Fluid management

4.1.1 Clinical situation

Fluid supplementation and parenteral nutrition are vital for the management of EP infants. Circulation is unstable in the first few days of life and careful adjustment of fluid volume and contents is essential. Extracellular fluid volume immediately after birth is greater in EP infants compared with that of more mature infants. As skin permeability decreases and kidney function matures, extracellular fluid slowly decreases and adapts to the extrauterine environment. Therefore, the main purpose of fluid management during the acute phase is to promote the excretion of extracellular fluid and to maintain the body water content along the same lines as mature infants It is also important not to induce dehydration, which can lead to circulatory collapse. It is important to consider insensible water loss, cardiac function, and renal function in the fluid management of EP infants.

A general method for vascular accesses for the infants under 24 weeks of gestation is shown in Table. Umbilical veins can be used for a venous line during the first week after birth. However, after that it should be removed to prevent catheter infection. After this, a double lumen PICC (peripherally inserted central catheter) can be inserted. An arterial line is essential for accurate blood pressure management, but sometimes causes various complications. In particular, a decrease in blood pressure at the time of blood collection through the catheter and infection caused by blood collection procedures are problematic. Therefore, the umbilical artery catheter is not essential, and is not necessarily required if the infant's general condition is good and urine volume is maintained.

4.1.2 General management

4.1.2.1 Water

In Japan, most hospitals try to reduce the insensible water loss by providing sufficiently humidity inside the incubator, which allows limitation of the amount of fluid given to the infant during the early stages of life. Once circulatory condition improves (as indicated by increased urine output, water infusion rates can be promptly increase. On the other hand, high humidification is not common outside Japan. In these circumstances, fluid volume given must be increased due to the surplus of huge

insensible water loss. As the results, some neonatal manuals recommend fluid supplementation of 100-150 ml/kg/day on day1, 120-150 ml/day on day 2 (1). Table 1 shows the typical fluid supplementation schedule and the humidification management in Japan. Water intake may need to be higher by about 10-20 ml/kg/day in SGA infants due to lower body water content compared to AGA infants (2).

Water balance during the acute phase often changes rapidly with fluctuations in hemodynamics, often within a few hours. This necessitates vigilant monitoring of SVC and IVC diameters with repeated ultrasonography. Changes of these values can help the evaluate water balance.

4.1.2.2 Electrolyte

Electrolyte supplementation is not necessary during the early phase after birth. Once the diuretic phase starts, serum Na tends to be elevated. Therefore, early sodium supplementation may increase the risk of hypernatremia. It is recommended to start the Na supplementation when sodium concentration begins to decline. Generally, sodium can be started on day 2-3 as shown in Table 3 (3). However, because renal function in EP infants is poor with excessive sodium loss, some infants may need more than 10 mEq/kg/day of sodium in later life.

Hyperkalemia may occur even during the diuretic phase, about 2 days after birth. Therefore, supplemental K is unnecessary until almost day 3, usually after Na supplementation starts. One the K supplementation started, as shown in Table 3, it is necessary to replace about 2 to 3 mEq/kg/day.

4.1.2.3 Mineral

Ca needs to be replenished at the beginning. The starting dose is at 30 mg/kg/ day, then daily doses should be increased up to 40-60 mg/kg/day (Table 3). Phosphorus also needs to be administered at the early phase, but available preparation is as sodium phosphate so do not replace with this combination until sodium levels are stable (usually after 24 hours after birth and after commencement of the diuretic phase). Phosphate replacements can occur at 20-30 mg/kg/day (Table 3).

Mg, like calcium and phosphorus, is an important mineral for the human body. It is abundant in cells and plays an important role in enzyme activity and neurotransmission. According to the guidelines of ESPGHAN, Mg supplementation is

recommended from the early postnatal period. However, in Japan, most hospitals do not start Mg supplementation until day 4-5 (2).

4.2 Parenteral nutrition

4.2.1 Clinical situation

EP infants are born with a little accumulation of various nutrients. In addition, it usually takes about 2-3 weeks to achieve sufficient enteral feeding for growth as EP infants have reduced gastrointestinal tract motility and function. The lack of essential nutrient supplementation after birth could result in rapid metabolic crisis. Therefore, parenteral nutrition started immediately after birth is necessary to prevent these problems. However, there is no clear evidence on the contents of nutrients and the duration 2). Recommended nutrients mentioned below are based on ESPGHAN guidelines 2018.

4.2.2 General management

4.2.2.1 Glucose

Glucose is essential for maintaining brain activity. Neurons can also use ketone bodies, but this is insufficient in EP infants. The amount of glucose produced in the liver is about 5 mg/kg/min. Because enzymes expression related to glycolysis and gluconeogenesis is low and there is a little glycogen storage, the initial glucose dose is started at 5 mg/kg/min and adjusted according to blood glucose levels (Table 3)(2). During the first 24 hours, glucose homeostasis is unstable so hyperglycemia may occur even at these doses. If blood glucose exceeds 200 mg/dL even after GIR is reduced, insulin should be considered.

Once blood glucose levels become stable, 8-10 mg/kg/min of glucose infusion is recommended from the ESPHHAN. Excess glucose cannot be used as an energy source but can consume extra energy when converted into fatty acids. Most infants can be maintained with doses below12 mg/kg/min.

4.2.2.2 Amino acids

Amino acids are essential to synthesize proteins which promote body growth. Cellular functions are believed to be depend on continuous supplementation of amino acids soon after birth. About 3.5-4 g/kg/day amino acids is used for fetal development (4), suggesting that a similar amount should be given via a parenteral route is necessary. Without this supplementation, protein can be catabolized at a rate of 1 g/kg/day 4). In AGA infants, the administration of 3 g/kg/day after birth seems to be safe (Table 3)(5).

Although no amino acid preparation is produced exclusively for EP infants in Japan, Pleamin-P® is available and used in most of Japanese hospitals. Table 4 shows the product name of amino acid preparations and contents of each preparation currently available in Japan and USA. Although they appear similar, Trophamine® and Premasol® contain higher amounts of glutamic acid (essential amino acids) and aspartic acid (non-essential amino acids).

4.2.2.3 Fat

Fat has the highest ratio of calorie per weight among nutrients and is a main source of energy for infants. Essential fatty acids are also important in many metabolic pathways. If caloric supply from fat is not enough, amino acids become the default source of energy, resulting in a catabolic state. Early administration of fat is therefore recommended. However, fat administration may affect respiratory conditions and close monitor is important during the acute phase. The recommended doses and timing are shown in Table 3 (6,7).

Currently, only the soybean oil derived preparations are available in Japan. Long term fat administration may increase the risk of cholestasis due to inflammation caused by ω6 fatty acids. On the other hand, the fish oil derived preparations containing a large amount of ω-3 fatty acid is effective for prevention and treatment of cholestasis (8). The preparation is already available outside Japan, but difficult to obtain inside Japan. Table 5 shows the product names and their contents currently available inside Japan, US, and Europe.

4.2.2.4 Vitamin and trace element

Like other preparations used for parenteral nutrition, no specific formulation of vitamins and trace elements are available for EP infants. Table 6 shows available vitamin product and their contents with recommend doses available in Japan and USA. The estimated requirement of each vitamin is also provided (9). Table 7 shows available trace element product in Japan and USA. The content of each trace element, the recommended dose, and the estimated requirement are also shown (10). The recommended doses fulfil the daily vitamin requirements, but overdose can occur for certain trace elements. Therefore, the long term trace element supplementation with these doses should be carefully considered. Each preparation should be administered from 3 days after birth.

4.2.2.6 Method

Because of the high osmotic pressure of parental nutritional fluids, a central venous catheter is always necessary. The catheters can be inserted via peripheral veins in EP infants, but for the infants of 22-23 weeks of gestation this may not be possible due to skin immaturity. In this case, umbilical vein catheters can be used as Table 1. A double lumen catheter is desirable to prevent composition changes inside a solution. No commercially ready to use solution is available in Japan. Each hospital must make them in house, so it is desirable to prepare inside a hood. The line for parenteral nutrition should be a closed circuit with an inline filter. Fat is preferably administered through a peripheral vein but if this is not possible, it can be given through a central catheter line without filtering.

