Original Article

Analysis of Death Due to Infectious Diseases in Patients Hospitalized in the Pediatric Ward of a Single Japanese Tertiary Medical Facility

Naoko Toda1, Takayuki Hoshina1,4*, Yuhki Koga1, Masayuki Ochiai1, Kenichiro Yamamura1, Hiroyuki Torisu1, Kenji Ihara1, Hidetoshi Takada1,3, Yoshihiko Maehara3, and Toshiro Harai1

1Departments of Pediatrics; 2Perinatal and Pediatric Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582; 3Pediatric Emergency & Critical Care Center, Kyushu University Hospital, Fukuoka 812-8582; and 4Department of Pediatrics, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu 807-8555, Japan

SUMMARY: In developed countries, the infection related-mortality rates in children hospitalized in tertiary medical facilities, where many patients with underlying disease are also hospitalized, are uncertain. We investigated the characteristics of infectious diseases-related fatal cases in the pediatric ward of a Japanese tertiary medical facility. A total of 188 patients who died in the pediatric ward or intensive care unit at Kyushu University Hospital from 2002 to 2011 were enrolled. The patient characteristics were investigated based on their medical records. A total of 35 patients died of infections, 31 of whom had underlying diseases. Most patients died of sepsis or pneumonia (n = 27). All 9 patients who died within 7 days of birth were premature. Nine of the 13 patients with malignancy or hematological disorders died of hematopoietic stem cell transplantation (HSCT)-associated infections. The ratio of infectious disease-related fatal cases to the total cases decreased in the latter half of the study period. In particular, the proportion of preterm infants who died of infections was significantly lower in the latter 5 years (p = 0.02). Many of the infectious disease-related fatal cases were in premature infants and HSCT or post-HSCT patients. However, the mortality due to infectious diseases decreased in these patient groups.

INTRODUCTION

The infectious disease-related mortality rate in children has been declining as a result of socioeconomic development and the introduction of new vaccines, and antimicrobial agents (1–3). However, the global rate is still high with 68% mortality in children younger than 5 years. The major causes of death are pneumonia (18%), diarrhea (15%), malaria (8%), and sepsis (6%) (2). Although a further reduction in infectious disease-related child mortality rate is expected due to the widespread use of vaccines such as pneumococcal conjugate vaccine; Haemophilus influenzae type b conjugate vaccine; and rotavirus vaccine (4–6), the results have been far from satisfactory. Even in developed countries with high immunization rates, infectious disease-related mortality accounts for approximately 20% of the deaths in children younger than 5 years; for instance, these rates are 20% in the USA; 16% in Germany; and 28% in France (2). The mortality rate in Japan is similar despite the gradual increase in the number of available vaccines (2,7).

The mortality rate data described above apply to the general pediatric population. However, in contrast to these findings, the mortality rates of children with underlying infectious diseases remain uncertain. In this study, we investigated the causes of death and the longitudinal changes in infectious disease-related mortality in the pediatric ward of a Japanese tertiary medical facility, where many patients with underlying diseases are also hospitalized.

MATERIALS AND METHODS

Study population: Kyushu University Hospital is a tertiary medical facility located in Fukuoka City, with a population of approximately 1.5 million. Many patients living not only in the Fukuoka prefecture, but also in the surrounding prefectures, visit and are admitted to our hospital. The pediatric ward can accommodate up to 60 patients. In addition, patients with severe diseases are hospitalized in the intensive care unit. A total of 10,405 pediatric patients were admitted to the Department of Pediatrics or the Emergency & Critical Care Center at the Kyushu University Hospital from January 1, 2002 to December 31, 2011. Of these, 188 (0–29 years old, 1.8%) died during hospitalization and were enrolled in the present study. The patients’ medical histories and causes of death were retrospectively analyzed based on the medical records and laboratory, and microbial data. According to the underlying diseases, the patients were classified into the following groups: ‘malignancy or hematological disorder,’ ‘neuromuscular disease, malformation syndrome and/or chromosomal disorder,’ ‘cardiovascular disorder,’ ‘endocrine or metabolic disorder,’ ‘prematurity,’ ‘renal disorder,’ ‘respiratory disorder,’ ‘gastrointestinal dis-
order’ and ‘no underlying diseases.’ For patients with more than 2 underlying diseases, classification was based on their most severe disorder. No suicide or trauma patients were included in the present study. The study was approved by the Institutional Review Board of the Kyushu University Hospital.

