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REVIEW ARTICLE

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Japan at the limits of viability: national experience and evolving outcomes of infants born at 22–23 weeks' gestation

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Infants born at 22–23 weeks' gestation represent the limits of viability with substantial international variation in outcomes. Japan has consistently reported some of the highest survival rates; however, the underlying healthcare systems and clinical practices have not been comprehensively synthesized. This review summarizes Japan's national experience using data from a nationwide network database, epidemiologic studies, clinical practice surveys, and international comparisons. Survival at discharge is approximately 60% and 80% for infants born at 22 and 23 weeks' gestation, respectively, with relatively low rates of severe intraventricular hemorrhage and necrotizing enterocolitis. Key healthcare system features include regionalized perinatal care promoting antenatal maternal transfer, a nationwide clinical network for benchmarking, and universal health insurance. Clinical practice is characterized by active resuscitation and meticulous, individualized, pathophysiology-based management, including invasive respiratory support, echocardiography-guided hemodynamic management, intensive neuroprotection, and specialized nursing care. The effectiveness of these practices remains uncertain, and further research is needed. Continuous outcome monitoring and quality improvement are essential to refine context-specific strategies.

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IMPACT:

- This review provides the comprehensive synthesis of Japan's national experience in the care of infants born at 22–23 weeks' gestation, integrating outcomes with healthcare system structures and clinical practices.
- It identifies key system-level and clinical factors—such as regionalized perinatal care, nationwide data-driven quality improvement, and pathophysiology-based management—that may contribute to Japan's high survival rates and relatively low morbidity.
- It highlights the importance of integrated "package-of-care" approaches and continuous outcome monitoring, offering insights that may inform strategies to improve outcomes at the limits of viability globally.

INTRODUCTION

Infants born at 22–23 weeks' gestation represent the extreme limits of viability, with substantial international variation in survival and morbidity. Japan has consistently reported some of the highest survival rates for these periviable infants, supported by a regionalized perinatal healthcare system, a nationwide neonatal network, and meticulous, individualized, pathophysiology-based care.[1–3] However, this experience has not been comprehensively summarized in a manner that integrates evolving outcomes with underlying management strategies across organ systems.

This review summarizes Japan's national experience in the care of infants born at 22–23 weeks' gestation, drawing on data from the Neonatal Research Network of Japan (NRNJ), nationwide epidemiologic studies and clinical practice surveys, and international comparisons from the International Network for Evaluating Outcomes of neonates (iNeo).[4,5] We describe temporal trends in survival and major morbidities and review key aspects of perinatal and neonatal management, including respiratory support, cardiovascular management, neuroprotection, nutrition, infection prevention, and system-level approaches.[6–8]

OUTCOMES OF INFANTS BORN AT 22–23 WEEKS' GESTATION AND THEIR TRENDS

Short-term outcomes

Based on the NRNJ data, recent survival rates at discharge were approximately 60% for infants born at 22 weeks' gestation and 80% for those born at 23 weeks' gestation among infants who

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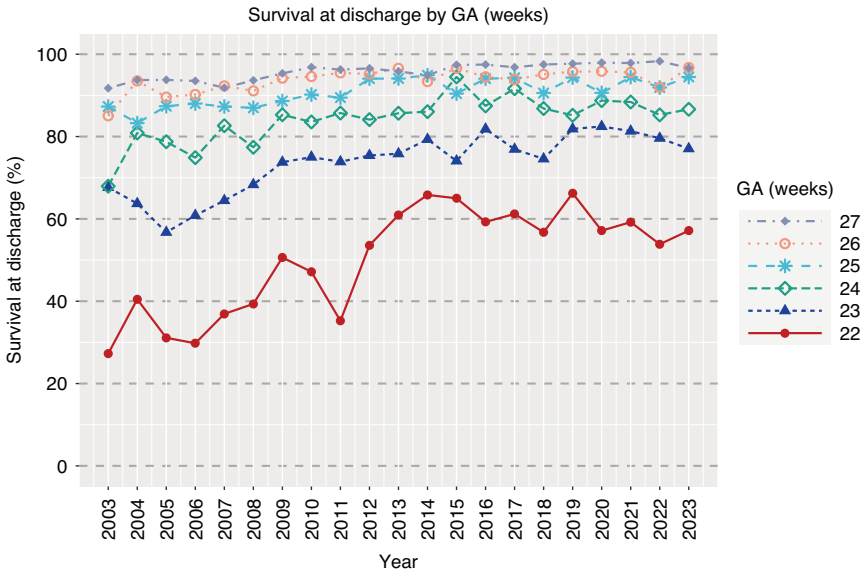


Fig. 1 Trends of survival at discharge by gestational age (weeks). Data from the Neonatal Research Network of Japan database, excluding infants with major congenital malformations. Abbreviation: GA, gestational age.

received active postnatal intensive care and were admitted to neonatal intensive care units (NICUs).[1] An international comparative study from the iNeo found that the survival rates at discharge in other neonatal networks, mainly from high-income countries, were 7–49% and 15–66% for infants born at 22 and 23 weeks, respectively. The rates from NRNJ were the highest among iNeo networks. The reasons for the highest survival rates of extremely preterm infants in Japan compared with many other countries remain unclear. However, several factors may contribute, including an active approach to resuscitation at the limit of viability, the organizational structure of neonatal intensive care units (NICUs), and clinical management strategies for extremely preterm infants.[6] These factors are discussed in the following sections of this article. Survival among infants born at 22 to 23 weeks' gestation improved substantially until around 2013; however, it has remained relatively stable over the past decade (Fig. 1).

