

## ***Invited Comment***

# **Care of Children With Trisomy 18 in Japan**

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Management of neonates with trisomy 18, a common and important chromosomal syndrome, is controversial. Withholding or withdrawal of intensive treatment (cesarean, resuscitation, respiratory support, and surgery) has been recommended because of the short life span (median survival time: 10–15 days; survival at age 1 year 5–10% [Rasmussen et al., 2003]) and profound mental retardation by many in the medical literatures [Bos et al., 1992; Paris et al., 1992]. Some authors indicated that management should be individualized and intensive treatment could be considered, placing significant weight on parental decision making in the context of the “best interests of the child” [Carey, 2005; Jones, 2006]. Cardiac surgery, an emblematic procedure of intensive treatment, has not been considered to be justified in infants with trisomy 18 by most institutes throughout the world. The most commonly cited evidence is based on the population-based study in the Northern sector of the Northern and Yorkshire Health Region [Embleton et al., 1996], showing that central apnea was the most common mode of deaths and that cardiac defects had been implicated in deaths in only 9% of patients, who had hypoplastic left heart and whose median survival time was 2 days. The modes of deaths in the others were described as “never stabilized” in 26% (median survival time: 4 hr), “apnea” in 29% (5 days), “episodic cyanosis” in 12% (3 days), “sepsis” in 9% (5 months), “extubation” in 9% (3 days), and “unknown” in 6% (28 days).

We showed, based on the data from Nagano Children’s Hospital, Japan, improved survival (median survival time 152.5 days; survival rate at age 1 year 25%) of patients with trisomy 18 who received intensive treatment consisting of resuscitation including intratracheal intubation, appropriate respiratory support, establishment of enteral nutrition including corrective and palliative surgery for gastrointestinal malformation, and pharmacological intervention for cardiac lesions. The common underlying factors associated with deaths were congenital heart defects and heart failure (96%), followed by pulmonary

hypertension (78%); the common final modes of deaths were sudden cardiac or cardiopulmonary arrest (26%) and progressive pulmonary hypertension-related events (26%) [Kosho et al., 2006]. Supposedly, both of these two studies did show “natural history” of patients with trisomy 18, with the former indicating that of patients on whom intensive treatment was withheld or withdrawn once the diagnosis was made and the latter showing that of patients who received intensive treatment without cardiac surgery.

In this volume, Kaneko et al. [2008] from Tokyo, Japan, show significantly improved survival of patients with trisomy 13 or 18 (median survival time 238 days; survival rate at age 1 year 29% for 7 patients with trisomy 18) through intensive cardiac management including pharmacological intervention for ductal patency and cardiac surgery. To my knowledge, this is the first series, which attempts to discuss efficacy of intensive cardiac treatment including surgery for patients with trisomy 13 or 18, although the sample size is small.

Worldwide readers of this journal may be interested in Japanese physicians’ attitudes toward critically sick neonates like trisomy 18. In this *Invited Comment*, I describe a brief history of how these patients have been treated and cared in Japan. In 1987, Nishida from Tokyo reviewed ethical issues in perinatal and neonatal medicine in Japan. In the article, Nishida reported data of a questionnaire-based analysis of ethical issues in neonatal medicine. The survey, administered to 35 leading neonatologists, was designed to demonstrate the circumstances of treating and caring for critically sick neonates at that time in Japan: treatment had been

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TABLE I. The Classification in Medical Decision Making of Caring Sick Neonates in Maternal and Perinatal Center of Tokyo Women's Medical University

Class A: All the possible treatment
Class B: Limited treatment (withholding of such aggressive treatment as major surgery and hemodialysis); for example, epidermolysis bullosa, congenital myopathy
Class C: Continue current treatment, including routine care such as temperature control, internal nutrition, skin care, and love; for example, trisomy 13, trisomy 18, anencephaly, severe asphyxia in a neonate <500 g or <25 weeks of gestation, and severe intraventricular hemorrhage in a extremely low birth weight neonate
Class D: Discontinue all treatment

From Nishida [1987] and Nishida et al. [1987].

withheld or withdrawn in 4.4% of neonates; 71% of the respondents had the experience of withdrawing treatment of sick neonates; 46% of the respondents would resuscitate actively asphyxiated neonates with trisomy 13 or trisomy 18 [Nishida, 1987]. Nishida [1987] also introduced a classification in medical decision making of caring for sick neonates adopted in Maternal and Perinatal Center of Tokyo Women's Medical University (Table I). It was based on a guideline proposed by Duff [1979] for deciding care of critically ill or dying patients, which classified patients into three categories: maximal therapeutic effort without reservation; selective limitation of therapeutic measures; and discontinuance of life-sustaining therapy. Nishida [1987] added a new category (Class C) in which no additional treatments were considered but ongoing life-supporting pro-

cedures or routine care was not withdrawn. This was included as in Japan where withdrawal of life-supporting procedures was not protected legally and any medical measure hastening deaths of patients were not acceptable to the general population. In another paper by Nishida et al. [1987], trisomy 18 was classified into this category (Table I). Nishida [1987] also mentioned that the category of withdrawal of all medical treatment (Class D) was not applicable to Japan. Another important point of the institutional classification was that the final decision should not be made by parents but by a physician in charge of the neonatal intensive care unit, for the purpose of relieving a burden on the parents of making such a critical decision [Nishida, 1987]. This classification has had a major impact on the field of neonatology in Japan; however, patients with trisomy 18 have actually been managed according to an individual approach at each hospital.