**Classification of the causes of death:** The patient’s cause of death, the progression of the underlying disease, and complications related to non-infectious diseases were classified into the group of infectious diseases or non-infectious diseases. We also assessed the patients’ conditions just prior to death based on their medical records and laboratory data. The cases where death occurred without symptoms of infection, with apparent progression of the underlying disease, and with uninfected complications, were classified as death due to non-infectious diseases. In cases where death occurred due to reasons other than those mentions above, the cause of death was classified as ‘unknown.’

**Definition of death due to infectious diseases:** The cause of death due to infectious disease was classified into the following 3 categories: confirmed cases where a pathogen (bacterium, fungus, or virus) was detected from a sterile site; probable cases where the patient was suspected to have an infection because of clinical symptoms and the detection of a pathogen from non-sterile samples obtained from the lesion specified by radiological imaging study; and possible cases where the patient was suspected to have an infection based on a serological examination or on the clinical symptoms and the radiological imaging study showing a presumable lesion, without sampling from the lesions. The patients suspected to have an infection based on the clinical symptoms and radiological imaging study, but in whom an infection was not specified, were classified to have an “unknown cause” of death.

**Statistical Analysis:** The SPSS statistical software (version 21; SPSS Inc., Chicago, IL, USA and IBM, Armonk, NY, USA) was used for all analyses. The chi-squared test, and the Fisher’s exact test when required, were used for qualitative analyses. The P-values, the odds ratios for mortality, and the 95% confidence intervals were automatically calculated by the software. P-values less than 0.05 were considered to be statistically significant.

**RESULTS**

Malignancy or hematological disorders (38.6%) was the most common disease in the patients admitted to our hospital during the investigation period, followed by neonates requiring intensive care (22.2%), cardiovascular disorder (12.1%), infectious diseases (11.7%), neuromuscular disease, malformation syndrome and/or chromosomal disorder (8.7%), renal diseases (3.2%), endocrinial or metabolic disease (2.7%) and others (0.8%). The most common underlying disease category in the fatal cases was malignancy or hematological disorder (n = 72, 38%), followed by neuromuscular disease, malformation syndrome and/or chromosomal disorder (n = 51, 27%), prematurity (n = 32, 17%), cardiovascular disorder (n = 20, 11%), metabolic disorder (n = 6, 3%), and others (1 case each of polyhemangioma and liver cirrhosis). No patients with renal disorder, respiratory disorder, or gastrointestinal disorder died at our department during the study period. Five patients (3%) were noted to have no underlying diseases before their hospitalization. Children less than 1 year of age accounted for 44% (n = 82) of the deaths and 57% (n = 47) of these deaths occurred during the neonatal period.

Of the 188 fatal cases, 35 (19%) patients, including 13 with malignancy or hematological disorder; 10 with prematurity; 8 with neuromuscular disease; malformation syndrome and/or chromosomal disorder; and 4 without underlying diseases, died of infections (Fig. 1). There were no infection-related deaths in the patients with other underlying diseases (Fig. 1). Two patients without underlying diseases died from viral myocarditis, while the remaining 2 died from acute encephalitis (Table 1). In these 35 infection-related cases, 23, 5, and 7 were classified as confirmed cases, probable cases, and possible cases, respectively. Seventeen of the fatal cases (49%) were under 1 year of age, and of them, 9 deaths occurred within the first week of life. Twenty (57%) and 7 (20%) patients died of bacteremia and/or meningitis, and pneumonia, respectively (Table 2). The other causes of death were encephalitis (n = 3), viral myocarditis (n = 2), intra-abdominal infections (n = 2), and visceral varicella (n = 1) (Table 2). All 9 patients who died within the first week of birth were born before 30 weeks of gestation, and 8 of these neonates had birth weights of less than 1,000 g (Table 3). Eight of the 9 neonates died from sepsis and 6 were born to mothers with premature rupture of membranes (PROM).