The recommended composition of parenteral nutrition fluid until day 5 is shown in Table 8 (11). Until then, no major changes in composition are needed. As enteral feeding progresses, the amount of fluid for parenteral nutrition is reduced accordingly. Once enteral feeding exceeds 100 ml/kg/day, parenteral nutrition is not an absolute necessity. Trace element and vitamin supplementation can be discontinued. The lack of nutrients at this point can be compensated with breast milk fortifier and oral supplements. When enteral feeding reaches about 120-140 ml/kg/day, intravenous infusions are no longer necessary. This can be achieved within 2-3 weeks after birth, if there are no complications. Parenteral nutrition must be continued if enteral feeding is impaired.

4.2 3 Evaluation

4.2.3.1 Monitoring

During the parenteral nutrition, close monitoring for complications are always necessary and include regular blood chemical tests. Table 9 shows items to evaluate and the frequency of assessment.

4.2.3.2 Complications

The most common complication is catheter related blood stream infection (CRBSI). When inserting a PICC, maximum precaution is required like the insertion of central venous catheter. Once inserted, a close inspection of color change at the insertion site with a repeated evaluation of CRP and CBC is useful to detect CRBSI early.

Cholestasis is also a common complication. The incidence of this is higher among SGA

and infants with difficulties tolerating enteral feeding.
Metabolic acidosis, hyperammonemia, and hyperlipidemia may be additionally observed. In this situation, it may be necessary to reduce the causative content.

Respiratory deterioration leading to death after fat infusion has been reported. The autopsy of this case revealed fat deposition in the lungs. Close assessment of respiratory condition is recommended during its administration.

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Table 1 Vascular access lines

GW(wk)	First 24 hours			-1wk			1wk-		
	V	A	P	V	A	P	V	A	P
22	UV	O	N	UV	O	M	N	N	M
23	UV	O	N	UV	O	M	N	N	M
24-	O	O	M	O	O	M	N	N	M

V: venous line, A: arterial line, P: peripherally inserted line

UV: umbilical vein, UA: umbilical artery, PICC: double lumen peripherally inserted central cather

N: not necessary, O: optional, M: mandatory

Tabel 2 Initial fluid volume and humidity in the incubator

Hours of Age	<24 h	24-48h	48-72h	72h<
Fluid volume (ml/kg/day)	50-60	70-80	90-100	100-120
Humidity (%)	90-95	85-90	80-85	80

Table 3. General dose of several nutrients for extremely preterm infants in Japan and recommended dose by ESPGHAN

	<24 h	24-48 h	48-72 h	Amount during first days of life (ESPGHAN 2018)	Target Amount for Growing (ESPGHAN2018)
Energy (kcal/kg/day)	40-50	70-80	100	45-55	90-120
GIR (mg/kg/min)	4-5	Increase gradually over 2-3 days		4-8	8-10
Amino Acid (g/kg/day)	1-1.5	2-3	2.5-3.5	1.5-2.5	2.5-3.5
Fat (g/kg/day)	0-1	1-2		0-1	2-3
Na (mEq/kg/day)	0	2-3	3	0-2	3-5
K (mEq/kg/day)	0	0-1	1-2	0-2	2-3
Ca (mg/kg/day)	25-40	30-40	60-80	32-80	64-140
P (mg/kg/day)	0	20-30	40-60	31-62	50-108
Mg (mg/kg/day)	0	0	0	2.5-5.0	5-7.5

Table 4. Comparison of Amino Acid Products for Pediatric Patients in Japan and US

		Japan	US		
		Pleamin-P® (7.6%)	TrophAmine® (10%)	Premasol® (10%)	Primene® (10%)
Each 100 mL contains:					
Essencial amino acids (g)	L-Isoleucine	0.8	0.82	0.82	0.67
	L-Leucine	1.6	1.4	1.4	1.00
	L-Lysine	0.48	0.82	0.82	1.10
	L-Methionine	0.15	0.34	0.34	0.24
	L-Phenylalanine	0.25	0.48	0.48	0.42
	L-threonine	0.24	0.42	0.42	0.37
	L-tryptophan	0.12	0.20	0.20	0.20
	L-valine	060	0.78	0.78	0.76
Non-essencial amino acids (g)	L-arginine	1.0	1.2	1.2	0.84
	L-histidine	0.25	0.48	0.48	0.38
	L-Glycine	0.20	0.36	0.36	0.40
	L-Alanine	0.52	0.54	0.54	0.80
	L-glutamic acid	0.08	0.5	0.50	1.00
	L-Aspartic acid	0.08	0.32	0.32	0.60
	L-proline	0.6	0.68	0.68	0.30
	L-Serine	0.4	0.38	0.38	0.40
	L-Tyrosine	0.06	0.24	0.24	0.045
	L-cysteine	0.15	<0.016	<0.016	0.189
	Taurine	0.020	0.025	0.025	0.06
E/N ratio		1.26	1.12	1.12	1.89

Table 5. Comparison of Fat product in Japan and US and/or Europe

		Japan	Europe	US, Europe	US, Europe
Product Name		Intralipos® (20%)	Lipoplus® (20%)	SMOFlipid® (20%)	Omegaven® (10%)
Oil source (%)	Soybean oil	100	40	30	0
	MCT	0	50	30	0
	Fish oil	0	10	15	100
	Olive oil	0	0	25	0
Fatty Acid Composition (%)	Linoleic acid (ω-6)	52.6	53	19.5	3.2
	α-Linolenic acid (ω-3)	7.4	8	2.5	1.3
	Eicosapentaenoic acid (ω-3)	0	13	2.3	20.1
	Docosahexaenoic acids (ω-3)	0		2.3	18.4
	Oleic acid (ω-9)	24.5	8	29	9.5
	Ratio of ω-6:ω-3 Fatty acid	7:1	2.7:1	2.5:1	1:8.2
Energy (Kcal/ml)		2.0	1.9	1.9	1.12

Table 6. Comparison of Multi Vitamin Product for Parenteral Nutrition in Japan and US

	Japan		US	Estimated needs for preterm infants (/kg/day) (ESPGAHAN 2018)
Product Name	VITAJECT® (per 1/5 kit/kg/day)	MULTAMIN® (per 1/5 vial/kg/day)	INFUTIVE pediatric® M.V.I. pediatric® (per 2 ml/kg/day)	
Lipid soluble				
Vitamin A (IU)	660	800	690	700-1500
Vitamin D (IU)	80	80	160	80-400
Vitamin E (IU)	3	3	2.8	2.8-3.5
Vitamin K (mcg)	0.4	0.4	80	10
Water soluble				
Thiamine (mcg)	600	1000	480	350-500
Riboflavin (mcg)	800	1000	560	150-200
Niacin (mg)	8	8	6.8	4-6.8
Pantothenate (mg)	3	3	2	2.5
Pyridoxine (mcg)	800	1000	400	150-200
Biotin (mcg)	20	20	8	5-8
Vitamin B12 (mcg)	2	2	0.4	0.3
Ascorbic acid (mg)	20	20	32	15-25
Folic acid (mcg)	80	80	56	56

Table 7. Comparison of Trace Element Product in Japan and US

	Japan	US	Estimated needs for preterm infants (ESPGHAN guidelines on paediatric parenteral nutrition 2018)
	Mineralin® (per 1/10 ampoule/kg/day)	Neotrace® (per 1/10 vial/kg/day)	
Fe (mcg)	196	0	200-250 mcg/kg/day
Mn (mcg)	5.5	2.5	≦1 mcg/kg/day in long term PN
Zn (mcg)	392	150	400-500 mcg/kg/day
Cu (mcg)	32	10	40 mcg/kg/day
I (mcg)	13	0	1-10 mcg/kg/day
Cr (mcg)	0	0.085	-
Se (mcg)	0	0	7 mcg/kg/day

