

# Neonatal Management of Trisomy 18: Clinical Details of 24 Patients Receiving Intensive Treatment

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Management of neonates with trisomy 18 is controversial, supposedly due to the prognosis and the lack of precise clinical information concerning efficacy of treatment. To delineate the natural history of trisomy 18 managed under intensive treatment, we reviewed detailed clinical data of 24 patients with full trisomy 18 admitted to the neonatal intensive care unit of Nagano Children's Hospital, providing intensive treatment to those with trisomy 18, from 1994 to 2003. Cesarean, resuscitation by intubation, and surgical operations were performed on 16 (67%), 15 (63%), and 10 (42%) of the patients, respectively. Mechanical ventilation was required by 21 (88%), and 6 (29%) of them were extubated. Survival rate at age 1 week, 1 month, and 1 year was 88%, 83%, and 25%, respectively. Median survival time was 152.5 days. Respiration was not stabilized in two patients

with left diaphragmatic eventration and hypoplasia accompanied by lung hypoplasia, even with maximal ventilation. The common underlying factors associated with death were congenital heart defects and heart failure (96%), followed by pulmonary hypertension (78%). The common final modes of death were sudden cardiac or cardiopulmonary arrest (26%) and possible progressive pulmonary hypertension-related events (26%). These data of improved survival, through neonatal intensive treatment, are helpful for clinicians to offer the best information on treatment options to families of patients with trisomy 18. © 2006 Wiley-Liss, Inc.

**Key words:** trisomy 18; neonate; intensive treatment; natural history; survival; causes of death

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## INTRODUCTION

Trisomy 18, first described by Edwards et al. [1960], is the second most common autosomal trisomy in liveborn infants. Patients with trisomy 18 have prenatal-onset severe growth retardation, characteristic craniofacial features, various visceral and skeletal malformations, and significant psychomotor mental retardation [Carey, 2001]. Several population-based studies showed a remarkably reduced life-span, with survival rates at age 1 year from 0 to 10% and with median survival time from 3 to 14.5 days [Carter et al., 1985; Young et al., 1986; Goldstein and Nielsen, 1988; Root and Carey, 1994; Embleton et al., 1996; Naguib et al., 1999; Nembhard et al., 2001; Brewer et al., 2002; Rasmussen et al., 2003]. The major causes of death were reported to be apnea and withdrawal of treatment [Embleton et al., 1996], and the presence of a congenital heart defect did not

seem be associated with early death [Embleton et al., 1996; Rasmussen et al., 2003].

Management of neonates with trisomy 18 is controversial. Withdrawal of intensive treatment such as cesarean, resuscitation, respiratory support, and surgical procedures has been recommended because of the lethality and severe mental retardation [David and Glew, 1980; Schneider et al., 1981; Carter et al., 1985; Rochelson et al., 1986; Goldstein and Nielsen, 1988; Bos et al., 1992; Embleton et al., 1996].

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It has also been argued that management should be individualized and intensive treatment should be considered in patients who could be expected longer survival and better quality of life through such treatment [Van Dyke and Allen, 1990; Carey, 2001; Derbent et al., 2001]. This controversy is related to lack of precise clinical data on survival and causes of death, evaluated in the aspect of efficacy of treatment.

Nagano Children's Hospital, established in 1993 as a tertiary prefectural hospital for sick children, has received neonates who were born in Nagano prefecture and required intensive care due to prematurity, asphyxia, and congenital malformation. Neonatologists of this hospital have often helped to resuscitate, stabilize, and transfer sick babies at other regional hospitals and obstetric clinics. Since 2000, when the obstetric department was established in this hospital, pregnant women whose fetuses were found to have severe abnormalities by ultrasonography have also been referred for further evaluation, genetic counseling, and delivery. In the neonatal intensive care unit of this hospital, patients with trisomy 18 have been managed under the principle of providing intensive treatment, based on careful discussion with the parents. The management consists of resuscitation including intratracheal intubation, appropriate respiratory support, establishment of enteral nutrition including corrective and palliative surgery for gastrointestinal malformation, and pharmacological treatment for congenital heart defects. To delineate the natural history of trisomy 18, and specifically survival and causes of death under this principle of intensive management, we reviewed detailed clinical data on patients with trisomy 18 admitted to this hospital from 1994 to 2003.

