J Microbiol Immunol Infect
2004;37:157-163

# Hemophagocytic syndrome: a review of 18 pediatric cases

**Chih-Jung Chen[1], Yhu-Chering Huang[1], Tang-Her Jaing[2], Iou-Jih Hung[2], Chao-Ping Yang[2], Luan-Yin Chang[1], Tzou-Yien Lin[1]**

*Divisions of [1]Pediatric Infectious Diseases and [2]Pediatric Hematology-Oncology, Department of Pediatrics, Chang Gung Children's Hospital, Taoyuan, Taiwan, ROC*

Received: June 11, 2003 Revised: July 9, 2003 Accepted: September 25, 2003

This retrospective study included 18 pediatric cases (median age, 3 years) with pathologically proved hemophagocytic syndrome (HPS) from a single institution during 1992 and 2001. There were 9 males and 9 females. Prolonged fever, cytopenia, liver dysfunction and hepatomegaly were the most common features at presentation. Sixteen (88.9%) cases were previously healthy. The case fatality rate was 61.1%, and all fatal cases died within 2 months of disease onset. The infectious agents associated with HPS were identified in 11 cases (61.1%), and 8 (72.7%) of them had evidence of Epstein-Barr virus (EBV) infection or reactivation. Underlying immunologic disorder or neoplastic disease was identified in 11.1% of the cases. Children less than 3 years of age with HPS were more vulnerable to neutropenia-associated bloodstream infection (85.7% vs 27.3%; $p$=0.025). *Pseudomonas aeruginosa* (3) and *Candida tropicalis* (2) were the 2 most commonly isolated pathogens. Regarding specific management of HPS, intravenous immunoglobulin and steroids were the first-line agents and were administered in 16 cases and 11 cases, respectively, while etoposide was administered in 5 refractory cases during the late phase of disease. Most HPS occurred in previously healthy children, and a substantial proportion of cases rapidly progressed to death. Most cases were associated with viral infection, particularly EBV, and young children tended to develop neutropenia-associated bacteremia during the active phase of the disease.

**Key words:** Child, Epstein-Barr virus, hemophagocytic syndrome

Hemophagocytic syndrome (HPS) is an unusual disorder characterized by prolonged fever, hepatosplenomegaly, cytopenia, coagulopathy, hypertriglyceridemia and hemophagocytosis in the bone marrow, liver, spleen or lymph nodes [1-3]. Two forms of HPS have been well characterized, primary/familial hemophagocytic lymphohistiocytosis (FHL) and secondary/reactive hemophagocytic syndrome. FHL is a rapidly fatal autosomal recessive disorder occurring most often in children less than 2 years of age [4]. Although sporadic cases have been identified in the literature, most of the cases with FHL had familial history for HPS. In addition to the familial form of disease, HPS can develop secondary to a variety of viral, bacterial, and parasitic infections as well as malignancy and collagen vascular diseases [1,5-11]. Reactive HPS can be encountered at any age and usually bares a more favorable outcome than FHL. Nevertheless, unpromising courses are still seen in patients with reactive HPS, especially in those cases associated with Epstein-Barr virus (EBV) infection. During the past 10 years, the therapeutic advances in immunochemical regimens and bone marrow transplantation have greatly improved the outcome of patients with HPS [12-15]. In this study, we reported the experience of 18 children with HPS in a single institution.