Table 8. Examples of parenteral nutrition during 5 days of age for 1000 g infant

	Day 0			Day 1			Day 2		
Route-1	50% glucose Pleamin-P® Sterile water Heparin	12 ml 16 ml 22 ml 0.05 ml	1.5 ml/hr	50% Glucose Pleamin-P® Sodium Phosphate Corrective Injection (0.5 mmol/mL) 10% NaCl Sterile water Heparin	28 ml 44 ml 4 ml 2 ml 22 ml 0.1 ml	2.0 ml/hr	50% Glucose Pleamin-P® Sodium Phosphate Corrective Injection (0.5 mmol/mL) 10% NaCl 1M KCl Sterile water Heparin	28 ml 40 ml 4 ml 2 ml 3 ml 23 ml 0.1 ml	2.8ml/hr
Route-2	50% glucose Pleamin-P® Carcicol® Sterile water Heparin	12 ml 16 ml 8 ml 14 ml 0.05 ml	1.0 ml/hr	50% glucose Pleamin-P® Carcicol® Sterile water Heparin	28 ml 44 ml 16 ml 12 ml 0.1 ml	1.0 ml/hr	50% glucose Pleamin-P® Carcicol® Sterile water Heparin	28 ml 40 ml 24 ml 8 ml 0.1 ml	1.0 ml/hr
Y-site of Route-1				Intralipos (20%)		0.2ml/hr	Intralipos (20%)		0.4ml/hr
	Fluid volume	60	ml/kg/day	Fluid volume	77	ml/kg/day	Fluid volume	100	ml/kg/day
	GIR	5	mg/kg/min	GIR	7	mg/kg/min	GIR	9	mg/kg/min
	Amino acid	1.5	g/kg/day	Amino acid	2.4	g/kg/day	Amino acid	2.8	g/kg/day
	Lipid	0	g/kg/day	Lipid	1.0	g/kg/day	Lipid	1.9	g/kg/day
	Na	0	mEq/kg/day	Na	3.1	mEq/kg/day	Na	4.0	mEq/kg/day
	K	0	mEq/kg/day	K	0	mEq/kg/day	K	2	mEq/kg/day
	Ca	30	mg/kg/day	Ca	30	mg/kg/day	Ca	45	mg/kg/day
	P	0	mg/kg/day	P	30	mg/kg/day	P	43	mg/kg/day

Table 8(continued). Examples of parenteral nutrition during 4 days of age for 1000 g infant

	Day 3-4			Day 5		
Route-1	50% Glucose Pleamin-P® Sodium Phosphate Corrective Injection (0.5 mmol/mL) 10% NaCl 1M KCl Vitaject® Sterile water Heparin	28 ml 40 ml 3 ml 2 ml 3 ml 0.2 kit (2ml) 22 ml 0.1 ml	3.5ml/hr	50% Glucose Pleamin-P® Sodium Phosphate Corrective Injection (0.5 mmol/mL) 10% NaCl 1M KCl Vitaject® Sterile water Heparin	28 ml 40 ml 3 ml 2 ml 3 ml 0.2 kit (2ml) 22 ml 0.1 ml	3.5ml/hr
Route-2	50% glucose Pleamin-P® Carcicol® Medlenic® Heparin	28 ml 40 ml 32 ml 0.5 ml 0.1 ml	1.0 ml/hr	50% glucose Pleamin-P® Carcicol® Magnesium Sulfate corrective Injection (1 mEq/mL) Medlenic® Heparin	28 ml 40 ml 31 ml 1ml 0.5 ml 0.1 ml	1.0 ml/hr
Y-site of Route-1	Intralipos (20%)		0.6ml/hr	Intralipos (20%)		0.6ml/hr
	Fluid volume	122	ml/kg/day	Fluid volume	122	ml/kg/day
	GIR	10	mg/kg/min	GIR	10	mg/kg/min
	Amino acid	3.3	g/kg/day	Amino acid	3.3	g/kg/day
	Lipid	2.9	g/kg/day	Lipid	2.9	g/kg/day
	Na	4.8	mEq/kg/day	Na	4.8	mEq/kg/day
	K	2.5	mEq/kg/day	K	2.5	mEq/kg/day
	Ca	60	mg/kg/day	Ca	58	mg/kg/day
	P	40	mg/kg/day	P	40	mg/kg/day
				Mg	5.4	mg/kg/day

Table 9. Monitoring of infants receiving parenteral nutrition

Measurement	Frequency
Body weight	Daily if infant condition is stable
Height and Head circumference	Weekly
In-Out balance	Every 8 hr
Glucose, electrolytes, blood gas analysis	Daily during acute period
NH3	Daily, As clinically indicated
CRP	Daily
AST, ALT, Al-p, BUN, Cr, TB, DB, Calcium, Phosphorus, TG, TC	Weekly

(Contributor: Isamu Hokuto, Audit: Tokuo Miyazawa)

5 Enteral feeding

5.1. Clinical Situation

Nutritional management for EP infants during the stay in NICU involves not only improving physical growth but also the prevention of mortality and morbidities including NEC, CLD, and ROP (1). Furthermore, it is also correlated with the neurodevelopmental outcome after discharge (2). Extrauterine growth restriction (EUGR) which is defined as less than 10 percentile of body weight standard of corrected age at NICU discharge has a great influence on the subsequent neurological development. Therefore, early aggressive nutrition (EAN) aiming to avoid EUGR is expected to improve the outcomes in EP infants.

EAN is a method to start parenteral nutrition composed of amino acids within 24 hours after birth along with minimal enteral feeding (MEF) and human milk fortification (HMF). In Japan, until the early 2000s, parenteral nutrition and enteral nutrition were withheld until the EP infant was stable, because of concerns of their immature digestive tract and metabolic function. However, since the early 2000s, EAN has been accepted as a standard nutritional strategy in NICUs.

Although parenteral nutrition is essential as nutritional management until the establishment of enteral nutrition, parenteral nutrition alone is not enough for critically premature infants. Additionally, exclusive parenteral nutrition is a risk factor for the atrophy of intestinal mucosa, bacterial translocation, parenteral nutrition associated liver disease (PNALD), and catheter related blood stream infection (CRBSI). Therefore, it is always desirable to establish enteral feeding and to withdraw the parenteral nutrition as early as possible.

5.2. General Management

5.2.1 Breastfeeding

The best nutrition for EP infants is the own mother's milk (OMM). OMM has many benefits such as the high bioavailability of various nutrients, the protective effects from immune factors against infection and NEC. Furthermore, it can enhance the attachment between mothers and children and the long term psychomotor development and prevent metabolic syndrome.

Prenatal visit to those who are in threatened preterm delivery should be considered as

much as possible to explain the benefits of breastfeeding for EP infants and to encourage the expression of breast milk at early stage (within 6 hours of birth, if possible, within 1 hour).

Combining manual milking with a hospital-grade electric milking machine (double pump type) may enhance the breast milk secretion. The effectiveness of manual milking early in the postpartum period with a small amount of colostrum has been reported

A system which allows colostrum to be given to the infants with an injection syringe and/or a cotton into the infant's mouth by the own mother should be established in the hospital.

If OMM is not available, AAP and ESPGHAN recommend the use of pasteurized donor milk (DM). In Japan, the Japan Breast Milk Bank Association was established in 2017. Donors are screened for infectious diseases including HIV, HTLV-1, HBV, HCV, and syphilis. The expressed milk is pasteurized (62.5 °C, 30 minutes) and transferred to the hospitals on demand (3).

In the 2015, according to a nationwide survey, 32 NICUs (25%) out of 126 responded that they used breast milk from other mothers (so-called "received milk") (4). Most of these hospitals performed the screening for infectious diseases of donor mothers, but pasteurization of donor milk was rarely performed. Now this method is not recommended due to the risk of infection.

5.2.2 Formula

Low birth weight infant formula is selected if breastfeeding is contraindicated or if OMM is not available and DM is difficult to obtain.

5.2.3 Minimal enteral feeding (MEF)

It is recommended to start enteral feeding with small amounts of breast milk ideally within 24 hours after birth, at the latest within 72 hours after birth.

The volume for MEF is about 10 to 20 mL/kg/day and does not exceed 25% of the total daily amount planned (Table 1)(5).

Immediately after MEF started, a small amount of residual milk with bile (gastric residual) is often aspirated before each lactation. The amount of residual milk or bile-

like properties are not considered as the onset of NEC or feeding intolerance (6). Instead of interrupting enteral nutrition, it is desirable to continue MEF as much as possible with carefully observing abdominal findings (such as abdominal distension, abdominal wall tone, presence or absence of intestinal peristalsis, etc.).

Enteral feeding can be withheld for up to 72 hours if DM or OMM is not available. Use formula with caution due to its association with NEC.

5.2.4 Tube feeding (feeding interval and advancement of feeding dose)

Tube feeding is basically carried out by an intermittent administration of milk through a nasal or oral gastric tube.

The interval of feeding for EP infants is usually every three hours (8 times a day) or every two hours (12 times a day). According to a survey of Japanese NICUs in 2017, two thirds of the hospitals fed every 3 hours but some would feed every 2 hours because of concerns of aspiration (7).

Duodenal continuous feeds are used in some hospitals for infants with silent aspiration or GER but its safety is not proven and there is an association with NEC. Careful observation is mandatory if this intervention is selected (8).

In general, the volume of enteral feeding can be safely increased by up to 20 mL/kg/day. A Cochrane review reported no difference in the incidence of NEC between slow volume (15-20 mL/kg/day) and fast volume advancement (30-40 mL/kg/day) (9).