## METHODS

### Patients

Twenty-six patients with karyotypically confirmed trisomy 18 were admitted to the neonatal intensive care unit of Nagano Children's Hospital from April 1994 to March 2003. We excluded two patients with 47,XX, +18/46,XX mosaicism, and evaluated the other 24 patients with full trisomy 18 (9 boys, 15 girls) (Tables I and II). Twenty peripheral blood lymphocytes were routinely analyzed for G-banded karyotyping. All the parents were informed of natural history of trisomy 18 based on the medical literature, and were presented the above-mentioned principle of management as an approach to care in this hospital. The parents could choose to accept or refuse this principle. If they refused, accepted part of the treatment was continued in the hospital or in other regional hospitals. After careful discussion, all parents except parents of Patient 9 consented. These

parents refused surgical correction of esophageal atresia; but accepted mechanical ventilation, intravenous hyperalimentation, administration of antibiotics, and blood transfusion.

Eleven patients were transferred to regional hospitals; after the diagnosis was confirmed by karyotyping, their treatment courses were determined and, no extensive procedures such as major surgery were for the time being required, and the parents consented to transfer. In every regional hospital, general pediatricians with training in neonatology continued the treatment according to the same principle.

## Methods

We collected clinical data about prenatal findings, delivery, complications, treatment, survival, and causes of death from medical records in Nagano Children's Hospital and regional hospitals where patients were given medical care before or after transfer.

From careful observation of each patient under intensive treatment, we found that the patients' conditions deteriorated gradually due to complex underlying factors such as heart failure and pulmonary hypertension resulting from congenital heart defects. They frequently died suddenly from cardiopulmonary arrest and possible pulmonary hypertension-related events. Therefore, causes of death were classified into underlying factors associated with death and final modes of death.

## RESULTS

### Prenatal Findings and Delivery

Data on prenatal findings and delivery are summarized in Table I. Fetal ultrasonographic abnormalities were detected during all pregnancies except for Patient 5, whose mother had received no obstetric examinations. However, no patient was diagnosed karyotypically including Patients 1, 16, and 19, who were suspected to have trisomy 18 clinically. Twelve patients were delivered in regional hospitals, seven in obstetric clinics (Patients 4, 8, 15, 16, 22, 23, and 24), four in this hospital (Patients 1, 2, 17, and 19), and one at home (Patient 5). Sixteen patients were born by cesarean (67%), which was elective in four (Patients 4, 16, 21, and 24) and emergent in 12. The common indications for cesarean were fetal distress in ten and intrauterine growth retardation in six. Fifteen patients needed resuscitation by intubation (63%). All but Patients 4, 5, 8, 15, and 22 were resuscitated and stabilized by neonatologists of Nagano Children's Hospital or general pediatricians in regional hospitals. Mean gestational age was 37 weeks and 5 days (range, 31 weeks and 4 days

TABLE I. Prenatal Findings, Delivery, Structural Defects, and Medical Complications