*Corresponding author: Dr. Yhu-Chering Huang, Division of Pediatric Infectious Disease, Department of Pediatrics, Chang Gung Children's Hospital, 5, Fu-Shin Street, Kweishan, Taoyuan, Taiwan 333, ROC.*
*E-mail: ychuang@adm.cgmh.org.tw*

## Materials and Methods

Children with HPS were identified from the personal files of all 3 pediatric hematologists in Chang Gung Children's Hospital between 1992 and 2001. The diagnosis of HPS was made according to the guidelines proposed in 1991 [16] with some modifications, which consisted of fever for ≥7 days with peaks of ≥38.5°C, hepatosplenomegaly ≥3 cm below the costal arch, cytopenia affecting ≥2 of 3 lineages in the peripheral blood, hypertriglyceridemia (triglyceride ≥200 mg/dL) and/or hypofibrinogenemia (fibrinogen ≤150 mg/L), and histopathological evidence of hemophagocytosis in the bone marrow, spleen or lymph nodes. The criteria for cytopenia was as follows: hemoglobin <9 g/dL, platelets <100,000/μL, and white blood cell (WBC)

count <4000/μL or neutrophils <1000/μL. In this study, the criteria for case inclusion were based on the pathologic findings of bone marrow, which would show an image of hemophagocytosis in the histiocytes. Patients with clinical features suggesting HPS, but not confirmed pathologically, were excluded. Over the 10-year period, there were 20 cases that fulfilled the inclusion criteria. Because of the unavailability of medical records, 2 fatal cases were excluded from the study. A total of 18 cases were included in this study, and the demographic, clinical and laboratory data of the 18 cases were collected for analysis. Among the 18 cases, 2 cases did not completely fulfill the proposed diagnostic guidelines for HPS [16], because serum fibrinogen and triglyceride levels were not measured in both cases. Furthermore, cytopenia involving only the WBC lineage and no obvious hepatosplenomegaly were also noted in one of them.

The serologic studies of EBV included the detection of anti-viral capsid antigen IgG (EBV-VCA IgG) and anti-early antigen IgG (EBEA IgG) using immunofluorescent assay, anti-viral capsid antigen IgM (EBV-VCA IgM) and anti-nuclear antigen (EBNA) with the ELISA method.

The 18 children were categorized in 2 groups, non-fatal and fatal. Categoric variables in the 2 groups were compared by means of the chi-squared or Fisher's exact test where appropriate. Differences in means were assessed by the Student's *t* test using SPSS 10.0 statistical software. Statistical significance was determined at $p<0.05$.

## Results

Of the 18 cases, 9 were male, and 9 were female. The age ranged from 2 months to 15 years, with a mean of 4.8 years and a median of 3.0 years. Two children were younger than 1 year of age. Children less than 2 years of age accounted for 38.9% of patients and had a case fatality rate of 57.1%. The case fatality rate was 63.6% for children greater than 2 years of age ($p=0.583$). The overall fatality rate was 61.1%.

### Underlying illness

Two patients had underlying conditions. One was a 2-month-old infant who had ventricular septum defect and left thumb polydactyly. His maternal history was remarkable with chronic hepatitis B, alcoholism and miscarriage twice for unknown reasons. The other was a 6-year-old boy, in whom bone marrow aspirations had been performed at another hospital twice. The results of both bone marrow studies were inconclusive and disclosed suspicious hemophagocytic syndrome and acute lymphoblastic leukemia (ALL), respectively. Previous treatment courses were unavailable. He had already had a fever and cytopenia for 1 week at presentation. The bone marrow study at admission was compatible with hemophagocytic syndrome. However, he developed ALL 5 months later. The other 16 cases were previously healthy and presented with acute illness at admission. A 10-year-old boy with acute onset of fever and severe cytopenia due to hemophagocytic syndrome presented with systemic lupus erythematosus (SLE).

### Clinical features

Fever, the most common clinical feature upon admission, was noted in all 18 cases (100%). The duration of fever prior to admission ranged from 1 to 30 days, with a mean of 8.7 days. The other manifestations, either identified on admission or developed during hospitalization, are illustrated in Fig. 1. Respiratory symptoms, including cough, shortness of breath and hypoxemia were noted in 6 cases (33.3%) at initial presentation. Gastrointestinal discomfort manifesting with vomiting, diarrhea, and abdominal pain was present in 8 cases (44.4%) on admission.