5.2.5 Human milk fortification

The nutritional stock of EP infants is very low and it is difficult to provide enough nutrition for their requirements even after full enteral feeds are established (Table 2)(10). This increases the risk of poor growth and metabolic bone disease. In order to prevent those problems, human milk fortification (HMF) can be used to compensate for the lack of nutrients in human milk while maintaining the benefits of breast feeding.

HMS-1 and HMS-2, which is further enriched with nutrients, Ca, and phosphorus, are products of Morinaga LTD, and are used in Japan (Table 3). Both of them are powdered formulations produced from cow milk protein. Liquid fortifiers are not yet available in Japan.

5.2.5.1 Practice

The fortifiers available in Japan do not contain vitamins nor trace elements such as iron, zinc and copper, so they must be administered separately if a shortage is suspected.

Start with a 1/4 supplement (1 package (0.8 g) in 120 mL of breast milk) once breast milk reaches 50 mL/kg/day for both HMS-1 and HMS-2.

Increase to a 1/4 supplement (1 package in 60 mL of breast milk) when reach 100 mL/kg/day.

Observe for several days, and if there is no abdominal distension or increase of residual milk, then use standard fortification (1 package for 30 mL of breast milk)

There is no clear guideline as to when HMF should be stopped. This very much depends on the policies of individual hospitals and/or the condition of the infant.

Ileus may occur due to fecal stones (fatty acid and calcium stone: fecaliths) with HMF supplementation. NEC has also been reported (11). Cases with poor gastrointestinal function and/or fat absorption due to bile congestion need careful attention. Cases with gastrointestinal allergy against milk protein contained in HMF have also been reported (12).

Nutritional components in breast milk may vary among mothers and is also dependent on the phase of lactation. In particular, protein concentration gradually decreases (Figure. 1). Even under standard HMS-2 fortification, inadequate intake of protein compared with a target value of 4.0 g/kg/day may occur (Figure 2).

Exclusive human milk diet (EHMD) using human milk-derived breast milk fortifiers has been reported to show beneficial effects such as a shortening of parenteral nutrition, preventions of NEC, CLD and ROP, and a shortening of hospitalization in Europe and USA (13).

5.2.5.2 Individualized HMF

Two methods of individualized human milk fortification (Individualized HMF) are

reported as effective for reaching target protein intake.

- Targeted HMF: Determine the amount of protein fortification based o component analysis of breast milk using human milk analyzer(14)
- Adjustable HMF: Adjust the amount of protein fortification to maintain 9-14 mg/dL of blood urea nitrogen value (BUN) as an index of protein intake without the analysis of breast milk components (15)

5.2.6 Probiotics

Administration of probiotics to EP infants are likely to delay or destroy the establishment of normal intestinal flora. Administration of probiotics can be expected to induce normal intestinal flora and to show beneficial effects on gastrointestinal physical function and immune modulation. A systematic review of Cochrane has shown that probiotics significantly reduce NEC (Bell classification stage II or grater) and significantly improve overall mortality and mortality associated with NEC (16).

The effectiveness of a single species such as Bifidobacterium and Lactobacillus has been reported. The administration of multiple bacterial species are also reported as effective. The majority of hospitals use Bifidobacterium breve in Japan.

5.2.6.1 Practice

There is no consensus on duration nor dose has not been fixed. Generally, it is administered from the beginning and until establishment of enteral feeding (average 4 weeks).

Bifidobacterium preparation of M-16V (Morinaga Milk Industry) distributed in Japan contains B. breve 5×10^9 cfu bacteria per 1 packet (1.2 g). Since dextrin is an excipient, the osmotic pressure significantly increases when the formulation is dissolved in breast milk or formula. It is isotonic if dissolved in 4 mL of distilled water. 4 ml can be divided if each enteral feeding is less than 4 ml or batch administered there is feeds are greater than 4 ml. Alternately, since ileus by corn starch as an excipient was reported, only the supernatant of the dissolve can be administered (17).

The preparation provided from Meiji Milk Industry does not contain dextrin, so the whole solution resolved in distilled water or milk can be administered.

5.2.6 Glycerin Enema

Glycerin enemas are widely used in Japanese NICUs for the purpose of preventing delay in meconium passage and feeding intolerance among EP infants. However, there is no clear evidence that glycerin enema can prevent NEC, meconium-related intestinal obstruction (MRI), or localized intestinal perforation (FIP) (18).

5.2.6.1 Practice

There is no definite consent about the start of administration, dilution method, dose, and interval of glycerin enema.

Start: From the initiation of MEF to 24 hours after birth

Dilution: 1/2 dilution (25%) or original solution (50%)

Dose: 1 to 2 mL/kg with original solution or 2 to 5 mL/kg with 1/2 diluted solution

Interval: every 6 to 8 hours

5.2.7 Standardization of enteral feeding

Standardization of enteral feeding for preterm infants at each center has been reported to reduce the risk of developing NEC by 78% (19). Therefore, it is recommended to standardize and document the items in Table 4.

5.2.8 NEC

NEC is the most frequent acute digestive tract disease in the neonatal period among preterm infants, and low birth weight infants account for over 90% of NEC cases. The incidence is reported as 7-10% in very low birth weight children in other countries but has been consistently maintained at a level of 1.5% in Japan for over 10 years (Figure 3) (20). Despite the fact that donor milk is not widely used, the reason why Japan has a lower incidence of NEC is unknown. Several factors including the difference in general management for EP infants such as nutritional care, circulatory care based on echocardiography performed by neonatologists, repeated CRP measurement using a POCT device as an inflammatory biomarker, use of antibiotics and antacid, genetic backgrounds and environmental factors in NICU can be considered.

The diagnosis of NEC is based on general and abdominal symptoms and characterized imaging findings. The Bell classification is used for staging (Table 5)(21). Stage IIa or greater with intramural emphysema or portal vein gas is often confirmed as a definitive diagnosis, but in EP infants, gastrointestinal perforation may occur suddenly without these findings, followed by shock and/or DIC.

Suspected or mild cases of NEC can be treated with multidisciplinary medical treatment. Discontinuation enteral feeding, decompression of the intestinal tract by gastric tube, and broad-spectrum antibacterial and antifungal drugs according to surveillance culture and antimicrobial susceptibility (antibiogram) of the indigenous bacteria in each facility should be commenced. Active care including respiratory and circulatory supports, parenteral nutrition, and treatment for DIC should be also followed.

Cases with intestinal perforation or poor response to medical treatment surgical treatment. Although resection of necrotic or enlarged intestinal segment and fistula formation may be needed, a one-step anastomosis may also be performed if the necrotic intestine is localized and the general condition is maintained.

If the infant is severely unwell, abdominal drainage can temporize the situation until definitive surgery can be performed.

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Table 1 Feeding protocol for extremely preterm infants

Birth weight	0-23 hours	24-47 hours	48-71 hours	72-96 hours
～599g	0.3mL×8/day	0.5mL×8/day	0.8mL×8/day	1.1mL×8/day
600～799g	0.5mL×8/day	0.8mL×8/day	1.3mL×8/day	1.8mL×8/day
800～999g	0.7mL×8/day	1.0mL×8/day	1.7mL×8/day	2.4mL×8/day
1,000g～1,250g	1.0mL×8/day	1.5mL×8/day	2.5mL×8/day	3.5mL×8/day

(Modified from reference 5)

Table 2 Nutritional needs of the low-birth-weight infants calculated by factor addition method

	Birth weight			
	500-700g	700-900g	900-1,200g	1,200-1,500g
Fetal body weight increase (g/kg/day)				
Protein(g/kg/day)				
Loss	1.0	1.0	1.0	1.0
Accumulation	2.5	2.5	2.5	2.4
Requirement intravenously	3.5	3.5	3.5	3.4
Requirement enterally	4.0	4.0	4.0	3.9
Energy (kcal/kg/day)				
Loss	60	60	65	70
Accumulation	29	32	36	38
Requirement intravenously	89	92	101	108
Requirement enterally	105	118	119	127
Protein/Energy (g/100kcal)				
Intravenously	3.9	3.8	3.5	3.1
Enterally	3.8	3.7	3.4	3.1

(Modified from reference 10)

Table 3 Comparison of HMS-1 and HMS-2

	Standard breast milk (per 100mL)	Increment by HMS-1 added	HMS-1 (per 100mL)	Increment by HMS-2 added	HMS-2 (per 100mL)
Protein (g)	1.3	0.7	2.0	1.0	2.3
Fat (g)	3.7	0	3.7	1	4.7
Carbohydrate (g)	7.7	1.5	9.2	1.8	9.5
Energy (kcal)	69	9	78	20	89
Osmolarity (mOsm)	280	60	340	80	360