| Patients | Sex | Gestational age (weeks/days) | Birth weight (g) | Apgar score (1 min/5 min) | Prenatal ultrasonographic findings | Cesarean section | Resuscitation by intubation | Congenital heart diseases | Heart failure (neonatal/post-neonatal) | PPHN | Gastrointestinal system          | Respiratory complications | Respiratory failure | Apnea | Seizures | Renal system |
|----------|-----|------------------------------|------------------|---------------------------|------------------------------------|------------------|-----------------------------|---------------------------|--|------|----------------------------------|---------------------------|---------------------|-------|----------|--------------|
| 1        | M   | 36/2                         | 1,048            | 1/1                       | P, IUGR, CHD                       | +                | +                           | AVSD, DORV                | +/                                     |      | TEF                              | TA, DE, LH                | +                   |       |          | HK           |
| 2        | M   | 31/4                         | 1,017            | 2/2                       | P, IUGR                            | +                | +                           | VSD, ASD, PDA             | +/                                     | +    | EA, TEF                          | DE, IH                    | +                   |       |          | HU, RD       |
| 3        | F   | 38/1                         | 2,038            | 6/9                       | P                                  | +                | +                           | PA, PDA                   | +/                                     |      |                                  |                           | +                   | +     |          |              |
| 4        | F   | 39/3                         | 1,956            | 2/4                       | P, IUGR, CHD                       | +                | +                           | VSD, ASD, PDA             | +/                                     |      | EA, TEF                          |                           | +                   |       | +        |              |
| 5        | F   | 41/1                         | 1,880            | —                         |                                    |                  |                             | VSD, PDA                  | +/+                                    |      |                                  |                           | +                   |       |          |              |
| 6        | M   | 35/4                         | 1,310            | 7/8                       | P, IUGR                            | +                | +                           | VSD, ASD                  | +/+                                    |      | EA, TEF                          | RDS, A                    | +                   |       | +        |              |
| 7        | F   | 38/3                         | 2,125            | 4/9                       | P                                  |                  |                             | VSD, ASD, PDA             | +/+                                    |      |                                  | TH, A                     | +                   |       | +        |              |
| 8        | F   | 40/6                         | 1,948            | 4/4                       | P, IUGR                            |                  |                             | VSD, PDA, CoA             | +/+                                    |      | EA, TEF, MI                      |                           | +                   |       | +        | HN           |
| 9        | M   | 36/0                         | 1,220            | 4/7                       | P, IUGR, EA                        | +                | +                           | VSD, PDA                  | +/+                                    |      |                                  |                           | +                   |       |          |              |
| 10       | F   | 42/0                         | 2,094            | 2/—                       | P, IUGR                            | +                | +                           | VSD, PDA                  | +/+                                    |      |                                  |                           | +                   |       |          |              |
| 11       | M   | 36/4                         | 1,552            | 2/3                       | IUGR                               | +                | +                           | VSD, PDA                  | +/+                                    |      | AA                               |                           | +                   |       |          |              |
| 12       | M   | 37/5                         | 2,018            | 2/2                       | P, IUGR, CHD, O                    | +                | +                           | TOF                       | +/+                                    | +    | O, M                             | TB, A                     | +                   |       |          |              |
| 13       | F   | 35/0                         | 1,177            | 3/6                       | IUGR                               | +                | +                           | VSD, ASD, PDA, CoA        | +/+                                    |      | EA, TEF, GER                     | RDS                       | +                   |       | +        |              |
| 14       | F   | 36/4                         | 1,804            | 1/1                       | P, IUGR, EA                        | +                | +                           | VSD, PDA                  | +/+                                    | +    | GER                              | RDS, A, BM                | +                   |       | +        |              |
| 15       | F   | 40/2                         | 2,135            | 7/10                      | P, IUGR                            | +                | +                           | VSD, PDA                  | +/+                                    |      |                                  |                           | +                   |       |          |              |
| 16       | F   | 40/5                         | 1,810            | 6/6                       | IUGR, CHD, EA                      | +                | +                           | VSD, DORV, PDA            | +/+                                    |      |                                  | LH                        | +                   |       |          | HN, HU       |
| 17       | F   | 41/2                         | 1,670            | 5/8                       | P, IUGR, CHD                       | +                | +                           | VSD, PDA                  | +/+                                    |      | AA                               |                           | +                   |       |          |              |
| 18       | M   | 36/6                         | 1,746            | 1/3                       | P, IUGR                            | +                | +                           | TOF, ASD                  | +/+                                    | +    |                                  | RDS                       | +                   |       |          |              |
| 19       | M   | 38/0                         | 2,042            | 1/4                       | P, IUGR, CHD                       | +                | +                           | VSD, ASD                  | +/+                                    | +    | GER                              | LH                        | +                   |       |          |              |
| 20       | F   | 36/2                         | 1,523            | 4/8                       | P, IUGR, CHD                       | +                | +                           | VSD, PDA (closed)         | +/+                                    |      |                                  | RDS                       | +                   |       |          |              |
| 21       | M   | 37/4                         | 1,747            | 4/6                       | P, IUGR, EA                        | +                | +                           | VSD                       | +/+                                    | +    | EA, TEF, AA                      | RP, CT                    | +                   |       | +        | HN, RUTI     |
| 22       | F   | 36/1                         | 1,422            | 8/9                       | P, IUGR                            |                  |                             | VSD (closed)              | +/+                                    |      | EA, TEF, AA, GER, PS (suspected) | A, RP                     | +                   |       | +        | RUTI         |
| 23       | F   | 38/3                         | 1,624            | 8/9                       | IUGR                               | +                | +                           | PDA (closed)              | -/-                                    |      |                                  | DE                        |                     |       |          |              |
| 24       | F   | 35/1                         | 1,420            | 5/8                       | P, IUGR                            | +                | +                           | PA, VSA, PDA              | +/+                                    |      | EA, TEF                          | RDS, A, RP                | +                   |       | +        |              |