Eleven (73%) of the 15 patients who died beyond 4 years of age had malignancy and/or hematological disorder. Of the 13 patients with malignancy and/or hematological disorders, 9 died after hematopoietic stem cell transplantation (HSCT) or during pre-transplantation conditioning therapy (Table 4). Of the 9 patients who received HSCT, 5 died more than a month after the transplant procedure, while receiving immunosuppressive agents, as a result of graft-versus host disease (GVHD). Three patients developed bacteremia during the relapse of acute lymphoblastic leukemia. 1 patient with severe combined immunodeficiency, who initially had cytomegalovirus (CMV) pneumonia, underwent HSCT, but the CMV infection was not controlled. Most neuromuscular disease, and malformation syndrome and/or chromosomal disorder patients younger than 3 years died of sepsis, whereas all adolescent patients with these diseases died of pneumonia (Table 5). However, neither the physical activity level of each patient nor the causative pathogen in each infection demonstrated any similarities.

| No. | Sex | Age | Diagnosis | Category of patient | Causative pathogen |
|-----|-----|-----|-----------|---------------------|--------------------|
| 1   | M   | 3 m | myocarditis | confirmed          | coxsackievirus B3   |
| 2   | F   | 4 m | myocarditis | possible           | not identified     |
| 3   | F   | 1 y 0 m | encephalitis | confirmed          | human herpes virus 6 |
| 4   | F   | 4 y 9 m | encephalitis | possible           | not identified     |
The definitive or presumptive causative pathogens in the confirmed and probable cases were: gram-positive coci in 8 cases (Staphylococcus epidermidis in 4, Enterococcus faecium in 2, S. aureus in 1, and Streptococcus pneumoniae in 1), gram-positive rods in 4 cases (Bacillus cereus), gram-negative rods in 12 cases (Pseudomonas aeruginosa in 4, Escherichia coli in 2, Haemophilus influenzae in 2, Klebsiella pneumoniae in
Table 3. Clinical characteristics of the patients who had fatal infections during neonatal period

| No. | Sex | Age (day) | Diagnosis | Category of patient | Gestational age (week) | Birth weight (g) | PROM | Causative pathogen | Treatment |
|-----|-----|-----------|-----------|---------------------|------------------------|------------------|------|-------------------|-----------|
| 1   | M   | 0         | bacteremia| confirmed           | 30                     | 1,060            | yes  | E. coli           | ABPC + GM |
| 2   | F   | 1         | bacteremia| probable            | 24                     | 686              | yes  | P. aeruginosa     | ABPC + CTX|
| 3   | M   | 1         | bacteremia| probable            | 24                     | 808              | yes  | E. coli           | CAZ       |
| 4   | M   | 2         | pneumonia  | possible            | 24                     | 582              | yes  | not identified    | ABPC + GM |
| 5   | F   | 2         | bacteremia| confirmed           | 23                     | 564              | no   | B. cereus         | ABPC + GM + FLCZ → PAPM/BP |
| 6   | M   | 4         | bacteremia| confirmed           | 25                     | 488              | yes  | B. cereus         | ABPC + CTX + FLCZ → PAPM/BP + VCM |
| 7   | M   | 4         | intra-abdominal infection| confirmed | 27 | 590 | no | B. cereus, CNS | ABPC + GM → CZOP + MCFG |
| 8   | M   | 6         | bacteremia| probable            | 29                     | 634              | no   | B. cereus         | ABPC + GM + FLCZ → PAPM/BP + TEIC |
| 9   | M   | 6         | bacteremia| confirmed           | 23                     | 732              | yes  | B. fragilis       | ABPC + GM + FLCZ → PAPM/BP + TEIC |

*1: P. aeruginosa was detected from bronchoalveolar fluid obtained at birth.*

*2: E. coli was detected from placenta, umbilical cord and bronchoalveolar fluid obtained at birth.*

*3: The patient developed intestinal perforation. B. cereus and CNS were detected from peritoneal fluid.*

PROM, premature rupture of membranes; ABPC, ampicillin; GM, gentamicin; CTX, cefotaxime; CAZ, ceftazidim; FLCZ, fluconazole; PAPM/BP, panipenem/betamipron; VCM, vancomycin; CZOP, cefozopran; MCFG, micafungin; TEIC, teicoplanin.

