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Clinical Analysis of Early Sepsis in Children with Severe -Thalassemia Major after Transplantation: A Postprint

Authors: Xu Yanjun, Li Chunfu, He Yuelin, Feng Xiaoqin, Pei Fuyu, Wu Xuedong

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Abstract

Objective To investigate the clinical characteristics of early-onset sepsis in children with severe -thalassemia major undergoing stem cell transplantation. Methods The medical records of children with severe -thalassemia major who developed early-onset sepsis following stem cell transplantation at the Pediatric Transplantation Center of Nanfang Hospital between January 2011 and June 2016 were collected, and a retrospective analysis was performed on factors influencing early infection occurrence, infection sites, distribution characteristics of pathogenic bacteria, and drug resistance profiles. Results Among 416 children with severe -thalassemia major who underwent allogeneic hematopoietic stem cell transplantation, 321 developed early-onset infections, with an infection rate of 77.16%; of these, 55 had positive blood cultures, yielding a positive rate of 17.13%. In the 55 children with sepsis, the most common infection route was oral mucosa (65.5%), followed by gastrointestinal tract, lungs, skin, and other sites. Pathogenic bacteria were predominantly Gram-negative bacilli, with the top three species being Escherichia coli (27.3%), Klebsiella pneumoniae (21.8%), and Pseudomonas aeruginosa (9.1%). One case of fungal sepsis was identified, caused by Candida tropicalis. Among the pathogenic isolates, there were 6 ESBL-producing (extended-spectrum -lactamase) cases, 2 MRSA (methicillin-resistant Staphylococcus aureus) cases, and 2 multidrug-resistant bacteria (MDR) cases. Conclusion In children with severe -thalassemia major undergoing stem cell transplantation, early-onset sepsis is predominantly caused by Gram-negative bacilli with high rates of drug resistance, and oral mucosa represents the most common infection site. Rational use of antimicrobial agents, empirical application of antifungal agents, and enhanced care for susceptible sites including the oral cavity, lungs, and anal region are important measures for preventing and treating early infections

in children with severe -thalassemia major undergoing hematopoietic stem cell transplantation.

Full Text

Clinical Characteristics of Early-Onset Nosocomial Sepsis in Children with Severe -Thalassemia after Stem Cell Transplantation

XU Yanjun, LI Chunfu, HE Yuelin, FENG Xiaoqin, PEI Fuyu, WU Xuedong
Department of Pediatrics, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

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Abstract (Chinese Version)

Objective To investigate the clinical characteristics of early-onset sepsis in children with severe -thalassemia following stem cell transplantation. **Methods** Clinical data were retrospectively analyzed for children with severe -thalassemia who developed early-onset sepsis after stem cell transplantation at the Pediatric Transplantation Center of Nanfang Hospital between January 2011 and June 2016. Factors influencing early infection occurrence, infection sites, pathogen distribution, and antimicrobial resistance patterns were analyzed. **Results** Among 416 children with severe -thalassemia who underwent allogeneic hematopoietic stem cell transplantation, 321 developed early infections (77.16% infection rate), with 55 children showing positive blood cultures (17.13% positivity rate). The most common route of infection in these 55 sepsis patients was oral mucosa (65.5%), followed by gastrointestinal tract, lungs, and skin. Pathogens were predominantly Gram-negative bacilli, with the top three being *Escherichia coli* (27.3%), *Klebsiella pneumoniae* (21.8%), and *Pseudomonas aeruginosa* (9.1%). One case of fungal sepsis due to *Candida tropicalis* was identified. Among the pathogens, 6 produced ESBL (extended-spectrum -lactamase), 2 were MRSA (methicillin-resistant *Staphylococcus aureus*), and 2 were multidrug-resistant (MDR) bacteria. **Conclusion** Gram-negative bacilli represent the predominant pathogens causing early-onset sepsis in children with severe -thalassemia after stem cell transplantation, with high average drug resistance rates. Oral mucosa is the most common infection site. Rational antimicrobial use, empirical antifungal therapy, and enhanced care of susceptible sites including oral cavity, lungs, and perianal region constitute important measures for preventing and managing early infections in children undergoing hematopoietic stem cell transplantation for severe -thalassemia.