Table 4 The items should be standardized about enteral feeding

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Timing of starting enteral feeding

Method of tube feeding (continuous or intermittent, interval, infusion rate)

Type of milk (OMM, DM, formula for low birth weight infants)

Increment of enteral feeding volume

Maximum volume

Extremely early feeding (timing, volume)

Responses to feeding intolerance and residual milk

Individualized responses according to different disorders (continue or discontinue, increase volume or decrease)

- -Sepsis
- -Indomethacin for PDA
- -Blood transfusion

Breast milk fortification (timing, duration, concentration)

Table 5 Bell's staging of NEC

Stage	Systemic signs	Abdominal signs	Radiographic signs
ⅠA Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, hemo-positive stool	Normal or intestinal dilation, mild ileus
ⅠB Suspected	Same as above	Grossly bloody stool	Same as above
ⅡA Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
ⅡB Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenica	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as ⅡA, plus ascites
ⅢA Advanced, severely ill, intact bowel	Same as ⅡB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as ⅡA, plus ascites
ⅢB Advanced, severely ill, perforated bowel	Same as ⅢA	Same as ⅢA	Same as above, plus pneumoperitoneum

Figure 1 Protein contents in breast milk sampled from mothers delivered extremely low birth weight infants (Department of Pediatrics, Showa University)

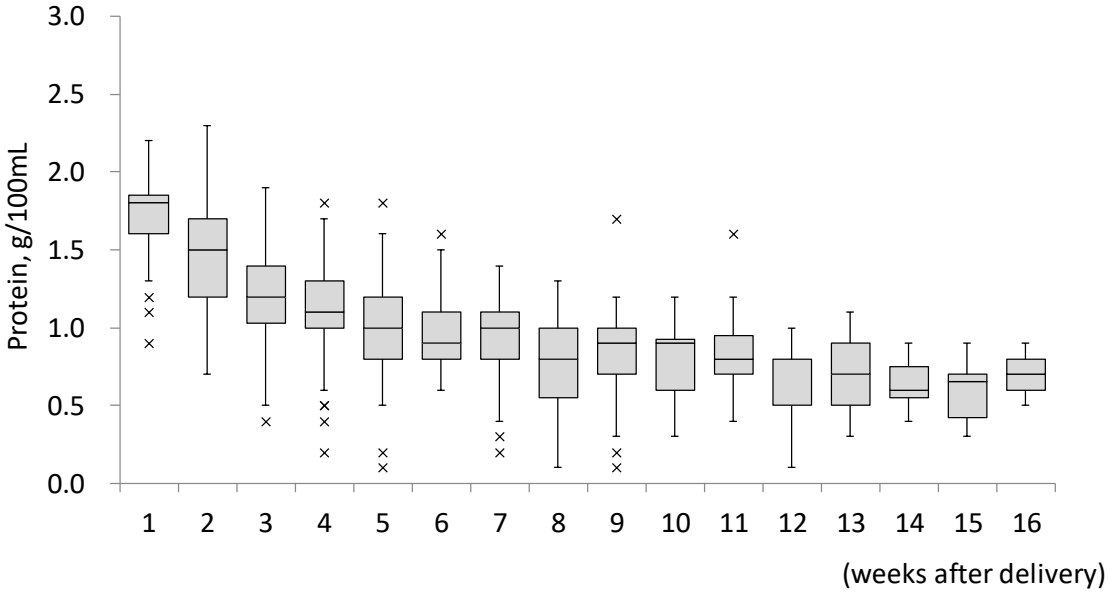


Figure 2 Nutritional intake in the infants of breast feeding with fortified by HMS-1 and HMS-s (Department of Pediatrics, Showa University)

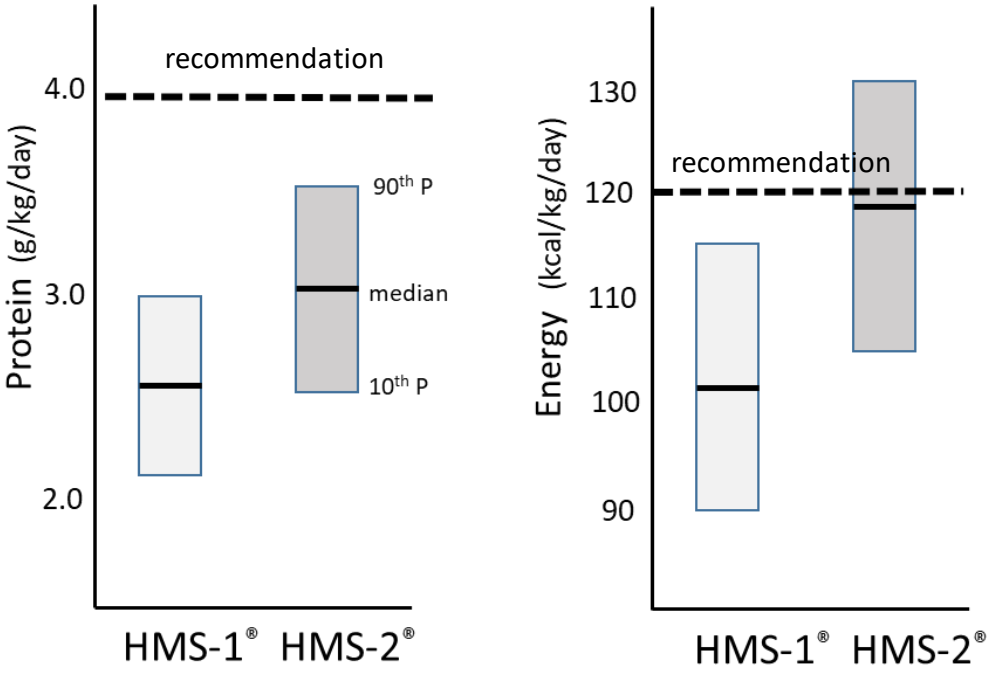
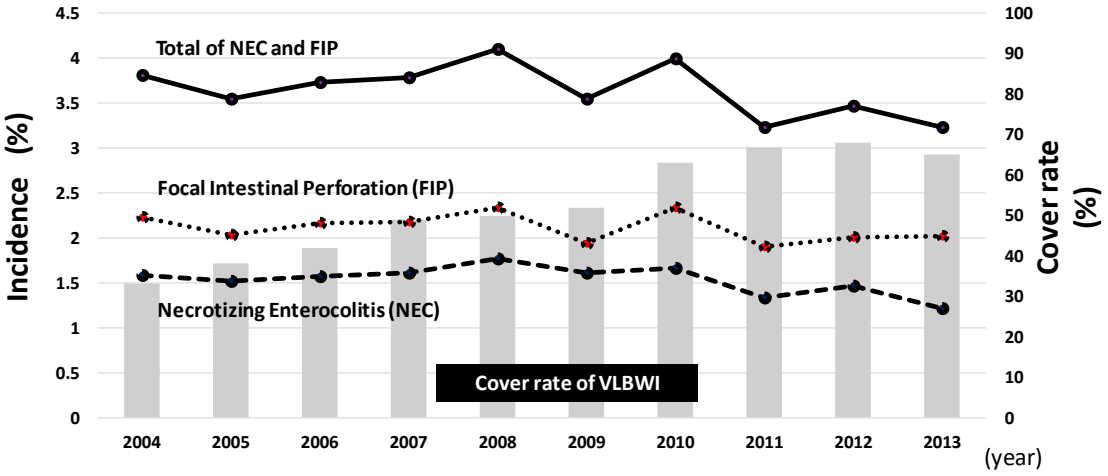


Figure 3 . Incidence of NEC in Japan (Data from Neonatal Research Network Japan)



(Contributor: Tokuo Miyazawa, Audit: Isamu Hokuto)

6 Infection control

6.1 Clinical situations

Infection is one of the most important morbidities affecting the outcomes of EP infants. Maternal conditions that significantly influence the risk of neonatal infection include such conditions like vertical infection, ascending infection with bacteria in the vagina, and birth canal infection. Since infants immediately after birth are basically in a sterile condition, NICU commensals can could colonize many infants. EP infants are particularly immature in immunity and, in addition, have low antibody transfer from the mother, which increases the risk of bacterial infection. Early diagnosis and early treatment are the principle measures to avoid death or serious complications due to infection. Therefore, it is very important not to overlook subtle changes in clinical symptoms and to confirm the diagnosis of infection referring several laboratory tests.