Cytopenia involving 2 or 3 cell lines simultaneously was observed in 17 cases (94.4%). Eight of them were identified on admission, and decline in blood cell count during hospitalization was noted in the other 9 cases. Leukopenia (white cell count <4000 cells/μL) and thrombocytopenia (platelets <100,000/μL) were the 2 most common blood pictures on admission, and were evident in 9 (50%) and 10 cases (55.6%), respectively. Hepatic derangement evidenced by elevated serum liver enzyme and/or bilirubin levels was found in 15 cases (83.3%). Coagulopathy with prolonged prothrombin time and/or activated partial thromboplastin time was noted in 13 (81.3%) of 16 cases with available data Hypertriglyceridemia and hypofibrinogenemia were observed in 86.7% and 78.6% of patients, respectively. Other laboratory findings included the highest value of C-reactive protein ≥100 g/L and lactate dehydrogenase >300 U/L in 52.9% and 88.9% of cases, respectively, and the lowest value of plasma albumin ≤2.5 g/dL in 76.9%.

The demographic data and laboratory findings of both the non-fatal and fatal cases are compared in Table 1. The means of the highest values of aspartate aminotransferase (AST), alkaline phosphatase (ALP), direct bilirubin and total bilirubin were significantly higher in the fatal group than in the non-fatal group