Keywords: stem cell transplantation; severe -thalassemia; children; nosocomial infection; sepsis

Abstract (English Version)

Objective To explore the clinical characteristics of nosocomial septicemia in the early stage after hematopoietic stem cell transplantation (HSCT) in children with major -thalassemia. **Methods** The clinical data were retrospectively analyzed of 55 consecutive children with major -thalassemia who developed septicemia early after HSCT between January, 2011 and June, 2016. **Results** Among the total of 416 consecutive children with major -thalassemia undergoing allogeneic HSCT, the incidence of nosocomial infection early after transplantation was 77.16% (321/416), and 55 (17.13%) children showed positive findings in blood culture test. The infections occurred most commonly in the oral cavity (65.5%), followed by the respiratory tract, intestinal tract and skin. Gram-negative bacteria, including *Escherichia coli* (27.3%), *Klebsiella pneumoniae* (21.8%) and *Pseudomonas aeruginosa* (9.1%), were the most common causes of infections. Fungal (*Candida tropicalis*) infection caused septicemia in 1 case. Of all the pathogens, extended-spectrum -lactamase (ESBL)-producing bacteria were found in 6 cases, methicillin-resistant *Staphylococcus aureus* (MRSA) in 2 cases, and multidrug-resistant (MDR) bacteria in 2 cases. **Conclusion** Gram-negative bacteria are the major pathogens causing septicemia in children early after HSCT for major -thalassemia, and the bacteria show a high level of drug resistance. Adequate preventive use of antibiotics and care of the oral cavity, the respiratory tract, and the perianal region following the transplantation are important measures to control nosocomial infection in these children.

Key words: hematopoietic stem cell transplantation; major -thalassemia; children; nosocomial infection; sepsis

Introduction

Thalassemia is a genetic disorder caused by gene mutations that impair globin peptide chain synthesis in hemoglobin, and hematopoietic stem cell transplantation (HSCT) currently represents the only curative treatment [1-2]. In 1982, Thomas et al. [3] first reported successful bone marrow transplantation for a thalassemia patient, marking the beginning of HSCT for this disease. In recent years, our institution has achieved remarkable results in HSCT for thalassemia, with a disease-free survival rate of approximately 90.4% at three years [4]. However, infection-related mortality remains a leading cause of transplant-related death, particularly in the early post-transplant period when hematopoietic function has not yet recovered, neutropenia is present, and factors such as intensive immunosuppression, broad-spectrum antibiotic use, and indwelling catheters significantly increase infection risk. Severe infections, especially sepsis, are common causes of death in these patients [5]. Early post-transplant infection generally refers to infections occurring within 30 days after transplantation,

with reported infection rates reaching 86.1% during this period [6]. Previous studies have reported sepsis incidence rates of 12%-34% after transplantation, with higher rates observed before engraftment than after [7-8]. Risk factors include HLA mismatch [9], prolonged neutropenia [10], severity of acute graft-versus-host disease (GVHD) [11], and underlying disease conditions. However, findings across studies have not been entirely consistent. Analysis of infection sites, pathogen distribution, and antimicrobial resistance patterns in early post-transplant sepsis can provide valuable guidance for clinical anti-infective therapy and nursing care, thereby reducing sepsis-related mortality. To date, no large-scale analysis of early sepsis after HSCT for thalassemia has been reported. This study summarizes the clinical presentation of early sepsis in children with severe -thalassemia who underwent HSCT at our pediatric transplantation center between January 2011 and June 2016.

1. Materials and Methods

1.1 Study Subjects

Inclusion criteria comprised a definitive diagnosis of severe -thalassemia based on genotype and undergoing HSCT at our center with early-onset sepsis, defined as positive blood cultures within 30 days post-transplantation. Between January 2011 and June 2016, 416 children with severe -thalassemia underwent HSCT at our center, among whom 55 children with positive blood cultures in the early post-transplant period were included in this study. The basic characteristics of these 55 patients were as follows: male-to-female ratio of 34:22, age range 2-14 years, median age 5 years. Donor sources included related donors in 31 cases (siblings in 24, mother in 2, father in 4, and aunt in 1) and unrelated donors in 24 cases. Transplant types consisted of bone marrow plus peripheral blood stem cell transplantation in 2 cases, peripheral blood stem cell transplantation alone in 38 cases, sibling peripheral blood plus cord blood transplantation in 10 cases, unrelated peripheral blood plus cord blood transplantation in 1 case, sibling cord blood transplantation in 1 case, and related peripheral blood plus unrelated cord blood transplantation in 3 cases.

1.2 Preconditioning Regimen

All patients received myeloablative conditioning regimens, primarily consisting of cyclophosphamide, busulfan, fludarabine, and thiotepa, with or without the addition of anti-human T-lymphocyte rabbit immunoglobulin or rabbit anti-human thymocyte immunoglobulin.

1.3 GVHD Prophylaxis

The primary prophylaxis regimen consisted of mycophenolate mofetil plus cyclosporine, with short-course methotrexate added for unrelated donor transplants.