The iNeo study also reported that the rates of severe brain injury (severe intraventricular hemorrhage [IVH] or periventricular leukomalacia [PVL]) in NRNJ were 24% and 17% for infants born at 22 and 23 weeks' gestation, respectively, which were lower than those reported in most other iNeo networks (ranges, 23–82% and 24–58%, respectively). Rates of necrotizing enterocolitis (NEC) in NRNJ (5% and 6%, respectively) were within the lower range of those reported in other iNeo networks (ranges, 0–13% and 0–32%, respectively). The rates of treated retinopathy of prematurity (ROP) in infants born at 22 and 23 weeks' gestation who survived to discharge were higher in NRNJ (58% and 49%, respectively) than in other iNeo networks (34–46% and 11–48%, respectively). The rates of chronic lung disease (CLD) at 36 weeks postmenstrual age in infants who survived at discharge were 84% and 77%, respectively, which were comparable to the rates in other iNeo networks (80–83% and 58–89%%, respectively). Trends in major morbidities in NRNJ are shown in Fig. 2. While the rates of severe IVH, NEC, and treated ROP were relatively stable over the past decade, the CLD rates among survivors have increased over the last two decades.

The outcomes of these infants should be interpreted with caution because the NRNJ captures only approximately 65% of the target population.[9] In addition, participating NICUs may not be representative of all NICUs in Japan and could be subject to selection bias toward higher-performing centers.

Long-term outcomes

The NRNJ registry collects follow-up data at 1.5 years of corrected age, and 3, 6, and 9 years of age. Figure 3 compares the proportions of infants with moderate to severe neurodevelopmental impairment (NDI) at 3 years of age with data from Sweden (2–2.5 years of age) and the United States (2 years of age).[10–13] Although survival rates are higher in Japan, the proportions of moderate to severe NDI among survivors appear similar to those in Sweden and the United States. Therefore, improved survival does not necessarily translate into parallel improvements in long-term neurodevelopmental outcomes.

SYSTEM-LEVEL APPROACHES SUPPORTING OUTCOMES

The Japanese medical system supporting perinatal and neonatal care of extremely preterm infants is characterized by regionalized perinatal care that promotes maternal transfer, a nationwide neonatal network with clinical databases, and universal health insurance coverage.

REGIONALIZED PERINATAL HEALTHCARE SYSTEM

A key component is the regionalized perinatal health care system established through the National Perinatal Healthcare System Development Project.[14] Under this system, each prefecture maintains a network consisting of comprehensive perinatal medical centers (tertiary centers) and regional perinatal medical centers. Comprehensive centers are expected to provide both advanced neonatal intensive care and high-level obstetric maternal–fetal care, including access to maternal–fetal intensive care units (MFICUs) and NICUs. Consequently, children's hospitals without obstetric services cannot be designated as comprehensive perinatal medical centers, even if they operate large tertiary NICUs. This policy has encouraged institutions providing advanced neonatal care to establish obstetric departments or to reorganize their services so that maternal and neonatal care are delivered within the same center or through coordinated, adjacent institutions.

The integration of obstetric and neonatal services has promoted antenatal maternal transfer to tertiary centers and reduced postnatal transfer of critically ill newborns. For example, the proportion of neonatal transfers among very low birth weight

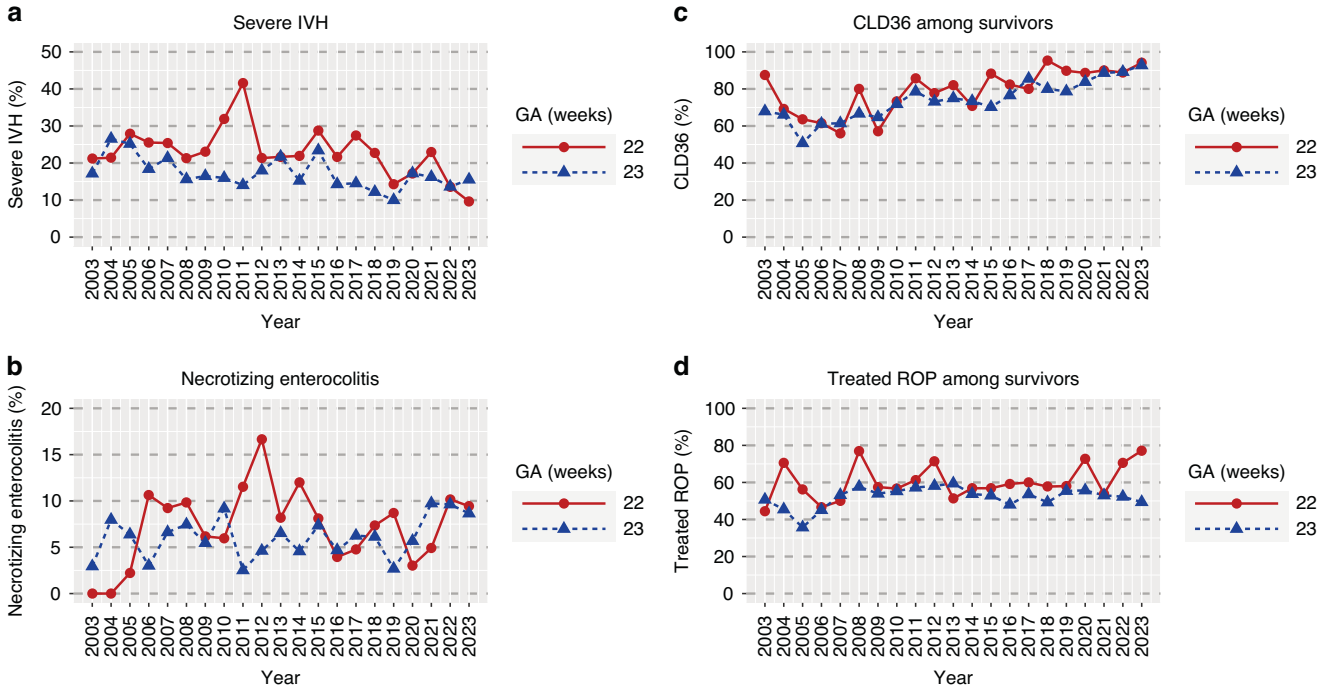


Fig. 2 Trends of major morbidities in infants born at 22 and 23 weeks' gestation. Data from the Neonatal Research Network of Japan database, excluding infants with major congenital malformations. Abbreviation: GA, gestational age.