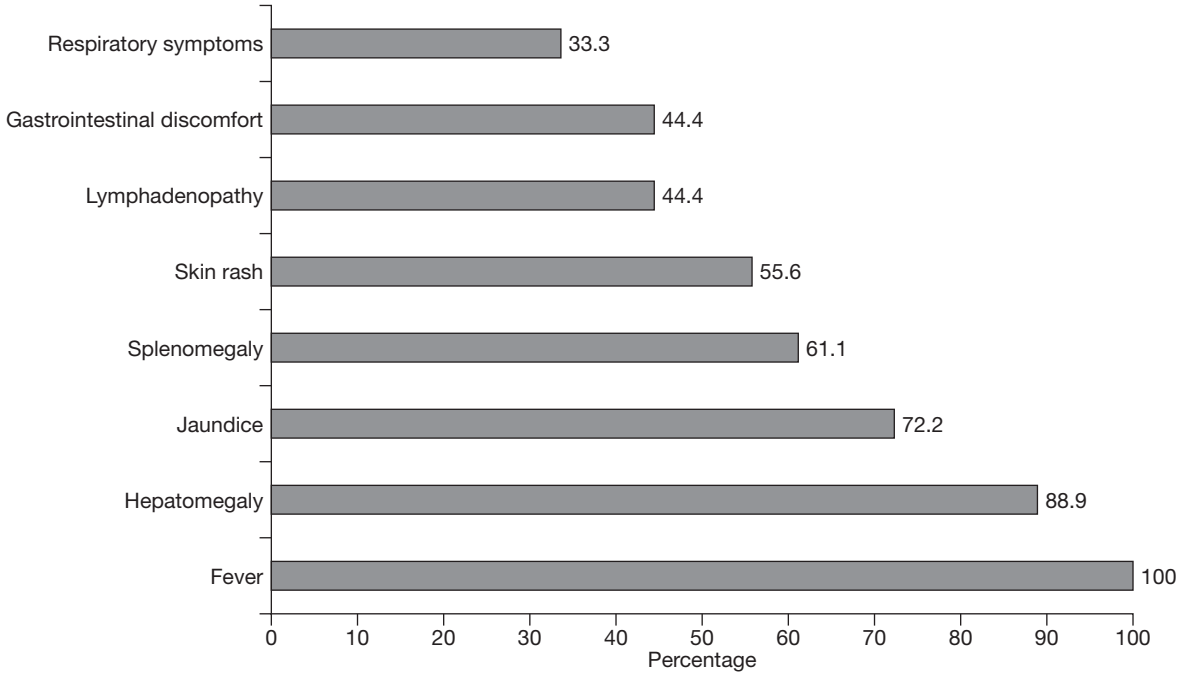


**Fig. 1.** The percentage of presenting symptoms at admission in 18 children with hemophagocytic syndrome.

**Table 1.** Demographic data, laboratory findings and therapeutic regimens of 18 children with hemophagocytic syndrome

| | Total n = 18 (%) | Non-fatal cases n = 7 (%) | Fatal cases n = 11 (%) | *p* |
|---|---|---|---|---|
| Mean age (years) | 4.8 ± 4.4 | 5.1 ± 4.8 | 4.5 ± 4.4 | NS |
| Less than 2 years old | 7 (38.9) | 3 (42.9) | 4 (36.4) | NS |
| Male gender | 9 (50.0) | 3 (42.9) | 6 (54.5) | NS |
| Laboratory value | | | | |
| Lowest WBC count (cells/μL) | 1520 ± 1287 | 1429 ± 637 | 1578 ± 1601 | NS |
| Lowest ANC (/μL) | 744 ± 967 | 637 ± 524 | 813 ± 1188 | NS |
| Lowest ANC < 500/μL | 11 (61.1) | 4 (57.1) | 7 (63.6) | NS |
| Lowest platelet count (cells/μL) | 49833 ± 49953 | 77286 ± 67260 | 32364 ± 25777 | NS |
| Highest AST (IU/L) | 903 ± 834 | 409 ± 446 | 1217 ± 886 | 0.041 |
| Highest ALT (IU/L) | 313 ± 347 | 182 ± 188 | 390 ± 403 | NS |
| Highest total bilirubin (mg/dL) | 10.0 ± 11.3 | 2.5 ± 3.3 | 14.1 ± 12.1 | 0.038 |
| Highest direct bilirubin (mg/dL) | 5.6 ± 6.3 | 1.4 ± 1.9 | 7.9 ± 6.8 | 0.037 |
| Highest LDH (U/L) | 1788 ± 2236 | 447 ± 385 | 2458 ± 2514 | NS |
| Highest ALP (U/L) | 424 ± 466 | 125 ± 83 | 573 ± 511 | 0.043 |
| Highest triglyceride (mg/dL) | 342 ± 142 | 313 ± 122 | 361 ± 158 | NS |
| Highest CRP (mg/L) | 130 ± 122 | 125 ± 108 | 134 ± 136 | NS |
| Lowest albumin ≤ 2.5 g/dL | 10/13 (76.9) | 2/3 (66.7) | 8/10 (80.0) | NS |
| Evidence of EBV infection | 8/16 (50) | 3/7 (42.9) | 5/9 (55.6) | NS |
| Therapeutic regimen | | | | |
| IVIG | 7 (38.9) | 2 (28.6) | 5 (45.5) | NS |
| IVIG and steroids | 4 (22.2) | 1 (14.3) | 3 (27.3) | NS |
| IVIG, steroids and etoposide | 5 (27.8) | 1 (14.3) | 4 (36.4) | NS |

Abbreviations: NS = not significant; WBC = white blood cell; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; ALP = alkaline phosphatase; CRP = C-reactive protein; EBV = Epstein-Barr virus; IVIG = intravenous immunoglobulin; SD = standard deviation

($p<0.05$). No significant differences were noted in the gender and age distribution. The use of therapeutic regimens had no obvious effect on the outcome.

## Associated infections

Serology studies for EBV were performed in 16 cases (Table 2). Eight of them had evidence of EBV primary infection or reactivation. Five cases (case 6, 7, 10, 11 and 16) had positive anti-VCA-IgM, and 1 case (case 3) had positive anti-EBEA, anti-VCA-IgG and negative anti-EBNA, indicating primary EBV infections. Two cases (case 12 and 14) had an elevated titer of anti-VCA-IgG, positive anti-EBEA and anti-EBNA, suggesting a reactivation of EBV.