In 2003, we performed a questionnaire-based analysis of patients with trisomy 18 and the families who belonged to Trisomy 18 Support Group in Japan (<http://18trisomy.com/>). In the series, a little less than 40% of patients were offered intensive treatment by their attending physicians [unpublished observation]. To date, 29 patients were reported to have a total of 38 cardiac surgeries in Japan, according to literature including regional publications, abstracts of medical meetings, and information from the support group. One of the most important social factors enabling such management is probably secure national health insurance

TABLE II. Guidelines for Healthcare Providers and Parents to Follow in Determining the Medical Care of Newborns with Severe Disease

- (1) All newborns have the right to be protected and to receive appropriate medical care.
- (2) Parents have the right and also the obligation to determine the course of their children's medical treatment as caretakers who are responsible for their children's growth and development.
- (3) Determination of the course of medical treatment must be based on the "best interests of the child".
- (4) Parents and healthcare providers must fully discuss all options in the process of making decisions regarding treatment.
- (5) Healthcare providers must attempt to establish a trusting relationship with the child's parents and treat them as equal partners in the decision-making process.
- (6) Healthcare providers have the obligation to promptly and accurately provide parents with all information regarding their child's condition and all treatment options, and to explain such in language that can be understood by the parents.
- (7) Healthcare providers should have the opportunity to present their opinions and information they are familiar with, and to express their emotions concerning the treatment of newborns.
- (8) The attending physician should determine the child's prognosis based on the latest medical information available given the child's condition, and should consult with physicians of other specialties and healthcare providers of other disciplines as necessary.
- (9) Withdrawal or withholding of life-sustaining medical treatment (hereinafter referred to as LSMT) must be discussed with extreme caution, as it could have irreversible consequences for a child's life. If parents or healthcare providers propose the withdrawal or withholding of LSMT, the "best interests of the child" must be fully discussed, complying with the principles set forth in Article 1 to Article 8.
  - 1) In considering withdrawal or withholding of LSMT, as many physicians as possible who are involved in the child's medical treatment should exchange opinions concerning this.
  - 2) In considering withdrawal or withholding of LSMT, it is necessary for physicians to fully discuss with the parents all available options. In so doing, the attending physician must, in the presence of other healthcare team members, listen to the parents' opinions and confirm their intentions.
  - 3) When the decision is made to withdraw or withhold LSMT, the following must be documented on the child's medical chart: the reason the decision was judged to be in the "best interests of the child," the process of decision and content of discussions with the family.
  - 4) Even after a decision to withdraw or withhold LSMT is made, medical treatment must be pursued in order to comply with the "best interests of the child," and maximum support should be given to the family.
- (10) The course of treatment should be able to be altered depending on changes in the child's condition or the wishes of the parents. Healthcare providers must inform parents in advance that they can modify the decision at any time if they wish.

From the website of Saitama Medical Center (<http://www.saitama-med.ac.jp/kawagoe/link08/link22/guidelines.html>).

covering almost all costs of medical treatment to every sick child.

Serious problems have been pointed out while acting according to the classification by Nishida: physicians' paternalistic attitudes toward parents of critically sick neonates that could suppress parental autonomy; physicians' cessation of consideration about management of these neonates because several disorders, including trisomy 18, were exemplified in the classification.

Tamura [2004] from Saitama and his colleagues proposed a guideline entitled "Guidelines for Health-care Providers and Parents to Follow in Determining the Medical Care" (<http://www.saitama-med.ac.jp/kawagoe/link08/link22/guidelines.html>) (Table II). Before proposing these guidelines, they sent a questionnaire about treating and caring for critically sick neonates to 207 institutes for neonatal medicine throughout Japan and 107 institutes replied to it. Forty-four percent of the institutes answered that they had had patients in whom withholding or withdrawal of treatment had been considered, and that the most common condition was trisomy 18. The guidelines do not present concrete management categories of severe disorders, but present a general principle of coping with families of critically sick neonates, stressing the importance of frank discussion and equal communication between medical staffs and families for seeking the "best interests of the babies." Currently, conscientious efforts are being made to disseminate the guidelines.

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