Table 4. Characteristics of the cases died after HSCT or during pretransplantation conditioning therapy

| No. | Sex | Age | Diagnosis | Category of patient | Underlying disease | Source of HSCT | Post-HSCT interval | GVHD | Causative pathogen |
|-----|-----|-----|-----------|---------------------|--------------------|----------------|-------------------|------|-------------------|
| 1   | M   | 1 y 7 m | bacteremia | confirmed | T-LBL (relapse) | no | — | — | P. aeruginosa |
| 2   | M   | 4 y 6 m | pneumonia | confirmed | ALL | yes | CBSCT | 3 months | yes | CMV |
| 3   | M   | 7 y 3 m | pneumonia | possible | plasmacytoma | yes | CBSCT | 2 months | yes | E. faecium |
| 4   | F   | 8 y 6 m | pneumonia | possible | CAEBV | yes | CBSCT | 11 days | no | not identified |
| 5   | F   | 8 y 11 m | bacteremia | confirmed | AML (relapse) | yes | PBSCT | 14 days | no | S. epidermidis |
| 6   | F   | 9 y 5 m | bacteremia | confirmed | neuroblastoma | yes | PBSCT | 8 months | yes | B. cepacia |
| 7   | M   | 12 y 5 m | bacteremia | confirmed | ALCL | no | — | — | E. faecium |
| 8   | F   | 15 y 9 m | bacteremia | probable | ALL | yes | BMT | 20 months | yes | Aspergillus sp. |
| 9   | M   | 18 y 6 m | bacteremia | confirmed | CAEBV | yes | PBSCT | 4 months | yes | S. epidermidis |

*1: P. aeruginosa was detected from bronchoalveolar fluid obtained at birth.*

*2: The patient developed intestinal perforation. B. cereus and CNS were detected from peritoneal fluid.*

*3: B. cereus and CNS were detected from nasal and throat swabs obtained at 2 day-old.*

HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; SCID, severe combined immunodeficiency; T-LBL, T-cell lymphoblastic lymphoma; ALL, acute lymphoblastic leukemia; CAEBV, chronic active Epstein-Barr virus infection; ALCL, anaplastic large cell lymphoma; BMT, bone marrow transplantation; CBSCT, cord blood stem cell transplantation; PBSCT, peripheral blood stem cell transplantation; CMV, cytomegalovirus; VZV, varicella zoster virus.

Table 5. Characteristics of the fatal cases having neurological disease, malformation syndrome and/or chromosomal disorder

| No. | Sex | Age | Diagnosis | Category of patient | Underlying disease | ADL | Tube feeding | Causative pathogen |
|-----|-----|-----|-----------|---------------------|--------------------|-----|-------------|-------------------|
| 1   | M   | 2 m | bacteremia | confirmed           | 21 trisomy         | indeterminable | yes | S. aureus |
| 2   | F   | 4 m | bacteremia | confirmed           | floppy infant      | indeterminable | no  | H. influenzae |
| 3   | M   | 4 m | antra-abdominal infection| possible | Crouzon syndrome | indeterminable | yes | not identified |
| 4   | F   | 1 y 7 m | meningitis | confirmed | malformation syndrome | bedridden | yes | K. pneumoniae |
| 5   | M   | 2 y 8 m | bacteremia | confirmed | Seckel syndrome | walking | no | H. influenzae |
| 6   | M   | 11 y 11 m | pneumonia | possible | dystonia | bedridden | no | P. aeruginosa |
| 7   | M   | 12 y 6 m | pneumonia | possible | undetermined | walking | no | not identified |
| 8   | M   | 16 y 3 m | pneumonia | possible | psychomotor retardation | lissencephaly | bedridden | yes | K. pneumoniae |

ADL, activities of daily living.
2. *Burkholderia cepacia* in 1, and *Bacteroides fragilis* in 1), CMV in 2 cases, and 1 case each of varicella-zoster virus, human herpes virus 6, coxsackievirus B3, and *Aspergillus* species (Table 6). The causative pathogens did not vary based on the underlying diseases.