M, male; F, female; P, polyhydramnios; IUGR, intrauterine growth retardation; CHD, congenital heart defects; EA, esophageal atresia; O, omphalocele; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; PA, pulmonary atresia; CoA, coarctation of aorta; TOF, tetralogy of Fallot; PPHN, persistent pulmonary hypertension of the newborn; TEF, tracheoesophageal fistula; MI, microileum; AA, anal atresia; M, malrotation; GER, gastroesophageal reflux; PS, pyloric stenosis; TA, tracheal atresia; DE, diaphragmatic eventration; LH, lung hypoplasia; RDS, respiratory distress syndrome; A, atelectasis; TH, tracheal hypoplasia; TB, bronchomalacia; RP, recurrent pneumonia; CT, chylothorax; HK, horseshoe kidney; HU, hydronephrosis; HN, hydronephrosis; RUTI, recurrent urinary tract infection.

TABLE II. Treatment, Prognosis, and Causes of Death

| Patients | Treatment       |                                |                   |                      | Prognosis |                   |                | Causes of death  |     |                      |  |                               |
|----------|-----------------|--------------------------------|-------------------|----------------------|-----------|-------------------|----------------|------------------|-----|----------------------|--|-------------------------------|
|          | Operation       | Mode of mechanical ventilation | Extubation (days) | Cardiovascular drugs | IVH       | Blood transfusion | Anticonvulsant | Discharge (days) | HOT | Survival time (days) | Underlying factors                                       | Final modes of death          |
| 1        |                 | IMV, HFO                       |                   |                      |           |                   |                |                  |     | 0                    | CHD, HF, lung hypoplasia, tracheal atresia, RF, asphyxia | Untreatable RF                |
| 2        | GS              | HFO                            |                   | DO, ISP, NG          |           | F                 |                |                  |     | 1                    | CHD, HF, PH, lung hypoplasia, RF, asphyxia               | Untreatable RF                |
| 3        |                 | IMV, nCPAP                     |                   | DO, PGE1             |           |                   |                |                  |     | 3                    | CHD, HF, PH  | SCA                           |
| 4        | GS              | IMV, nCPAP                     |                   | DO, D                | +         | R, F, P, E        | PB             |                  |     | 12                   | CHD, HF, PH  | Aspiration pneumonia          |
| 5        |                 | IMV, HFO                       |                   | D                    |           | R, F, P           | PB             |                  |     | 31                   | CHD, HF, PH  | SCA                           |
| 6        | GS, EA          | IMV, HFO                       |                   | DO, D                |           |                   |                |                  |     | 32                   | CHD, HF, PH, RF  | Postoperative mediastinitis   |
| 7        |                 | IMV                            |                   | D                    |           |                   |                |                  |     | 35                   | CHD, HF, PH, RF  | PH crisis                     |
| 8        |                 | IMV                            |                   | D, PGE1              |           |                   | PB             |                  |     | 39                   | CHD, HF, PH, infection                                   | SCA                           |
| 9        | GS              | IMV                            |                   | DO, D                | +         | R                 |                |                  |     | 41                   | CHD, HF, PH, malnutrition                                | PHE                           |
| 10       |                 | IMV                            |                   | D                    |           |                   |                |                  |     | 75                   | CHD, HF, PH, RF  | PHE                           |
| 11       | CS              | IMV                            | 10                | D                    |           |                   |                |                  |     | 106                  | CHD, HF, PH, RF, apnea                                   | Progressive RF                |
| 12       | O               | IMV                            | 12                | D, BB                |           |                   |                |                  |     | 145                  | CHD, HF  | Anoxic spell                  |
| 13       |                 | IMV, HFO                       | 51                | DO, PGE1             |           | R                 |                |                  |     | 160                  | CHD, HF, PH, RF  | SCA                           |
| 14       | GS, EA          | IMV, HFO, nCPAP                | 109               | DO, NG, D            | +         | R, F              | PB             | 137              | +   | 210                  | CHD, HF, PH, RF, apnea                                   | Sudden cardiopulmonary arrest |
| 15       |                 | IMV                            |                   | DO, D                |           | R                 |                |                  |     | 218                  | CHD, HF, PH, RF  | PHE                           |
| 16       |                 | IMV                            |                   | D                    |           | R                 |                |                  |     | 222                  | CHD, HF, PH, RF  | Progressive HF                |
| 17       |                 |                                |                   | D                    |           |                   |                | 58               |     | 280                  | CHD, HF  | Respiratory tract infection   |
| 18       |                 | HFO, IMV                       |                   | DO                   |           |                   |                |                  |     | 288                  | CHD, HF, RF  | SCA                           |
| 19       |                 | IMV, nCPAP                     | 102               | D                    |           |                   |                | 248              | +   | 368                  | CHD, HF, PH, hepatoblastoma                              | Progressive PH                |
| 20       |                 | IMV                            |                   | D                    |           |                   |                |                  |     | 436                  | CHD, HF, PH, RF  | Progressive RF                |
| 21       | GS, EA, CS, TS  | IMV, HFO                       |                   | DO, NG, D            | +         | F, R, P           | PB, VPA        |                  |     | 518                  | CHD, HF, PH, RF, aspiration pneumonia, liver dysfunction | PH crisis, PHE                |
| 22       | GS, EA, IS      | IMV                            |                   | D                    | +         | R, F              |                |                  |     | 580                  | Renal insufficiency, malnutrition                        | Acute renal failure           |
| 23       |                 |                                |                   |                      |           |                   |                | 30               |     | 999                  | Alive  | Alive                         |
| 24       | GS, EA, TS, TEF | IMV                            | 513               | PGE1, D, DG          |           | R, F, E           |                | 947              | +   | 1,786                | CHD, HF, PH, RF  | Tube trouble                  |