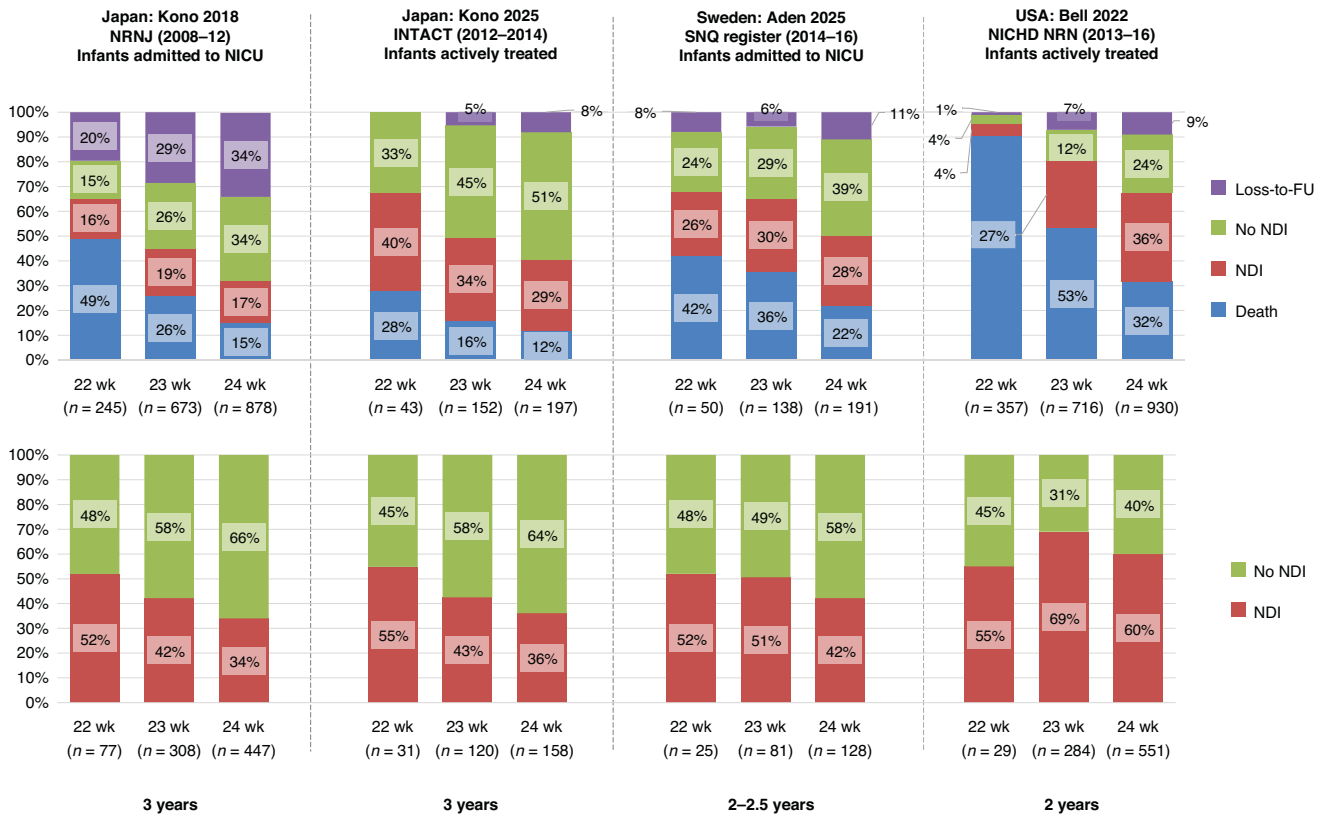


Fig. 3 Neurodevelopmental impairment at 2–3 years of corrected age. The neurodevelopmental impairment (NDI) includes moderate to severe NDI. Loss-to-follow-up includes those who attended follow-up clinics but did not have the assessment of neurodevelopmental impairment. Abbreviation: GA, gestational age; INTACT, Improvement of NICU practices and Team Approach Cluster-randomized controlled Trial; FU, follow-up; n, number of infants; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; NICU, neonatal intensive care unit; NDI, neurodevelopmental impairment; NRN, Neonatal Research Network; NRNJ, NRN of Japan; SNQ, Swedish Neonatal Quality Register; wk, weeks.

infants decreased from approximately 12% in 2003 to 4% in 2022.[2,15] Because infants born in tertiary centers generally have better outcomes than those transferred after birth, this system of centralized perinatal care is considered a structural factor contributing to the favorable outcomes of extremely preterm infants reported in Japan.[16]

NATIONWIDE NEONATAL NETWORK WITH CLINICAL DATABASES

The NRNJ established a nationwide registry for high-risk infants in 2003, which serves as a platform for neonatal research and quality improvement across Japan.[9] Currently, approximately 170 NICUs participate, capturing about 65% of very preterm or very low birth weight infants born in Japan.[9] The registry collects detailed clinical information during NICU hospitalization and follow-up outcomes after discharge at 1.5 years of corrected age, and at 3, 6, and 9 years of age. These data enable benchmarking among centers, support multicenter research, and facilitate quality improvement initiatives.

Because various clinical practices are implemented even in areas with limited evidence, individual institutions use data from the NRNJ database to benchmark against high-performing centers. By gradually modifying their own management strategies, while continuously assessing individual patients' treatment responses and monitoring trends in institutional outcomes, each center iteratively refines and improves its clinical practice. In addition, NRNJ provides important evidence for antenatal counseling and clinical decision-making regarding at the threshold of viability.