Cytomegalovirus (CMV) infection was found in 2 cases with positive results for CMV IgM, of which simultaneous primary EBV infection was evident in 1 case (case 10) and EBV reactivation was noted in another (case 12). A throat swab for virus isolation was performed in 11 cases. Enterovirus was identified in 2 cases (case 5 and 13) and parainfluenza virus type 3 in 1 case (case 4). The serologic studies for other viruses, including human herpes virus 6, human simplex virus type 1 and 2, varicella zoster virus, hepatitis A, B, and C, parvovirus B19, etc., in limited cases all showed negative findings. The cases with evidence of EBV infection had no greater fatality than those without EBV infection (Table 1).

During hospitalization, bacterial or fungal bloodstream infections were documented in 7 cases (38.9%), including *Pseudomonas aeruginosa* in 3 cases, *Candida tropicalis* in 2 cases, methicillin-resistant *Staphylococcus aureus* in 1 case and simultaneous viridans streptococci and *E. coli* in 1 case. The onset of bloodstream infection after admission ranged from 5 to 48 days, with a mean of 21.1 days. The occurrence of bloodstream infection was significantly more common in children with young age (Table 3). In addition,

**Table 2.** Associated infections, illness, specific treatments and outcomes in 18 children with hemophagocytic syndrome

| Case no. | Age (years) | Gender | Pathogen in blood stream infection | EBV profile | | | | Treatment | Outcome | Other associated infectious agents and/or illnesses |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | VCA IgM | VCA IgG | EBNA | EBEA | | | |
| 1 | 0.15 | M | *Pseudomonas aeruginosa* | - | 80 | + | n/a | IVIG, ST, VP | D | |
| 2 | 0.32 | M | *Pseudomonas aeruginosa* | - | 20 | n/a | n/a | IVIG | A | |
| 3 | 1.38 | F | - | - | 320 | - | 40+ | IVIG | A | |
| 4 | 1.39 | F | *Pseudomonas aeruginosa* | - | - | - | - | IVIG | A | Parainfluenza type 3 |
| 5 | 1.42 | F | *Candida tropicalis* | - | n/a | n/a | n/a | IVIG, ST, VP | D | Enterovirus |
| 6 | 1.61 | F | - | + | n/a | n/a | 20+ | IVIG | D | |
| 7 | 1.81 | M | *E. coli,* viridans streptococci | + | 160 | + | n/a | IVIG, ST | D | |
| 8 | 2.16 | F | *Candida tropicalis* | - | n/a | n/a | n/a | IVIG, ST, VP | D | |
| 9 | 2.95 | M | - | - | 160 | n/a | n/a | IVIG | D | |
| 10 | 3.13 | M | - | + | 1280 | + | 320+ | IVIG, ST | D | CMV IgM(+) |
| 11 | 3.60 | F | MRSA | + | + | n/a | n/a | IVIG, ST | A | |
| 12 | 6.11 | M | - | - | 320 | + | 320+ | IVIG, ST, VP | A | CMV IgM(+), ALL |
| 13 | 6.43 | F | - | - | 160 | n/a | n/a | IVIG, ST, VP | D | Enterovirus |
| 14 | 6.57 | M | - | - | 1280 | + | 160+ | IVIG | D | |
| 15 | 8.29 | M | - | n/a | n/a | n/a | n/a | IVIG | D | |
| 16 | 10.64 | M | - | + | 320 | n/a | n/a | ST | A | SLE |
| 17 | 12.27 | F | - | - | 320 | n/a | n/a | ST | A | |
| 18 | 15.38 | F | - | n/a | n/a | n/a | n/a | IVIG, ST | D | |

Abbreviations: M = male; F = female; MRSA = methicillin-resistant *Staphylococcus aureus*; VCA = viral capsid antigen; EBNA = Epstein-Barr virus nuclear antigens; EBEA = Epstein-Barr virus early antigens; IVIG = intravenous immunoglobulin; ST = steroids; VP = etoposide; n/a = not available; D = died; A = alive; ALL = acute lymphoblastic leukemia; SLE = systemic lupus erythematosus; CMV = cytomegalovirus; IgG = immunoglobulin G; IgM = immunoglobulin M