6.1.1 Classification by the timing of onset

Neonatal infections are divided into early-onset infection and late-onset infection according to the timing of onset. Early-onset infection generally refers to sepsis/meningitis that occurs within 48-72 hours after birth. E. coli can be a main pathogen as an ascending infection, a transplacental infection, and a birth tract infection. Clinical symptoms are usually serious. Late-onset infection develops after 48-72 hours of age. Although E. coli can be transmitted from the mother, horizontal infections and medically associated infections are more common. Table 1 shows the differences between the early and late onset sepsis.

6.1.1.1 Early onset infection (1)

Group B Streptococcus (GBS), E. coli and Listeria are representative pathogens. Since the amniotic membrane normally acts as a barrier for bacteria, the fetus basically resides in a sterile environment. When the amniotic membrane is damaged, chorioamnionitis due ascending to bacteria including E. coli can occur. The incidence of chorioamnionitis depends on gestational age, with risks increasing with prematurity. Risk factors for early onset infection includes prematurity, a GBS colonized pregnant woman, prolonged premature rupture of membranes for more than 18 hours, and chorioamnionitis. Preterm birth and low birth weight infants are particularly important risk factors.

6.1.1.2 Late onset infection (2)

Late onset infection may develop as sepsis after a certain period resulting from bacteria transfer from the birth canal at delivery or may develop as sepsis resulting from horizontal infection. Besides S. epidermidis, S. aureus, and GBS, gram-negative bacilli such as E. coli and P. aeruginosa, and Candida spp. can be pathogens. The risk factors for EP infants of late onset infection include reduced transfer of antibodies from the mother, immaturity of neutrophil function, many occasions of bacterial invasion such as intratracheal intubation, central venous catheter insertion, etc.

6.2 General Management

Early detection of infection and early treatment improves prognosis. Although early symptoms may be unclear, empirical treatment should be started any time when infection is suspected.

6.2.1 Sepsis

Sepsis refers to a condition in which an infection causes serious organ damage. The pathogens invading into the blood stream can cause circulatory failure, coagulation disorders, organ damage, and when if severe, to multiple organ failure with disseminated intravascular coagulation (DIC). Sepsis in EP infants may progress rapidly and greatly affects mortality and neurological outcomes.

Symptoms at the early stage of onset are often nonspecific include general malaise, enteral intolerance, apnea, hypothermia or hyperthermia, jaundice, irritability and the likewise. Diagnosis should be based on the positive blood culture and blood test values. Early onset sepsis is often associated with meningitis.

Treatment involves the administration of antibacterial agents that covers putative pathogens, a combination of penicillin and aminoglycoside should be started. Once the bacterial pathogen and its drug sensitivity have been identified, focusing on one effective antibacterial drug and continuing for necessary and sufficient periods is the rule. If hypotension and/or respiratory distress appeared, supportive treatment including inotropic agents and mechanical ventilation. In the most severe cases, exchange blood transfusion or plasmapheresis may be introduced to remove pathogens and cytokines in the blood stream.

6.2.2 Meningitis

Meningitis, most often bacterial meningitis, is a serious disease associated with an

increased risk of mortality or neurological sequelae, Routes of infection include vertical infection from the mother, horizontal infection, and nosocomial infection. In the early onset type, GBS, E. coli and Listeria are the main causative bacteria as well as sepsis. In the late onset type, in addition to GBS and E. coli, other gram-negative bacilli, S. aureus and S. epidermidis become dominant. Typical signs of meningeal inflammation in older children such fever, neck stiffness, and loss of consciousness are usually not common. There are, instead, nonspecific symptoms such as malaise and lethargy, sluggishness, poor feeding, apnea and vomiting are prominent.

Diagnosis is made by the detection of pathogenic organism from a spinal fluid sample. Gram staining of cerebrospinal fluid is useful to estimate the causative organism.

Treatment is with the maximum dose of antimicrobial drugs that can cover the putative bacteria. After the bacterial pathogen and its drug sensitivity are identified, the appropriate antibiotics should be administered for a sufficient period. Retest the cerebrospinal fluid 24-48 hours after the starting antibiotics to ensure acceptable treatment effect.

6.2.3 Nosocomial infection

6.2.3.1 Catheter-related bloodstream infection

Catheter-related bloodstream infection (CRBSI) is a bloodstream infection that originates after insertion or an infusion line site. The diagnosis is made when blood culture becomes positive with signs of infection and other infections are ruled out. Gram-positive cocci, in particular, S. epidermidis and S. aureus are the major causative bacteria. In the cases with prolonged use line use, the risk of infection with gram-negative bacteria also increase. EP infants are also at risk of fungal infection.

The main principle of treatment is to administer effective antimicrobial drugs for a sufficient duration. The decision of whether to remove the catheter should be determined according to the response to the initial treatment and the pathogen.

Prophylaxis is important. All medical personnel should adhere to the practice of preventing CRBSI during insertion and maintenance of catheter.

6.2.3.2 Ventilator-associated pneumonia

Ventilator-associated pneumonia (Ventilator associated pneumonia: VAP) refers to

pneumonia that develops within 48 hours of mechanical ventilation. EP infants are at high risk of developing VAP. Staphylococcal bacteria and Pseudomonas aeruginosa are the main cause for VAP during the early stages of hospitalization. After prolonged hospitalization, methicillin resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa may colonize the infant and become pathogens. Again, fungi should be considered as a pathogen in EP infants.

The treatment is to administer effective antimicrobial drugs for a sufficient period. In addition to this, appropriate hand hygiene should be implemented for all medical personnel and use of a closed suction system and oral care are important for the prevention of VAP.

6.2.3.3 Fungal infection

Fungal infections in infants are mostly caused by Candida species, of which Candida albicans is the most common. It is generally classified into superficial fungal infection and deep fungal infection. In the early stages of the deep fungal infection, as with bacterial infections, no specific symptoms are noted. Central venous catheter placement is one of the risk factors for deep fungal infection. The diagnosis is based on the isolation of the fungus from culture tests. With blood tests, unknown and weak inflammatory responses are often the only early signs. Therefore, early diagnosis is usually difficult. Thrombocytopenia is often associated in systemic candidiasis. Although β-D-glucan measurement is useful as an adjunct diagnosis, it is not a test specific to the fungal infection. Systemic administration of antifungal drugs should be used for treatment. Prophylactic administration of fluconazole, off-labelled use, occurs in some hospitals in Japan.

6.2.4 Optional treatments

If the infection is severe, respiratory and circulatory supports should be provided. If the administration of antimicrobial drugs is insufficient, the administrations of immunoglobulin and granulocyte colony-stimulating factor (G-CSF) are considered. In order to remove inflammatory cytokines and endotoxins, exchange blood transfusion or plasmapheresis using endotoxin absorptive columns can be considered at selected hospitals.

6.3 Evaluation

6.3.1 Physical examinations

The initial symptoms of infection among EP infants are non-specific, and this must be reminded. In neonatal care, the condition of "somewhat worse than usual" is defined as "not doing well" which includes vague signs of poor feeding, poor skin color, etc. In such cases, detailed observations and examinations are required. It is also important to check for common changes in vital signs, such as body temperature, respiratory rate and heart rate.

6.3.2 Laboratory test

6.3.2.1 Culture

If infection is suspect, cultures of various site must be always be obtained before administering antibiotics. Blood culture is essential for the diagnosis of sepsis and bacteremia. The samples must be collected with an aseptic technique so that contamination from the flora on skin surface can be avoided. Minimize blood sample volumes to avoid iatrogenic anemia in EP infants. However, insufficient blood sample volume risks false negative results. Therefore, a blood volume of at least 1.0 mL should be taken. Other cultures of tracheal secretions, skin, urine, catheters, intratracheal intubation tubes, etc. are only performed if indicated, based on the clinical symptoms of the infant.

6.3.2.2 Blood test

Various blood tests are used as marker of infection or criteria for the diagnosis of infectious diseases. In particular, complete blood cell count (CBC) and C-reactive reaction (CRP) are widely used. However, the interpretation of these results is performed based of full understanding of the sensitivity and specificity of the diagnosis.

・ CBC

Because the white blood cell count (WBC) of newborns is affected by maternal status such as gestational age and pregnancy hypertension syndrome, the sensitivity of diagnosis for infection is low with reduced WBC alone. On the other hand, the ratio of white blood cell fraction is useful for diagnosis. The ratio of the number of immature neutrophils to the total number of neutrophils (I/T ratio) over 0.2 is diagnostic [1)]. However, since the white blood cell count and the I/T may change dramatically immediately after birth, it should be careful to interpret the results immediately after birth.