UNIVERSAL HEALTH INSURANCE SYSTEM

Another important factor supporting care is Japan's universal health insurance system. All citizens in Japan are covered by national health insurance, and hospitalization costs for preterm infants admitted to NICUs are largely covered through insurance and public subsidy programs.[14] In particular, the Premature Infant Care Medical Benefit System covers NICU hospitalization expenses for high-risk infants, resulting in essentially no out-of-pocket costs for families.[14] This financial protection allows medical decisions to focus primarily on clinical considerations rather than economic burden.

ETHICAL CONSIDERATIONS AND DECISION-MAKING ON ACTIVE RESUSCITATION

Although Japanese ethical guidelines address communication and decision-making in the care of children with serious illness, including periviable preterm infants, they do not specify gestational age or birth weight thresholds for initiating intensive care in extremely preterm infants.[17] Since the amendment of the Eugenic Protection Act in 1991 (later renamed the Maternal Protection Act), which prohibits induced abortion after 22 weeks of pregnancy, infants born at 22 weeks 0 days' gestation or later have generally been considered viable in Japan.[18]

Following this amendment, some centers gradually began to provide active resuscitation for infants born at 22–23 weeks' gestation.[19] As experience accumulated and early reports suggested that survival outcomes were not as poor as previously expected, an increasing number of hospitals adopted a similar approach.[19] Consequently, many facilities have come to take a more active stance toward resuscitation and intensive care for infants born at these gestational ages.

A recent national survey found that, among infants born at 22 and 23 weeks' gestation in tertiary perinatal centers caring for these infants, approximately 85% and 98%, respectively, received active resuscitation after birth, whereas 15% and 2%, respectively, received palliative care alone.[6] As larger numbers of these infants were actively resuscitated and treated, clinical practices and management strategies also evolved.

Consistent with this trend, data from NRNJ show that survival rates for infants born at 22–23 weeks' gestation improved markedly over the past two decades, suggesting that the accumulation of clinical experience and the development of perinatal care systems may have contributed to improved outcomes (Figs. 1 and 2).[15,20]

DELIVERY MODES AND UMBILICAL CORD MANAGEMENT

Cesarean section

Based on NRNJ data, cesarean section rates at 22 and 23 weeks' gestation were 41% and 73%, respectively, higher than those in other iNeo networks.[1] En caul caesarean delivery, in which the fetus is delivered within intact membranes, is commonly used in many tertiary perinatal centers in Japan.[6,21] The procedure may involve delivery entirely within the intact sac (total en caul) or rupture of the membranes late in the delivery process (partial en caul).[22] Although intended to minimize mechanical trauma, evidence supporting its effectiveness remains limited.

Cut umbilical cord milking

Most NICUs in Japan use cut cord milking—performed after clamping and cutting the umbilical cord—rather than delayed cord clamping for infants born at 22–23 weeks' gestation.

Although the International Liaison Committee on Resuscitation (ILCOR) recommends deferred cord clamping (> 60 s) for preterm infants not requiring immediate resuscitation, deferred cord clamping is not yet common in Japan and most infants born at 22–23 weeks' gestation require immediate resuscitation after birth; therefore, this recommendation is often not applicable.[23,24]

ILCOR guidelines suggest against intact cord milking—performed before cord clamping—in infants born before 28 weeks' gestation because of a possible increased risk of severe IVH.[24] Hemodynamic disturbances, including rapid increases and fluctuations in systemic blood pressure occurring before the reduction in pulmonary vascular resistance, are thought to contribute to this risk.[25,26]

Cut-cord milking may have physiological effects different from those of intact-cord milking. It is typically performed once and slowly after positive pressure ventilation or spontaneous breathing has been initiated.[27] At this stage, pulmonary vascular resistance has decreased, and pulmonary blood flow has increased, allowing additional placental transfusion to be accommodated by the pulmonary circulation.[28] This condition may mitigate the risk of volume overload and blood pressure fluctuation associated with cord milking; however, evidence from human clinical trials remains limited.[24,26,28]

NEONATAL RESUSCITATION AND RESPIRATORY MANAGEMENT

Respiratory care for extremely preterm infants in Japan remains predominantly invasive, in contrast to the global trend toward non-invasive strategies. A national survey showed that the initial trial of continuous positive airway pressure (CPAP) after birth is rare (1%) for infants at 22–23 weeks' gestation, and most are intubated immediately after birth.[6] This approach extends to infants born at 24–28 weeks' gestation.

International data from iNeo indicate that NICUs in Japan more frequently prefer invasive ventilation than other networks.[29] This preference likely reflects the emphasis on immediate respiratory stabilization to improve survival and reduce IVH. Although noninvasive strategies reduce chronic lung disease, Japanese clinicians prioritize early physiological stability, even at the risk of

ventilator-associated lung injury.[30–32] There is limited evidence to suggest that noninvasive respiratory management itself increases the risk of death or IVH. However, previous studies have reported that the failure of noninvasive respiratory support, leading to disturbance in CO_2 levels and subsequent intubation, may be potential risk factors for IVH.[33–36]

Synchronized intermittent mandatory ventilation (SIMV) is the predominant initial ventilation mode, with many centers subsequently switching to high-frequency oscillatory ventilation (HFOV) several days after birth. Concerns about the increased IVH risk from historical studies have limited early HFOV use; however, recent evidence suggests no increased risk.[37,38] Consequently, HFOV is often introduced later —once the risk of intraventricular hemorrhage has decreased—to reduce chronic lung disease through the lung-protective effects of HFOV.[38]