**Table 3.** Comparison of children with and without bacteremia during the active phase of hemophagocytic syndrome

| | Children with bacteremia (n = 7) | Children without bacteremia (n = 11) | $p^a$ |
|---|---|---|---|
| Age (mean ± SD) | 1.54 ± 1.2 | 6.80 ± 4.5 | 0.003 |
| <3 years old | 6 (85.7%) | 3 (27.3%) | 0.025[a] |
| Male gender | 3 (42.9%) | 6 (54.5%) | NS |
| Leukocyte count (μL) | 1271.4 ± 1321.3 | 1678.2 ± 1303.2 | NS |
| ANC | 250.6 ± 331.2 | 1058.3 ± 1115.8 | 0.043 |
| Duration of ANC <500 cells/μL (days) | 14.6 ± 14.3 | 3.6 ± 3.8 | 0.089 |
| Use of steroids | 3 (42.9%) | 7 (63.6%) | NS |
| Use of etoposide | 2 (28.6%) | 3 (27.3%) | NS |
| Mortality | 4 (57.1%) | 7 (63.6%) | NS |

Abbreviations: ANC = absolute neutrophil count; SD = standard deviation; NS = not significant
[a]Fisher's exact test (one-sided).

the bloodstream infections were directly related to the absolute neutrophil count. Children with a longer duration of neutropenia were also at greater risk of bloodstream infection, but the relationship did not reach statistical significance. Use of immunomodulative agents had no obvious effect on the occurrence of bloodstream infection. The final outcome was not significantly different between children with or without bloodstream infection (Table 3).

### Treatment and outcome

Intravenous immunoglobulin (IVIG) was the most commonly administered therapeutic agent, which was given to 16 cases (88.9%) within 2 to 10 days (mean, 5.3 days) of admission. Steroids (dexamethasone, prednisolone or hydrocortisone) were administered to 11 cases (61.1%). Etoposide was administered to 5 patients (27.8%) who were unresponsive to IVIG and/or steroids. No case received a CNS-directed treatment such as intrathecal chemotherapy or cranial irradiation. There was no significant difference in the outcome in terms of the therapeutic regimen (Table 1).

Eleven (61.1%) patients died within 2 months (6 died within 1 month) after the onset of disease. For the other 7 patients who survived, defervescence and recovery of blood cell count were noted within 3 weeks. Five of them had disease-free survival. The other 2 cases later developed SLE and ALL, respectively. The patient with SLE was followed up by the rheumatologist for at least 6 years without hematologic complications. The patient with ALL achieved remission after chemotherapy.

## Discussion

The diagnostic guidelines for HPS was proposed by Henter et al and the FHL Study Group of the Histiocyte Society in 1991, which included clinical, laboratory and histopathological criteria [16]. In this series, certain laboratory tests, though pathognomic for HPS, were not measured in 2 cases, and thus both cases did not fulfill the laboratory criteria for HPS completely. However, they were diagnosed as such according to the clinical and pathological features by both the hematologists and the infectious disease specialists. We believe that this condition is common in clinical practice.

In contrast to patients in western countries, the familial form of HPS is unusual in Asian patients [12]. A single institution in northern Taiwan reported that none of 27 children with HPS had evidence of FHL [12,17]. In the present study, most of the patients enrolled were previously healthy. Parental consanguinity or family history for HPS was not noted in any case. The median age at onset was also much higher in our patients than in children with FHL from previous reports [18] (3 years vs 2.9 months). Furthermore, the case fatality rate was not greater in young children (<2 years) when compared with older children (>2 years) (57.1% vs 63.6%; $p$=0.583). All these findings suggested the rarity of the familial form in this series; in contrast, reactive HPS accounted for the majority. Nevertheless, the familial form of HPS might have been a possible diagnosis for a 2-month-old infant because of his young age at onset, no evidence of active EBV infection, and succumbing to fatality rapidly in spite of aggressive therapy with IVIG, steroids and etoposide.