GS, gastrostomy; EA, esophageal atresia correction; O, omphalocele correction; CS, colostomy; TS, tracheostomy; IS, ileostomy; TEF, tracheoesophageal fistula resection; IMV, intermittent mandatory ventilation; HFO, high frequency oscillation; nCPAP, nasal continuous positive airway pressure; DO, dopamine with or without dobutamine pressors; ISP, isoproterenol; NG, nitroglycerin; PGE1, prostaglandin E1; D, diuretics; BB, beta blocker; DG, digoxin; IVH, intravenous hyperalimentation; F, fresh frozen plasma; R, packed red blood cells; P, platelet; E, exchange transfusion; PB, phenobarbital; VPA, valproic acid; HOT, home oxygen therapy; CHD, congenital heart defects; HF, heart failure; PH, pulmonary hypertension; RF, respiratory failure; SCA, sudden cardiac arrest; PHE, pulmonary hemorrhage.

to 42 weeks and 0 day), with three patients delivered after 41 weeks. Mean birth weight was 1,708 g (range, 1,017–2,135 g). Mean Apgar score was 4.0 (range, 1–8) at 1 minute and 6.0 (range, 1–10) at 5 min.

### Structural Defects and Medical Complications

Data on structural defects and medical complications are summarized in Table I.

All patients had congenital heart defects and the defects were classified into two groups according to the hemodynamic state: those that reduced pulmonary blood flow in Patients 3 and 24 with pulmonary atresia, and Patients 12 and 18 with tetralogy of Fallot; and those that increased pulmonary blood flow in the others. Twenty-three patients had heart failure (96%). Patient 12, who did not have heart failure in the neonatal period, manifested heart failure thereafter resulting from progressive pulmonary artery stenosis. Patient 22, who had heart failure in the neonatal period, did not manifest heart failure thereafter because of spontaneous closure of ventricular septal defect. Only Patient 23, who had a spontaneously closed small patent ductus arteriosus and is still alive, has never manifested heart failure. The tendency of prolonged pulmonary hypertension was observed in most of the patients, including six patients who developed persistent pulmonary hypertension of the newborn.

Among non-cardiac structural defects, C-type esophageal atresia with tracheoesophageal fistula was the most common (33%). Patient 22 was suspected to have pyloric stenosis retrospectively, in consideration of complicated episodes of gastroesophageal reflux and difficulty in inserting a feeding tube via gastrostomy into the duodenum. Respiratory failure of various etiologies and severity occurred in 21 patients (88%). Patients 1 and 2 had left diaphragmatic eventration and hypoplasia accompanied by lung hypoplasia. Additionally, Patient 1 had tracheal atresia with tracheoesophageal fistula and Patient 2 had esophageal atresia with tracheoesophageal fistula. Five patients had seizures: subtle-type (mouth movement) in Patient 6, tonic-type in Patient 21, tonic-clonic-type in Patient 8, and myoclonic-type in Patient 14, according to the classification presented by Volpe [2001].