CARDIOVASCULAR MANAGEMENT AND HEMODYNAMIC SUPPORT

One of the most distinctive characteristics of clinical management for extremely preterm infants in Japan is tailored hemodynamic management guided by frequent echocardiography performed by neonatologists.[8,39] In approximately 90% of NICUs, echocardiography is performed at least twice daily during the first 3 days after birth in infants born at 22–23 weeks' gestation.[6] Serial assessments enable meticulous pathophysiology-based management targeting conditions such as myocardial dysfunction with or without afterload mismatch, hypovolemia, hemodynamically significant patent ductus arteriosus (PDA), and pulmonary hypertension (Fig. 4).[6,7] Key echocardiographic parameters commonly used in Japan include: (1) cardiac function and volume status, assessed by left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVDd), the left atrium–to–aortic root ratio (LA/Ao), and inferior vena cava (IVC) diameter; (2) ductus arteriosus status, assessed by ductal diameter, shunt flow pattern, and diastolic flow in the left pulmonary artery; (3) peripheral organ perfusion, assessed by blood flow patterns in the anterior cerebral artery (ACA), renal artery (RA), and superior mesenteric artery (SMA); and (4) pulmonary hypertension, assessed by interventricular septal configuration and tricuspid regurgitation.[6,7]

Because the hemodynamic status of extremely preterm infants often changes within hours after birth, tailoring treatment based on serial echocardiographic and clinical assessments is essential to optimize outcomes. This approach is feasible because most physicians in Japanese NICUs, including neonatologists and NICU fellows, are trained in functional echocardiography.[6]

Several hemodynamic management strategies of extremely preterm infants in Japan are noteworthy, including treatment of afterload mismatch, active treatment of hemodynamically significant PDA, hydrocortisone use for hypotension, and inhaled nitric oxide for pulmonary hypertension.

ASSESSMENT AND TREATMENT OF AFTERLOAD MISMATCH

Approximately 70% of NICUs in Japan assess and treat afterload mismatch in extremely preterm infants.[6] This condition occurs when the immature left ventricle cannot overcome increased systemic vascular resistance (afterload) after birth, resulting in low cardiac output.[39,40] After birth, removal of the low-resistance placental circulation markedly increases systemic vascular resistance, resulting in an increased systemic afterload. The myocardium of extremely preterm infants is structurally immature, with low contractility and low compliance, and may not tolerate even modest increases in afterload.[39,40] A Japanese study by Toyoshima et al. suggested that afterload mismatch in extremely preterm infants may lead to pulmonary hemorrhage and IVH through biventricular congestive heart failure associated with ventricular interaction.[39] Therefore, early recognition and management of afterload mismatch may be important for preventing these serious complications of extremely preterm infants.

End systolic wall stress (ESWS) is used to assess afterload. It is calculated from left ventricular end-diastolic dimension, posterior wall thickness at end-systole, and end-systolic blood pressure (often approximated by mean blood pressure).[39,41] Because ESWS is subject to inter- or intra-observer variability, clinicians often use an integrated assessment that includes left ventricular systolic function

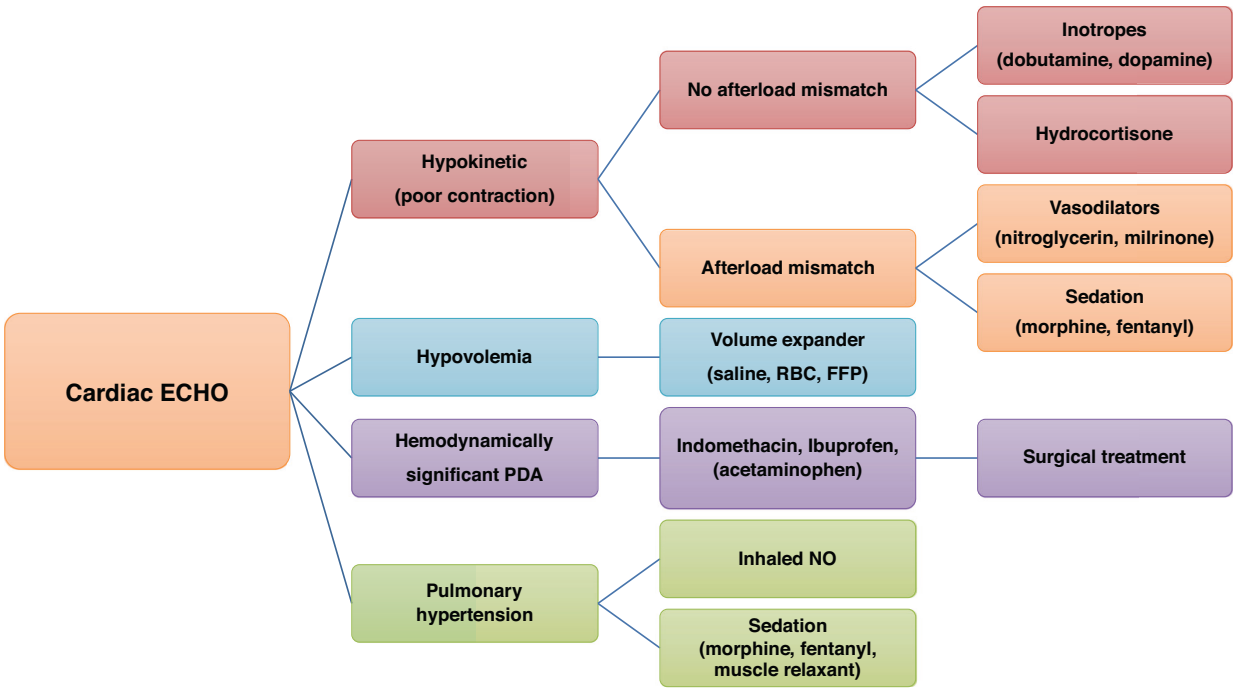


Fig. 4 ECHO-guided circulatory management. This figure is adapted from *Isayama T. Transl Pediatr. 2019;8(3):199* (CC BY-NC-ND 4.0). Abbreviations: ECHO, echocardiography; FFP, fresh frozen plasma, NO, nitric oxide; PDA, patent ductus arteriosus; RBC, red blood cell.