We compared the mortality rates during the first 5 years (2002–2006) with those during the latter 5 years (2007–2011). The proportion indicates the ratio of fatal cases due to infectious disease-related fatalities to the total cases. The mortality rates and the ratio of infectious disease-related fatal cases to the total cases were lower in the latter 5 years, but the differences were not statistically significant.

### Table 6. Age distribution by causative pathogens

| Age (years) | GPC | GPR | GNR | CMV | VZV | HHV6 | CB3 | Fungus | Total |
|-------------|-----|-----|-----|-----|-----|------|-----|--------|-------|
| 0–6 d       | 2   | 4   | 4   | 0   | 0   | 0    | 0   | 0      | 10    |
| 1–11 m      | 1   | 0   | 1   | 1   | 0   | 0    | 1   | 0      | 4     |
| 1–2 y       | 0   | 0   | 3   | 0   | 0   | 1    | 0   | 0      | 4     |
| 3–5 y       | 0   | 0   | 0   | 1   | 1   | 0    | 0   | 0      | 2     |
| 6–10 y      | 2   | 0   | 1   | 0   | 0   | 0    | 0   | 0      | 3     |
| 11–15 y     | 1   | 0   | 1   | 0   | 0   | 0    | 0   | 1      | 3     |
| 16 y–       | 2   | 0   | 2   | 0   | 0   | 0    | 0   | 0      | 4     |
| Total       | 8   | 4   | 12  | 2   | 1   | 1    | 1   | 1      | 30    |

Multiple pathogens were detected in 2 patients.

1: *S. epidermidis* 4, *E. faecium* 2, *S. aureus* 1, *S. pneumoniae* 1.
2: *B. cereus* 4.
3: *P. aeruginosa* 4, *E. coli* 2, *H. influenzae* 2, *K. pneumoniae* 2, *B. cepacia* 1, *B. fragilis* 1.
4: *Aspergillus* sp. 1.

GPC, Gram positive cocci; GPR, Gram positive rods; GNR, Gram negative rods; CMV, cytomegalovirus; VZV, varicella zoster virus; HHV6, human herpes virus 6; CB3, coxsackievirus B3.

### Table 7. Comparison of the mortality rates during the first 5 years and the latter 5 years of the study period

| Age (years) | Total patients, n | Fatal cases, n (%) | Fatal cases due to infectious disease, n (%) | Preterm infant, n | Fatal cases, n (%) | Fatal cases due to infectious disease, n (%) | HSCT patient, n | Fatal cases, n (%) | Fatal cases due to infectious disease, n (%) |
|-------------|-------------------|--------------------|---------------------------------------------|-------------------|--------------------|---------------------------------------------|-----------------|--------------------|---------------------------------------------|
| 2002–2006   | 4,438             | 79 (1.8)           | 17 (21.5)                                   | 348               | 14 (4.0)           | 7 (50.0)                                    | 39              | 18 (50.0)          | 6 (33.3)                                    |
| 2007–2011   | 5,967             | 109 (1.8)          | 18 (16.5)                                   | 511               | 18 (3.5)           | 2 (11.1)                                    | 71              | 22 (31.0)          | 3 (13.6)                                    |

| Odds ratio (95% CI) | p |
|---------------------|---|
| Total               |   |
| 1.03 (0.77–1.38)    | 0.86 |
| Fatal cases due to infectious disease | 0.72 (0.35–1.51) | 0.38 |
| Preterm infant      | 0.87 (0.43–1.78) | 0.70 |
| Fatal cases due to infectious disease | 0.13 (0.02–0.76) | 0.02 |
| HSCT patient        | 0.53 (0.23–1.17) | 0.11 |
| Fatal cases due to infectious disease | 0.32 (0.07–1.51) | 0.25 |

1): The proportion indicates the ratio of fatal cases due to infectious disease to the total cases.
2): The patients died during pretransplantation conditioning therapy were included.