Thrombocytopenia with platelet counts under  $15 \times 10^4/\mu\text{l}$  had been noted in 20 patients. Radial aplasia (Patients 1, 2, and 15), cleft lip and palate (Patients 2 and 16), ocular abnormalities (Patients 10 and 13), umbilical cord cysts (Patients 4 and 18), choanal atresia (Patient 17), and syndactyly (Patient 18) were also observed. Patient 19 exhibited hepatoblastoma at age 10 months.

### Treatment and Course

Data on treatment are summarized in Table II. Ten patients (42%) underwent a total of 21 operations.

Seven of eight patients with esophageal atresia and tracheoesophageal fistula had gastrostomy safely and only Patient 14 needed reoperation due to insufficient suture. Five of the eight patients underwent surgical correction of esophageal atresia (anastomosis of esophagus and resection of tracheoesophageal fistula); whereas the others did not because of uncontrollable respiratory failure in Patient 2, fulminant infection in Patient 4, and parental refusal in Patient 9. Postoperative course of corrective surgery was complicated in Patient 6 with mediastinitis resulting in death, and in Patient 24 with reopening of the tracheoesophageal fistula necessitating resection. Ileostomy was performed on Patient 22 with gastric obstruction supposedly due to pyloric stenosis, who thereafter showed bowel dysfunction because of inappropriate positioning of the stoma. Colostomy and surgical repair of omphalocele were successful. Tracheostomy was also accomplished safely in Patients 21 and 24, and the latter patient could be discharged to home. Enteral duodenal tube was effectively placed in three patients with gastroesophageal reflux. No patient received cardiac surgery.

Mechanical ventilation, including intermittent mandatory ventilation, high frequency oscillation, and nasal continuous positive airway pressure, was performed on 21 patients (88%). High frequency oscillation was applied successfully to Patients 13 and 14 with severe respiratory distress syndrome in the neonatal period, and both were extubated thereafter. But it could not achieve respiratory stabilization in Patients 1 and 2 even with the maximal setting. Pulmonary surfactant was administered to eight patients for respiratory distress syndrome (Patients 6, 13, 14, 18, 20, and 24) and/or for pneumonia or atelectasis (Patients 6, 14, 21, and 22) with partial or complete effectiveness, while it was ineffective for lung hypoplasia in Patient 2. Patients 8, 22, and 24 with severe apnea needed intermittent mandatory ventilation; and Patient 3 with moderate apnea received nasal continuous positive airway pressure. Six patients were extubated (29%), and the median duration of mechanical ventilation in them was 76.5 days (range, 10–513 days).

Cardiovascular drugs were used in 22 patients (92%). Diuretics (furosemide with or without spironolactone) and dopamine with or without dobutamine pressors were commonly used for heart failure. Prostaglandin E1 was administered to four patients with PDA-dependent congenital heart defects. It was discontinued after long-term use in Patient 13 (Day 88) and Patient 24 (Day 33). In both patients, the ductus had narrowed in the first few weeks of life in accordance with tapering of dosage. Nitroglycerin was given to three patients with severe persistent pulmonary hypertension of the newborn, and they could survive this critical period except Patient 2 with uncontrollable respiratory failure. Beta-blocker,

used in Patient 12 who exhibited progressive pulmonary artery stenosis associated with tetralogy of Fallot with frequent anoxic spells, had only temporary effect.

All patients received parenteral therapy. Five patients with esophageal atresia had intravenous hyperalimentation due to poor enteral feeding. Platelet transfusion was given to three patients with disseminated intravascular coagulation resulting from severe infections. Exchange transfusion was applied to Patient 4 with fulminant infection and Patient 24 with severe hyperbilirubinemia. For the control of seizures, Patients 4 and 6 had single use of phenobarbital, Patients 8 and 14 regular use of phenobarbital, and Patient 21 regular use of phenobarbital and valproic acid. Aminophylline had a partial effect on apnea in Patient 11.

### Prognosis

Prognosis is summarized in Table II. Five patients were discharged to home (21%); three of them needed home oxygen therapy due to hypoxia associated with pulmonary hypertension or respiratory failure. Median hospital stay among the five patients was 137 days (range, 30–947 days). Survival rates at age 1 day, 1 week, 1 month, and 1 year were 96%, 88%, 83%, and 25%, respectively. Median survival time for both sexes was 152.5 days, (range, 0–1,786 days). It was longer for girls (210 days) than for boys (106 days).