(e.g., ejection fraction and fractional shortening), ventricular dimensions, and blood pressure in addition to ESWS.[42] Vasodilators (e.g., nitroglycerin, milrinone) are the most frequently used treatments, followed by diuretics and sedations and analgesia.[6]

MANAGEMENT OF PATENT DUCTUS ARTERIOSUS

Most NICUs in Japan actively treat hemodynamically significant PDA. The iNeo survey showed that 85% of NICUs treat pre-symptomatic PDA based on echocardiography findings, higher than in other iNeo networks (6–75%).[43]

Although PDA management remains controversial, recent evidence indicated that early pharmacologic treatment does not improve outcomes and may increase mortality.[44–46] A recent large randomized controlled trial reported similar findings.[47] Based on these data, updated clinical practice guidelines in Japan discourage routine COX inhibitor use within the first 7 days but recommend individualized decision-making based on clinical and echocardiographic findings.[48]

A multicenter cohort study demonstrated that COX inhibitor therapy in Japan is typically initiated early (majority within 48 h) and discontinued after one or two doses (i.e., before the full course of three doses was completed) based on repeated echocardiographic assessment, representing an early, response-guided strategy.[43] Notably, such an approach has not been evaluated in previous randomized controlled trials.

Prophylactic indomethacin is used in approximately 65% of NICUs.[6,8] In practice, prophylactic courses are often discontinued after a single dose (59%) or converted to therapeutic treatment (20%), with modifications to the dose, dosing interval, and/or administration rate, and only 10% complete the full three-dose course.[8] This approach further reflects a tailored, echocardiography-guided approach to PDA management.

HYDROCORTISONE USE FOR HEMODYNAMIC STABILIZATION

Hydrocortisone is frequently used to treat or prevent hypotension in extremely preterm infants in Japan during both the acute and chronic phases. In the acute phase, a majority of NICUs (57%) administer corticosteroids within the first 3 days after birth, primarily to prevent or treat hypotension.[6] Notably, approximately one-third of NICUs routinely administer corticosteroids within 24 h after birth regardless of hypotension.[6]

A multicenter cohort study in Japan reported that 37% of infants born at 23–29 weeks' gestation received hydrocortisone within the first 3 days after birth.[49] Although timing and dosing may vary, hydrocortisone is typically administered once or twice at 0.5–2 mg/kg per dose early after birth (often within 24 h). This differs from prior trials evaluating early hydrocortisone for CLD, in which treatment was continued for 7–12 days after birth (e.g., PREMILOC trial).[50–52] In Japan, only a few doses of hydrocortisone are typically used to stabilize hemodynamics and prevent or treat hypotension with the aim of improving survival or reducing IVH.

Hydrocortisone is also used to treat late-onset circulatory collapse (LCC), typically occurring 2–3 weeks after birth. LCC is characterized by sudden onset of hypotension, oliguria, hyponatremia, pulmonary edema, and increased oxygen demand, with a marked response to hydrocortisone.[53,54] It is thought to result from a relative adrenal insufficiency under stress.[55] Incidence increases with decreasing gestational age, affecting approximately 20–30% of infants born at 22 and 23 weeks' gestation in Japan.[15] Because LCC is associated with adverse neurodevelopmental outcomes, early diagnosis and treatment are considered important.[56]

INHALED NITRIC OXIDE FOR PPHN

A national survey reported that 72% of the NICUs in Japan use inhaled nitric oxide (iNO) for persistent pulmonary hypertension of the newborn (PPHN) in extremely preterm infants.[57] The majority of these NICUs initiated inhaled nitric oxide at ≤10 ppm.[57] Importantly, all NICUs using inhaled nitric oxide confirmed PPHN using echocardiography (e.g., measurements of peak velocity of tricuspid regurgitation, detection of right-to-left shunt via ductus arteriosus or foramen ovale, and assessment of interventricular septal configuration).[57] Differences between pre- and post-ductal oxygen saturation (SpO_2) are also used to detect PPHN.[57] The survey showed that most NICUs recognized the importance of distinguishing true pulmonary hypertension, defined as elevated pulmonary arterial pressure due to increased pulmonary vascular resistance, from right-to-left shunting secondary to systemic hypotension despite normal pulmonary arterial pressure when determining treatment strategies.[57] For true pulmonary hypertension, iNO is considered first-line therapy. In contrast, for right-to-left shunting due to systemic hypotension, initial management focuses on hemodynamic stabilization using anti-hypotensive measures (e.g., volume expansion, catecholamines, and corticosteroids).[57]

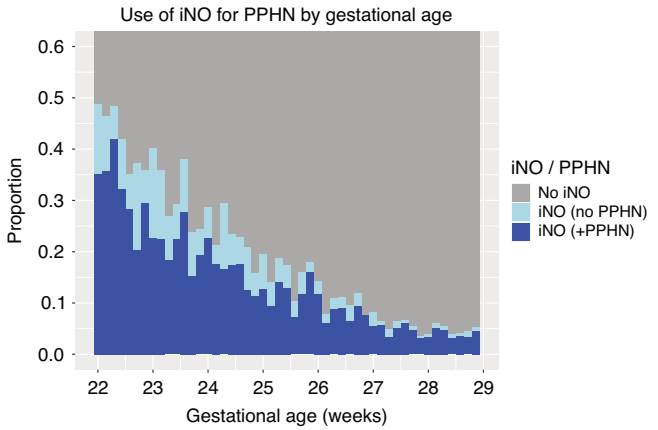


Fig. 5 Use of iNO for PPHN by gestational age. Data from the Neonatal Research Network of Japan database, including infants born in 2018–23, excluding infants with major congenital malformations. The "iNO (+ PPHN)" is considered iNO use for PPHN. The "iNO (no PPHN)" is considered iNO for other conditions such as pulmonary hypertension related to chronic lung disease. Abbreviation: iNO, inhaled nitric oxide; PPHN, persistent pulmonary hypertension of newborn

Use of iNO has increased over time, even among infants born at 22–23 weeks' gestation.[58] According to the NRNJ data, approximately 30% of infants at 22 weeks and 15–20% of infants at 23 weeks receive iNO for PPHN (Fig. 5). In Japan, the use of iNO is not restricted by gestational age and is indicated for hypoxic respiratory failure with pulmonary hypertension.[59] Post-marketing data suggest comparable effectiveness in preterm infants born at <34 weeks' gestation and more mature infants.[59]