・ C-reactive protein (CRP)

CRP is an acute phase reactant that rises with inflammatory reaction and tissue destruction. The sensitivity is low in early diagnosis because the response needs 6-8 hours with infection or inflammation [2]. Therefore, negative CRP only cannot rule out infection. For an accurate diagnosis of infection among EP infants, it is important to evaluate CRP values over time using small blood samples and repeat evaluations in intervals e.g. every 6 hours. (2)

・ Procalcitonin

Procalcitonin is a precursor of calcitonin and rises 3-6 hours after infection. Although a significant difference can be seen between infectious disease and inflammatory response, the usefulness of procalcitonin in EP infants is unknown and not established.

6.3.2.3 Cerebrospinal fluid examination

Sampling and culture of cerebrospinal fluid are essential in the diagnosis of bacterial meningitis. Spinal tap is therefore mandatory for the infants of suspected meningitis. However, since spinal tap is extremely invasive for EP infants, if general condition is poor, it may be performed after general condition becoming relatively stable.

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Table 1

	Early onset infection	Late onset infection
Timing of onset	< 72hours	>/= 72hours
Antepartum/intrapartum complications	common	less common
Percentage of preterm birth	about 25%	less common
Infection routes	birth canal	birth canal, hospital-acquired
Clinical symptoms	respiratory distress, shock	non-specific
Mortality rate	5-15%	2-10%

（Contributor: Masahiro Hayakawa, Audit: Isamu Hokuto）

7 NICU environment

7.1 Medical Workforce in Japanese NICU

7.1.1 Relationship between prognosis of preterm infants and NICU volume
A high volume of admissions of VLBW infants (>100 per year) including higher levels of care were associated with significantly lower odds ratios for death.

・Guidelines in UK and Canada for operating NICU
NICUs in the UK should admit at least 100 very low birth-weight infants (VLBW) infants per year
Canada recommends high volume and high level NICUs because high volume (> 100 per year) and higher levels of care are associated with significantly lower odds ratio for death.

In Japan, the mortality of VLBW infants also correlates with the number of deliveries, the number of NICU doctors, and the number of nurses (1). (Figures 1 and 2). However, centralization of NICU hospitals in Japan is not similar to overseas (Figure 3)(2).

It is speculated that factors other than centralization may contribute towards lower mortality VLBW rates in Japanese infants, as reported in the Neonatal Research Network of Japan (1).

7.1.2 Characteristics of NICU in Japan
Professor Costeloe kindly gave us a comment at the lecture of network quality improvement conference held in 2010 as shown in Figure 4.

7.1.3 Relationship between performance and several NICU characteristics in Japan
NRNJ examined the relationship between the NICU performance and several characteristics (3,4).

76 perinatal centers were involved in the study. Standardized mortality ratio (SMR) less than 1500g (born in 2009) was compared using several outcomes at each hospital.

SMR is calculated as follows; actual number of deaths/expected (adjusted) number of deaths × 100. Adjustment factors were chosen as follows; birth weight, gestational age, gender, multiple births, out-of-hospital birth, birth position, maternal PIH, maternal

steroid administration, fetal heartbeat, delivery mode, 1 minute Apgar, congenital abnormality.

The first analytic result is that the average years of experience of neonatologists (ie all physicians including residents) working in each NICU was not correlated with SMR (Figure 5)(4). However, the year of experience of the neonatologist in the No. 2 position was inversely correlated with SMR. The number of working years longer than 10 years increases mortality significantly ($p<0.043$) (Figure 6). Furthermore, NICU ranks of SMR and average years of pediatrician's services in NICU were significantly correlated (Figure 7)(4). Facilities with an average working life of less than 5 years showed significantly poorer ranks of SMR ($p<0.001$) as did facilities with an average working life of more than 12 years ($p = 0.15$).

As a result of this study, the following became clear;
Performance is best in NICUs where the average years of experience for the core group of pediatricians is between 5 and 12 years.
SMR was worst in NICUs where the average years of experience of pediatricians were less than 5 years.
The NICUs in USA and Europe are staffed with residents with less than 5 years' experience as their core staff. This may correlate the outcomes of VLBW infants.
SMR may tend to increase when senior doctors of >12 years' experience make up the core staff.

In summary, neonatologists working in NICU between 5 and 12 years is best. Senior doctor service rather than resident service can maintain the level of NICU in Japan.

Education to young neonatologists with less than 5 year experience and senior neonatologists with more than 13 year experience is warranted.

7.2 Current neonatal care system in Japan

A nationwide survey on Japanese perinatal centers performed on December 2009 showed following results (2).

There are 76 facilities (response rate 97.4%) with the designation of general perinatal centers from both national and prefectural governments are located in at least one prefecture. 85.1% of them are equipped with a system to manage available NICU beds.

but only 40% contribute to an NICU database.

Neonatal transport with center staff is performed in 90.5% of units, and a so-called triangle neonatal transport is also performed in about 60%. Centers with a large number of neonatal transports tend to be operated with a large number of fulltime neonatologists. Neonatal transport is carried out by neonatologists only in 45%, neonatologists and nurses in 44%. Only 42% of the centers have a special ambulance designed for neonatal transport.

The average number of NICU is 13.1 and GCU is 20.9. The average number of deliveries per year is 778.2.

The highest distribution of the number of positions for fulltime neonatologists is 5 in 19 centers. The total number of the posts for neonatologists is 370 but 42 of them are vacant. The number of fulltime neonatologists is still not sufficient. The highest distribution of the number of neonatal trainees is 1 or 2 in 29 centers. Only 9 centers had 3. The total number of the posts for neonatal trainees exists 107.5 but 25 are vacant.

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Figure 1 Correlation between the number of deliveries or the number of nurses at night shift and mortality among very low birth weight infants in Japan

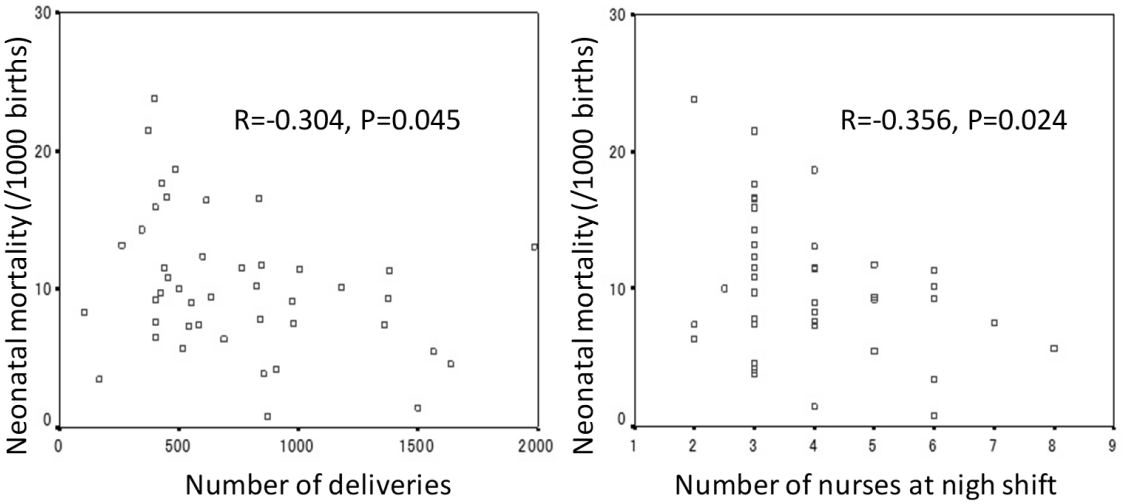


Figure 2　Correlation between neonatal mortality and the number of pediatricians among very low birth weight infants in Japan