Several patients showed sucking movements, gazed up parents and caregivers, and moved their limbs. Patient 23 accomplished head control, rolling over, smiling, and babbling at the time of this study. Patient 24 could play with a toy and be fed with a spoon.

### Cause of Death

Causes of death are summarized in Table II. The most frequent underlying factors associated with death were congenital heart defects and heart failure (22 patients, 96%), followed by pulmonary hypertension (18 patients, 78%), and respiratory failure (14 patients, 61%). Pulmonary hypertension was noted in Patients 3 and 24 who had congenital heart defects with reduced pulmonary blood flow. Progressive pulmonary artery stenosis resulting in heart failure was noted in Patients 12 and 18 with tetralogy of Fallot. Patient 9 had malnutrition due to micro-ileum. Patient 21 showed severe liver dysfunction after aspiration pneumonia, on the background of increasing dose of valproic acid. Patient 22 had renal insufficiency due to recurrent urinary tract infection and malnutrition associated with malpositioned ileostomy. Most patients had complex underlying factors that were interrelated.

The most frequent final mode of death was sudden cardiac or cardiopulmonary arrest (six patients, 26%). All of the patients who died finally of sudden cardiac or cardiopulmonary arrest had congenital heart defects and heart failure, and five had pulmonary hypertension as underlying factors associated with death. Intensive resuscitation was not effective in this condition. Observed triggers were crying and procedures that could cause stress: after crying (Patient 5), while changing a diaper (Patient 8), after crying and suctioning (Patient 13), and after cleansing the body (Patient 18). Possible progressive pulmonary hypertension-related events including pulmonary hemorrhage and pulmonary hypertensive crisis occurred in six patients (26%). Untreatable respiratory failure from birth was noted in Patients 1 and 2 with left diaphragmatic eventration and hypoplasia accompanied by lung hypoplasia. Patients 11 and 20 had progressive respiratory failure associated with pulmonary congestion. Patient 22 died of acute renal failure due to rhabdomyolysis.

### DISCUSSION

We have presented detailed clinical information on 24 patients with trisomy 18, managed under the principle of providing neonatal intensive treatment. Although the treatment was did not include cardiac surgery, the results suggested improved survival compared with previous population-based studies.

Selection bias could be present in this institution-based data. Although many neonates, born in Nagano prefecture, who required intensive care and surgery have been transferred to Nagano Children's Hospital; there might have been patients with trisomy 18 that were treated in regional hospitals throughout their lives, and those that died undiagnosed without karyotyping. In this prefecture, there has been no surveillance system for birth defects or registry for death. Moreover, mosaicism including normal cell line could contribute to longer survival in some patients, because we did not perform further karyotyping such as analysis of many peripheral blood lymphocytes or analysis of cells from other tissues in patients with longer survival. However, the most accurate estimate in live births with only minimal influence by prenatal screening indicated a figure in live births of about 1 in 6,000 [Root and Carey, 1994]. Considering that approximately 20,000 babies are born annually in Nagano prefecture, the total number of live births with trisomy 18 during this time period could be estimated as 33. The fact that almost all patients in this study had fetal ultrasonographic abnormalities could bias survival negatively. Finally, if resuscitation by intubation in 15 patients or corrective surgery for esophageal atresia in Patients 21 and 22 had not been performed; the median survival time would have

been much shorter, probably within a week; and the survival rate at age 1 year would have been much smaller, probably 4% (only Patient 23 could have survived long). Thus, the patients in this study did not seem to compose at least a positively biased population with respect to survival, but a substantial portion of babies born with trisomy 18 in this prefecture during this time period.