NEUROPROTECTION AND BRAIN INJURY SURVEILLANCE

Frequent cranial ultrasound monitoring

The first 72 h after birth are critical for preventing IVH, as approximately 80% of IVH occurs during this period.[60] During this critical period, in most Japanese NICUs, cranial ultrasound is performed two to three times per day.[6] This practice differs from recommendations from the American Academy of Pediatrics, which suggest screening at 7–10 days of age.[61] Serial cranial ultrasound is used to detect new IVH and assess cerebral blood flow. When new low-grade IVH is detected, efforts are made to prevent progression to severe IVH. These measures may include increasing sedation and analgesia, optimizing cardiopulmonary status, correcting coagulopathy as needed, and minimizing handling. However, evidence supporting the effectiveness of these strategies in preventing IVH progression is limited.

Frequent imaging also helps estimate the timing of IVH onset and potential triggers, such as desaturation after suctioning, a rapid rise in blood pressure after severe hypotension, or hemodynamic changes related to PDA.[62]

Sedation and analgesia during acute phase after birth

Approximately three-fourths of Japanese NICUs use sedatives and analgesics in the majority of mechanically ventilated infants born at 22–23 weeks' gestation during the first week after birth.[6] Opioids (fentanyl and morphine) are most commonly used, followed by phenobarbital.[6] These agents are primarily used to prevent IVH, although existing evidence does not support this indication.[63–65]

Several RCTs have evaluated opioid use in preterm infants; however, the overall evidence base is largely influenced by the NEOPAIN trial conducted by Anand et al.,[66] which had the largest sample size.[63,66] Opioids, particularly morphine, are associated with the increased risk of hypotension, a known risk factor of IVH.[66] A secondary analysis of the NEOPAIN trial reported that hypotension during or after morphine infusion was not significantly associated with severe IVH.[67] In Japan, meticulous hemodynamic management using frequent echocardiography may mitigate the adverse effects of opioid-associated hypotension.[39]

Gentle nursing care

Specialized nursing care may contribute to the high survival rates of extremely preterm infants in Japan, although evidence is limited. Nursing care in Japan emphasizes individualized developmental care, whereby nurses tailor care, paying close attention to every detail, such as securing tape, to each infant to minimize stress and pain and support neurodevelopment based on careful observation of infant behavior. In the acute phase, infants born at <28 weeks' gestation are typically cared for by nurses with at least 2–3 years of experience, whereas those born at 22–23 weeks' gestation are usually managed by nurses with at least 3–5 years of experience. Key characteristics of the nursing care in Japan include minimal and gentle handling with close monitoring of physiological stability and stress cues, maintenance of appropriate body positioning, and meticulous skin care.[68]

Minimal and gentle handling

To ensure minimal and gentle handling, Japanese NICU nurses warm their hands and medical equipment (e.g., stethoscopes, thermometers) before contact, closely monitor infants' physiological stability and stress signs, and minimize both the frequency and duration of handling. When necessary, nurses perform "holding" (gentle containment using both hands) to reduce stress during care. For moderately stressful procedures, such as endotracheal suctioning or repositioning, care is often performed by two nurses, typically until around 28 weeks' postmenstrual age.

Body positioning

Appropriate body positioning is considered essential to stabilize vital signs, reduce stress, and promote neurodevelopment. Positioning cushions or products (either commercially available or locally prepared) are commonly used for nesting or swaddling, with limbs flexed and shoulders adducted. Infants are initially placed in the supine position for at least 72 h after birth and are transitioned to the prone position after several days, once umbilical catheters are removed and the risk of IVH is reduced.[6] In the prone position, an appropriately sized cushion is placed under the infant's chest and abdomen. This allows the infant to embrace the cushion with the limbs, promoting a flexed, fetal-like posture, with the head positioned slightly lower than the back. Approximately half of NICUs in Japan use midline head position in the acute phase after birth.[6]

Skincare

Infants born at 22–23 weeks' gestation have extremely fragile skin characterized by a thin epidermis, an underdeveloped stratum corneum, and a fragile dermis with limited collagen and elastic fiber. Urethane mattresses developed by the Japan Society of Pediatric Stoma and Continence Management are often used.[69]

During the hyperacute phase, when repositioning is not possible, body pressure is relieved by placing a hand under the sheet on the infant's back. To prevent medical device related pressure ulcers or injuries, non-adhesive gauze may be placed under monitoring probes, probes may be cut to minimize their sizes, and heart rates may be monitored using SpO_2 alone without ECG leads. Various skin dressings (e.g., silicone-based non-adhesive gauze, polyurethane foam) are often used to prevent or treat skin injuries.

High incubator humidity (90–95%) is often used to reduce insensible water loss and is gradually reduced by approximately 5% every 2–3 days to promote skin maturation.

Sponge bathing with sterile warm water is initiated around one week after birth for heavily soiled areas (groin, axilla, neck, and postauricular). Although routine ointment use is uncommon, white petrolatum may be applied to dry or erythematous areas.

CERTIFIED NURSES IN NEONATAL INTENSIVE CARE

The Certified Nurses in Neonatal Intensive Care (CNs-NIC) program is Japan's only formal post-diploma neonatal nursing education and is not degree-based.[70,71] There are no other specialized or advanced neonatal nurse courses, such as clinical nurse specialists or nurse practitioners in the USA.[72]

Currently, only one institution offers a one-year CNs-NIC training program. Admission requires at least five years of clinical experience, including three years in neonatal care. Currently, approximately 400 CNs-NIC are practicing nationwide, with most tertiary NICUs caring for infants born at 22–23 weeks' gestation employing one or two CNs-NIC.