Enterovirus and parainfluenza type 3 isolated from throat swabs of 3 cases in this study may represent concomitant infections or colonization. However, since HPS has been reported to be associated with these 2 infectious agents [19,20], the possibility that HPS was secondary to enterovirus or parainfluenza infection could not be ignored here. In this study, EB virus accounted

for 72.7% of 11 patients with evidence of viral infection, which was consistent with previous reports [6].

Nosocomially-acquired bloodstream infections occurred in 39% of the 18 cases, and the majority of these were less than 3 years of age. The risk of infection in these cases was related to the severity and duration of neutropenia, as seen in patients with febrile neutropenia secondary to chemotherapy. *P. aeruginosa* was the most common pathogen in this series. Use of immunomodulative agents such as steroids or etoposide, however, was not associated with the subsequent bloodstream infection. The outcome of the patients was not affected by the concomitant bloodstream infections in this study.

EBV-associated HPS was thought to be fatal in a substantial proportion of HPS cases; however, the introduction of an etoposide-based regimen in this disease had greatly prolonged the survival time [12,15]. According to the study reported by Imashuku et al [14], the probability of long-term survival was about 90% when etoposide treatment was begun in the early stage (less than 4 weeks of diagnosis), which was significantly higher than that for patients receiving this agent late or not at all (56%, $p<0.01$). In Taiwan, etoposide-containing regimens also have appeared to be an effective initial therapeutic option for childhood HPS [21]. In a report by Chen et al [21], of 22 children with HPS receiving etoposide with or without IVIG and prednisolone, 12 (54.5%) achieved complete remission, and only 3 experienced early mortality within 1 to 2 weeks. The overall survival was 45.5% and 40.9% at 1 and 5 years, respectively. In this series, the case fatality rate was as high as 61.1%, and all fatal cases died within 2 months of disease onset. The case number in this study may be too small to draw a definite conclusion on this point; however, either late or no administration of the aggressive chemotherapy agent may have contributed to the unfavorable outcome in our patients.

In this series, IVIG with or without steroids was given in the early phase of the disease, in most cases with an indefinite effect. In the literature, the effect of these immunomodulative agents for HPS was also inconclusive. Some cases were responsive [12,22, 23], while others were unresponsive, even leading to a deleterious course [24]. The mechanism of action of IVIG is complicated, and the role of IVIG in treating HPS needs to be clarified in further studies.

In the current study, there was no significant difference between fatal and non-fatal cases in terms of age, gender, associated viral infections, and occurrence of neutropenia-associated bacteremia. The use of aggressive chemotherapy (e.g., use of etoposide), although significantly improving the long-term survival in previous reports, was not associated with favorable outcomes in this retrospective-based study. However, the finding that fatal cases had significantly higher levels of AST, ALP, and direct and total bilirubin, indicated the greater severity of liver injury in such patients. These findings suggest that the extent of liver damage is the most important factor in predicting the final outcome of children with HPS.

In conclusion, HPS usually occurred in previously healthy children, and a substantial proportion of HPS cases rapidly progressed to death. Association with viral infections, especially EB virus, was not uncommon. The cases less than 3 years of age and with a low absolute neutrophil count tended to develop neutropenia-associated bacteremia, but the occurrence of bacteremia had no significant impact on outcomes. On the other hand, the extent of the liver involvement significantly affected outcomes. An effective therapeutic regimen should be further defined.