There has been little documentation of the precise reason for death in infants with trisomy 18 [Carey, 2001]. In a population-based study by Embleton et al. [1996], the major causes of death were cited as apnea and withdrawal of treatment. Another population-based study by Rasmussen et al. [2003] showed that the presence of a congenital heart defect did not seem to affect survival. A support group-based study by Baty et al. [1994] showed the major cause of death as cardiopulmonary arrest. The review by Carey, [2001] mentioned that central apnea, or its presence with a combination of other factors, was the primary pathogenesis of the increased infant mortality. However, in a detailed pathological study by Kinoshita et al. [1989], the major causes of death were heart failure and pulmonary hemorrhage resulting from congenital heart defects. Both a large ultrasonographic study by Musewe et al. [1990] and an autopsy-based study by Van Praagh et al. [1989], concerning heart defects of trisomy 18, suggested that patients might exhibit unusually early development of pulmonary vascular obstructive diseases resulting in early progression of pulmonary hypertension leading to death. In our observation under intensive treatment, the major underlying factors associated with death were heart failure and pulmonary hypertension resulting from congenital heart defects, frequently accompanied by respiratory failure. The major final modes of death were sudden cardiac or cardiopulmonary arrest and possible progressive pulmonary hypertension-related events. The result that most of the events of sudden cardiac or cardiopulmonary arrest were observed in the patients with pulmonary hypertension and were triggered by crying or stressful procedures suggested that these events might also be related to progressive pulmonary hypertension.

Although present data suggested that medical treatment, such as cardiovascular drugs and respiratory support, might be effective for cardiopulmonary lesions in the aspect of survival, we are unable to evaluate the effectiveness of cardiac surgery. We experienced, during this time period, only one palliative surgery (ligation of patent ductus arteriosus) to a mosaic patient with heart failure due to ventricular septal defect, atrial septal defect, and patent ductus arteriosus, in addition to myelomeningocele and pyloric stenosis, which were also corrected surgically. The ligation surgery improved heart failure and enabled the patient to be discharged and prolonged survival (553 days). To date, several

case reports described five patients who underwent seven cardiac surgeries [Van Dyke and Allen, 1990; Baty et al., 1994; Teraguchi et al., 1997; Derbent et al., 2001]. Research by the Support Organization for Trisomy 18, 13 and Related Disorders (SOFT) Registry group found that eight of twelve patients who underwent cardiac surgery (seven intracardiac repairs and five palliative) survived to be discharged [Carey, 2001]. A recent multicenter registry-based report by Graham et al. [2004] showed that 21 of 24 patients who underwent cardiac surgery including intracardiac repair survived to be discharged. Detailed clinical review of each patient who underwent cardiac surgery will be needed to evaluate effectiveness of the procedure.

High rates of mechanical ventilation and unfavorable pulmonary outcome seemed to be related to factors such as birth asphyxias, lung hypoplasia, respiratory distress syndrome, infections, pulmonary hypertension, congestion due to heart failure, mechanical lung injury, and apnea. However, two patients with severe respiratory failure in the early neonatal period due to respiratory distress syndrome were successfully extubated, suggesting that initial severity of respiratory status might not be a definitive predictor of poor prognosis. We observed that, left diaphragmatic eventration accompanied by lung hypoplasia was consistently seen as a predictor of lethality even with maximized interventions.

Perinatal management of trisomy 18 has been discussed as an ethical issue. Chervenak and McCullough [1990] categorized trisomy 18 as a condition in which a choice between aggressive management and non-aggressive management should be made, due to probable lethality or absent cognitive developmental capacity if the patient survived. In Japan, there has been no established principle in caring critically sick neonates like trisomy 18. Nishida et al., [1987] introduced a classification in medical decision making of caring them [Nishida and Sakamoto, 1992]. In this classification, trisomy 18 was categorized into a condition in which no additional treatments were considered but ongoing life-supporting procedures or routine care (temperature control, enteral nutrition, skin care, and love) was not withdrawn. Although this principle has had a certain impact on the society of neonatology in Japan, patients with trisomy 18 have actually been managed under a principle of each hospital, including intensive treatment for longer survival and better quality of life like Nagano Children's Hospital. This situation might have been supported by a secure national health insurance covering all costs of treatment to every sick child, general respect for life, and the families' strong wishes to prolong the patients' lives, just as Sakakihara et al. [2000] suggested in the study on physicians' attitude toward long-term ventilator support in patients with Werdnig-Hoffmann disease in Japan [2000].

In conclusion, the patients with trisomy 18 managed under intensive treatment survived longer than those described in previous population-based studies, with the median survival time as 152.5 days and the survival rate at age 1 year as 25%, but with many medical procedures and long hospital stay. They frequently died of sudden cardiac or cardiopulmonary arrest and possible progressive pulmonary hypertension-related events, on the basis of congenital heart defects with heart failure and pulmonary hypertension. These data are helpful for clinicians to offer the best information on treatment options to families of patients with trisomy 18.

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