After training completion, CNs-NIC obtain outstanding knowledge and skills of bedside neonatal nursing. CNs-NIC play key roles in delivering high-quality advanced care, educating NICU staff, developing protocols, and promoting family-centered care. Although many CNs-NIC publish clinical articles in Japanese, peer-reviewed English publications are limited. The lack of academic faculty and structured research training programs for neonatal nursing have hindered the development of multicenter neonatal nursing research in Japan, representing a major ongoing challenge.

OTHER ASPECTS (NUTRITIONAL MANAGEMENT AND INFECTION CONTROL)

Nutritional management

Nutritional management of infants born at 22–23 weeks' gestation in Japan includes early enteral feeding (typically within the first day of life), use of probiotics (mainly Bifidobacterium species), and oropharyngeal administration of small amounts of breast milk.[6] Feeding practices vary across institutions, but many NICUs initiate feeding at 0.5–1.0 mL per feed, administered eight times daily, and advance volumes by 10–20 mL/kg/day (based on nationwide survey data not included in the published report).[6]

Donor human milk use has increased since the establishment of the Japan Human Milk Bank Association in 2017. However, its availability remains limited and it is currently used in only approximately half of NICUs managing these infants.[6]

A distinctive practice in Japan is the routine use of glycerin enemas, typically initiated within the first 3 days after birth and administered two to three times daily. While this may facilitate meconium passage, evidence for benefits on clinically important outcomes, such as feeding advancement or prevention of necrotizing enterocolitis, remains limited.[73]

Infection control

In Japan, infection control is characterized by frequent measurement of C-reactive protein (CRP).[7] Although CRP is not useful for the early detection of rapidly progressive infections due to its delayed rise, it may help identify more slowly evolving infections, assess treatment response, and support the diagnosis of culture-negative sepsis. Routine glove use during patient examinations is also common.[6] Furthermore, approximately two-thirds of NICUs administer immunoglobulin to infants born at 22–23 weeks' gestation, either routinely or when immunoglobulin levels are low, and approximately three-quarters routinely administer antifungal agents.[6] However, evidence supporting the effectiveness of these practices remains limited. While rates of late-onset sepsis among extremely preterm infants in Japan are reportedly lower than those in other countries, the extent to which this is attributable to these practices remains unclear.[74]

CONCLUSIONS AND FUTURE DIRECTIONS

Table 1 summarizes the key characteristics of NICU systems and clinical practice for infants born at 22–23 weeks' gestation in Japan. Overall, management is characterized by a pathophysiology-based approach that accounts for the extreme immaturity of all organ systems, combined with meticulous, individualized care guided by continuous assessment of each infant's condition. In particular, intensive management aimed at preventing IVH during the first week after birth is a defining feature. Furthermore, even in areas with limited evidence, institutions monitor their own outcomes, evaluate individual responses to treatment, and—drawing on data from the NRNJ database as well as practices from high-performing centers—develop and iteratively refine institution-specific care packages.

It remains unclear which practices contribute to favorable outcomes in Japan. The NRNJ database is not designed to identify which specific clinical practices directly contribute to improved survival, nor can it determine whether certain interventions may be redundant or potentially counterproductive. Evidence is limited, and future research is needed to evaluate the effectiveness of commonly used strategies in Japan.

Randomized clinical trials are essential for evaluating individual interventions; however, they may not be feasible for many aspects of care. Moreover, individual practices may not be effective in isolation,

Table 1. Summary of NICU system characteristics and clinical practices for infants born at 22–23 weeks' gestation in Japan.

System-level approach
• Regionalized perinatal health system with comprehensive perinatal centers providing both high-level obstetric maternal-fetal care and advanced neonatal care.
• The Neonatal Research Network of Japan as a platform for neonatal research and quality improvement
• Universal health insurance system providing all citizens with access to advanced neonatal care
Consensus favoring survival-focused care
• Active resuscitation for infants born at 22–23 weeks' gestation
Delivery, resuscitation, and respiratory management
• En caul cesarean section
• Cut-cord milking
• Immediate intubation after birth
• Initial SIMV, often transitioned to HFOV after several days
Cardiovascular management
• Individualized hemodynamic management using frequent echocardiographic assessment performed by neonatologists
• Assessment and treatment of afterload mismatch
• Proactive treatment of hemodynamically significant PDA
• Hydrocortisone use for hemodynamic stabilization or treatment of hypotension
• Low threshold to initiate inhaled nitric oxide for PPHN, guided by frequent echocardiographic assessment
Neuroprotection
• Close monitoring of IVH and cerebral blood flow using frequent cranial ultrasonography
• Use of sedation and analgesia during the acute postnatal phase
Nursing care
• Minimal and gentle handling, with close attention to physiological stability and stress signs
• Maintaining appropriate positioning and posture using cushions or positioning device
• Meticulous skin care to prevent pressure ulcers and medical device-related skin injuries
• High ambient humidity during the acute phase
• Certified nurses in neonatal intensive care (CNs-NIC) providing high-quality advanced care and contributing to education and training NICU staff
Other aspects
• Early enteral feeding with probiotics supplementation
• Routine use of glycerin enema
• Use of gloves during infant examinations
• Frequent monitoring of C-reactive protein

HFOV high-frequency oscillatory ventilation, *IVH* intraventricular hemorrhage, *PDA* patent ductus arteriosus, *SIMV* synchronizing intermittent mechanical ventilation

as multiple components of care are interdependent. Accordingly, there may be no single optimal approach, and different combinations of strategies may contribute to improved outcomes. This concept is consistent with previous reports demonstrating substantial variation in clinical practices among high-performing centers caring for infants born at 22–23 weeks' gestation.[6,75–78] Therefore, a package of care, rather than a single intervention, may be necessary to improve outcomes.[78] Continuous outcome monitoring and institutional quality improvement efforts are also important, enabling iterative refinement of context-specific care packages.[78,79]

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design of the study, and to the acquisition, analysis, and interpretation of data. T.I. drafted the manuscript. H.N., M.K., M.Ko., M.F., S.H. and S.K. critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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