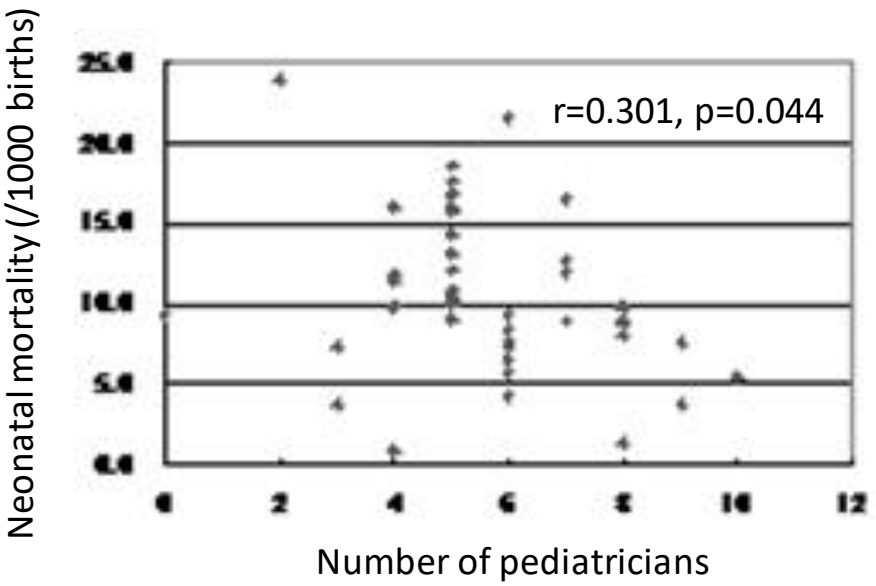
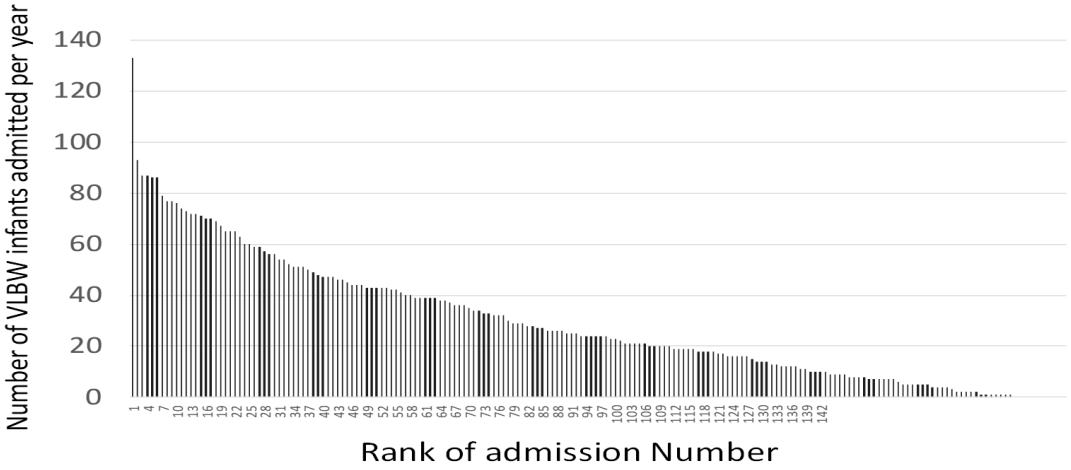


Figure 3 Number of very low birth weight infants admitted per year at each hospital



Figue 4 Neonatal network quality improvement conference in Tokyo in 2010

Impression of Neonatal Database Quality Improvement Conference in 2010 in Tokyo by Prof. Kate Costeloe at Homerton University Hospital, London.

It was fascinating to be able to talk to people about the very high survival rates of preterm babies on Japanese units. The most striking difference is how hard the doctors work and their level of involvement with the hands on care of the babies. I fear we have gone too far the other way.

Figure 5 Correlation between the standardized mortality rate and the average years of service in NICU among very low birth weight infants in Japan

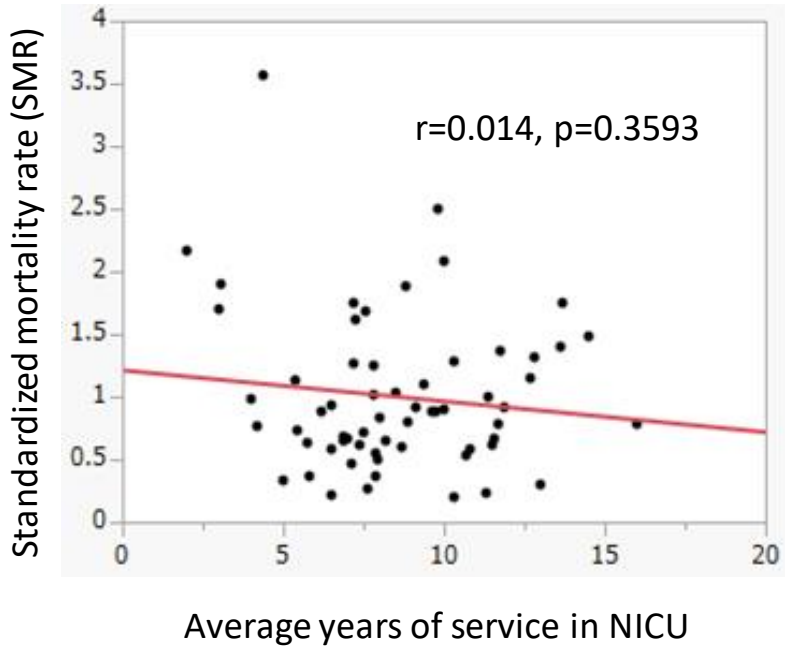


Figure 6 Correlation between the standardized mortality rate and the years of the neonatologist in the No. 2 position working in NICU among very low birth weight infants in Japan

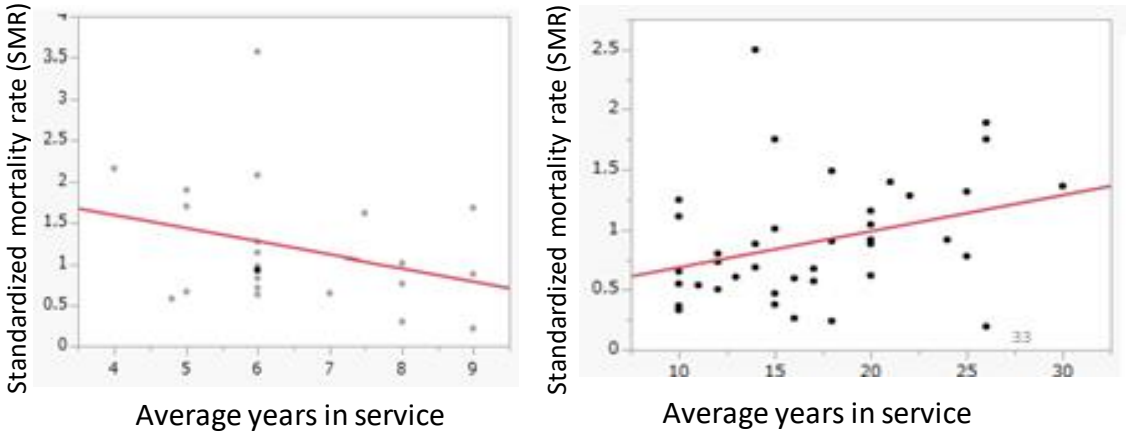
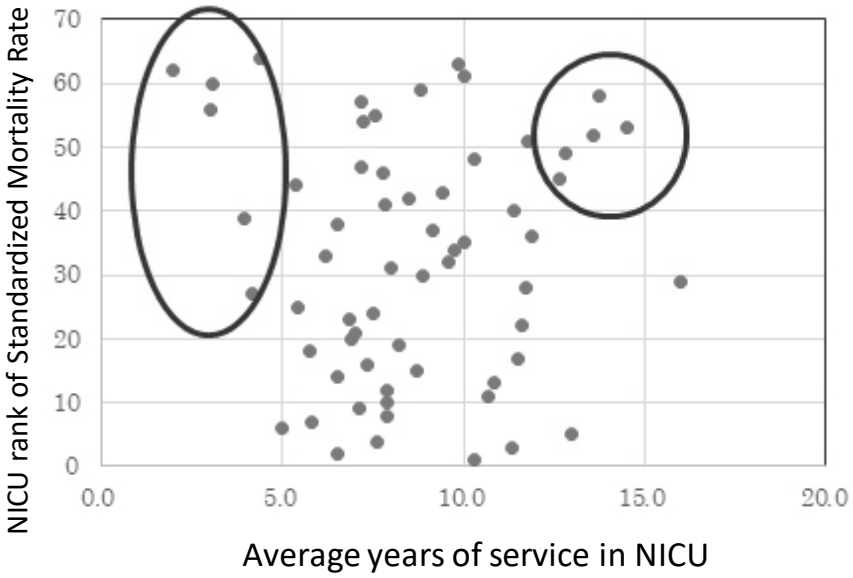


Figure 7 Correlation of the ranking between the standardized mortality rate and the average years of neonatologists working in NICU among very low birth weight infants in Japan



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