## References


1. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour HH Jr, Simmons RL, et al. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer 1979;44:993-1002.
2. Wong KF, Chan JK. Reactive hemophagocytic syndrome—a clinicopathologic study of 40 patients in an oriental population. Am J Med 1992;93:177-80.
3. Tsuda H. Hemophagocytic syndrome (HPS) in children and adults. Int J Hematol 1997;65:215-26.
4. Henter JI, Arico M, Elinder G, Imashuku S, Janka G. Familial hemophagocytic lymphohistiocytosis. Primary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 1998;12:417-33.
5. Fisman DN. Hemophagocytic syndromes and infection. Emerg Infect Dis 2000;6:601-8.
6. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 1998;12:435-44.
7. Takagi M, Unno A, Maruyama T, Kaneko K, Obinata K. Human herpesvirus-6 (HHV-6)-associated hemophagocytic syndrome. Pediatr Hematol Oncol 1996;13:451-6.
8. Imashuku S. Differential diagnosis of hemophagocytic syndrome: underlying disorders and selection of the most effective treatment. Int J Hematol 1997;66:135-51.
9. Kikuta H. Epstein-Barr virus-associated hemophagocytic

syndrome. Leuk Lymphoma 1995;16:425-9.
10. Takami A, Yamauchi H, Asakura H, Ishiyama K, Nakao S. Tsutsugamushi disease (scrub typhus)-associated hemophagocytic syndrome. Int J Hematol 2002;75:337-8.
11. Chen YC, Chao TY, Chin JC. Scrub typhus-associated hemophagocytic syndrome. Infection 2000;28:178-9.
12. Chen RL, Lin KH, Lin DT, Su IJ, Huang LM, Lee PI, et al. Immunomodulation treatment for childhood virus-associated haemophagocytic lymphohistiocytosis. Br J Haematol 1995; 89:282-90.
13. Imashuku S. Advances in the management of hemophagocytic lymphohistiocytosis. Int J Hematol 2000;72:1-11.
14. Imashuku S, Kuriyama K, Teramura T, Ishii E, Kinugawa N, Kato M, et al. Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J Clin Oncol 2001;19:2665-73.
15. Imashuku S, Hibi S, Ohara T, Iwai A, Sako M, Kato M, et al. Effective control of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis with immunochemotherapy. Blood 1999; 93:1869-74.
16. Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Semin Oncol 1991;18:29-33.
17. Chen RL, Su IJ, Lin KH, Lee SH, Lin DT, Chuu WM, et al. Fulminant childhood hemophagocytic syndrome mimicking histiocytic medullary reticulosis. An atypical form of Epstein-Barr virus infection. Am J Clin Pathol 1991;96:171-6.
18. Arico M, Janka G, Fischer A, Henter JI, Blanche S, Elinder G, et al. Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. Leukemia 1996;10:197-203.
19. Guerin C, Pozzetto B, Berthoux F. Hemophagocytic syndrome associated with coxsackie virus A 9 infection in a non-immunosuppressed adult. Intensive Care Med 1989;15: 547-8.
20. Kaito K, Kobayashi M, Katayama T, Otsubo H, Ogasawara Y, Sekita T, et al. Prognostic factors of hemophagocytic syndrome in adults: analysis of 34 cases. Eur J Haematol 1997;59: 247-53.
21. Chen JS, Lin KH, Lin DT, Chen RL, Jou ST, Su IJ. Longitudinal observation and outcome of nonfamilial childhood haemophagocytic syndrome receiving etoposide-containing regimens. Br J Haematol 1998;103:756-62.
22. Freeman B, Rathore MH, Salman E, Joyce MJ, Pitel P. Intravenously administered immune globulin for the treatment of infection-associated hemophagocytic syndrome. J Pediatr 1993;123:479-81.
23. Estlin EJ, Palmer RD, Windebank KP, Lowry MF, Pearson AD. Successful treatment of non-familial haemophagocytic lymphohistiocytosis with interferon and gammaglobulin. Arch Dis Child 1996;75:432-5.
24. Nagasawa M, Okawa H, Yata J. Deleterious effects of high dose gamma-globulin therapy on patients with hemophagocytic syndrome. Int J Hematol 1994;60:91-3.