DISCUSSION

There are few recent reports from developed countries analyzing the long term characteristics of pediatric fatalities at tertiary medical facilities. The ratio of infection-related fatalities to the total cases treated at our tertiary hospital was 18.6%. Most infection-related fatalities in the premature neonates occurred during the neonatal period due to sepsis. Sepsis and pneumonia after HSCT or during pre-transplantation conditioning therapy were the major causes of death in older children.

The epidemiological trends of early-onset neonatal sepsis have shown a decreasing incidence of group B streptococcus (GBS) disease owing to the implementation of prenatal screening and treatment protocol (8). The morbidity associated with early-onset GBS infection has dramatically decreased from 1.95 in 1986–1994 to 0.32 of 1,000 live births in 1999–2008 (8,9). In our study, no neonatal death occurred due to a GBS infection. PROM is also at a high risk factor for early delivery and neonatal sepsis (10). In the present study, 6 of the 9 neonates were born to mothers with preterm PROM. However, only 1 of these patients died during the latter 5 years of the study period. Routine prescription of antimicrobial agents to patients with preterm PROM is associated with prolongation of pregnancy and a reduction in short-term neonatal complications, but is not associated with a significant reduction in the perinatal mortality (11,12). The efficacy of antimicrobial agent administration to neonates born to mothers with preterm PROM is uncertain. In our study, all neonates born to mothers with PROM received prophylactic ampicillin and gentamicin. Our results indicate that early antimicrobial therapy for preterm infants born to mothers with PROM might be useful in reducing the neonatal mortality due to infectious diseases. In the first 5 years, *B. cereus*, a representative nosocomial outbreak pathogen, was more frequently detected as a causative pathogen. However, the initial antimicrobial treatment and guidance for the administration of im-
munoglobulins remained same throughout the investigation period. Although no association with contaminated linen was confirmed, we speculated that the strict routine of infection control precautions may have contributed to the reduction in B. cereus infections during the latter 5 years.

Blood stream infections are a serious complication of HSCT (13). In the present study, the most common causes of infectious diseases in the fatal cases with malignancy or hematological disorders were sepsis after HSCT, or during pre-transplantation conditioning therapy. The number of patients undergoing HSCT is increasing yearly, whereas the HSCT-related mortality and the ratio of infectious disease-related fatal cases to the total cases has been decreasing; albeit insignificantly, as has been reported in previous studies (14,15). It is plausible that the proactive administration of antimicrobial and/or antifungal drugs before and after HSCT may have decreased the infectious disease-related mortality in these cases (16,17). The treatment for infectious diseases in patients with malignancy and/or hematological disorder remained unchanged during the investigation period. Therefore, the reduction may be attributed to the rapid and precise diagnosis of bacterial infection. The strengthened bacteriology laboratory system at our hospital may have enabled the early administration of appropriate antimicrobial agents. Furthermore, a reduction in the development of severe acute GVHD, and improvements in the protocols for GVHD treatment might also have contributed to the reduction of HSCT-related infections (18,19). In addition to the infection control of the host, it is important to educate the patients and their family members about infection prevention, and to improve the hospital room environment for patients undergoing HSCT (16,20).

There are some limitations in this retrospective study. First, we could not always rule out non-infectious diseases as the cause of death in patients, except in the confirmed cases. Second, the patients in whom death occurred due to non-infectious diseases might have died of unidentified infections. The retrospective nature of this study posed certain limitations despite the detailed analysis based on medical records. A prospective study, on the other hand, is warranted to generate more accurate results. Finally, this was a single-center study. Our hospital is a relatively large scale Japanese tertiary center, and covers an area that encompasses approximately 5% of the total population of Japan. However, the sample size in the present study was small, and there may have been a bias as it involved a single center. Moreover, the generalization potential of the present results is limited as the patient demographics are unique to our institution. Further multicenter studies are needed to confirm the present findings.

In conclusion, despite the increase in the number of patients with risk factors for an infection, the proportion of cases of mortality due to infectious diseases among those admitted to the pediatric ward of a tertiary medical facility, has been gradually decreasing following trends in the overall Japanese pediatric population. In particular, the rate of mortality due to infectious diseases in premature infants has significantly reduced during the past few years. Further advances in medical technology are desired to further decrease pediatric deaths due to infections.

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Conflict of interest None to declare.

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