1.4 Infection Prevention and Treatment Principles

Following total body disinfection, patients were admitted to sterile laminar airflow rooms with 100-grade air quality for total environmental protection and received sterile diets. Daily measures included skin surface disinfection, deep venous catheter care, ultraviolet room disinfection, and chlorhexidine cleaning of floors and items, with all healthcare personnel following strict aseptic techniques when contacting patients. Prophylactic ganciclovir was administered for 7 days beginning 10-14 days before transplantation to prevent cytomegalovirus infection. Routine prophylactic antibacterial therapy was given for 3 days after subclavian vein catheterization. Non-absorbable oral antibiotics were administered for 3 days during the week before conditioning to prevent intestinal infection. Prophylactic antifungal therapy with itraconazole was routinely initiated 2-5 days post-transplantation and discontinued when neutrophil counts remained above 0.5×10 /L for three consecutive days. The treatment principle mandated that broad-spectrum antibiotics, either as monotherapy or combination therapy (including imipenem, meropenem, vancomycin, linezolid, and levofloxacin), be initiated upon any sign of infection. For patients with positive blood cultures, antimicrobial therapy was adjusted according to drug susceptibility testing results, with repeated cultures performed until negative. If symptoms failed to improve after 72-96 hours, empirical antifungal therapy was initiated.

1.5 Diagnostic Criteria

The diagnostic criteria for post-transplant infection [12] were defined as axillary temperature >38°C or two consecutive measurements (2 hours apart) >37.5°C, after excluding the effects of transfusion, medications, and patient condition. The diagnostic criteria for sepsis included: temperature >38.5°C, with bilateral blood cultures and susceptibility testing performed before intravenous antibiotic administration, and diagnosis established based on clinical manifestations including temperature, heart rate, respiratory rate, blood pressure changes, and bilateral blood culture results [13].

1.6 Drug Susceptibility Testing

Drug susceptibility testing was performed using the minimum inhibitory concentration (MIC) method and the SIEMENS WA40SI microbial analyzer, strictly following the standards and guidelines of the Clinical and Laboratory Standards Institute (CLSI).

1.7 Statistical Analysis

Statistical analysis was performed using SPSS 20.0 software. Data were analyzed using t-tests and ^{2} tests, with $P<0.05$ considered statistically significant.

2. Results

2.1 Overall Infection Rate

Between January 2011 and June 2016, 416 children with severe -thalassemia underwent HSCT at our transplantation center. Early post-transplant infections occurred in 321 cases, yielding an infection rate of 77.16%. Infection sites were most commonly oral mucosa (56.70%), followed by lung (28.35%), gastrointestinal tract (22.43%), and skin (6.85%). Among children with early infections, the male-to-female ratio was 193:128. Fifty-five patients had positive blood cultures, representing a positivity rate of 17.13%. This included 34 males (17.62% positivity rate) and 21 females (16.41% positivity rate), with no statistically significant difference between genders (^{2}=0.063, $P>0.05$).

2.2 Sites of Sepsis Infection

The primary infection site in children with sepsis was most commonly oral mucositis, occurring in 34 cases (65.5%), followed by intestinal tract (34.6%), lung (21.8%), perianal region (14.6%), and skin (9.1%). Twenty patients had infections involving two sites, most frequently oral mucositis combined with diarrhea and perianal pain. Ten patients had infections involving three or more sites, typically oral mucositis combined with diarrhea and skin/soft tissue infections (Table 1).

2.3 Characteristics of Pathogenic Strains

Gram-negative bacteria accounted for 67.3% of isolates, totaling 37 cases, with *Escherichia coli* (27.3%), *Klebsiella pneumoniae* (21.8%), and *Pseudomonas aeruginosa* (9.1%) being the most common. ESBL-producing pathogens were identified in 6 cases (10.9%), including 4 *E. coli* and 2 *K. pneumoniae* isolates. Gram-positive bacteria comprised 17 cases (30.9%), predominantly *Staphylococcus aureus* (10.9%), *Staphylococcus epidermidis* (9.1%), *Streptococcus pneumoniae* (3.6%), and viridans streptococci (3.6%) (Table 2).

2.4 Antimicrobial Resistance Patterns

Among the 55 pathogenic isolates, 6 produced ESBL (extended-spectrum -lactamase), 2 were MRSA (methicillin-resistant *Staphylococcus aureus*), and 2 were multidrug-resistant (MDR) bacteria. *E. coli*, *K. pneumoniae*, and *P. aeruginosa* exhibited average resistance rates exceeding 45% to most antibiotics but remained uniformly susceptible to carbapenems such as meropenem and imipenem. *E. coli* demonstrated resistance rates >45% to 18 different antibiotics. *P. aeruginosa* showed varying resistance to the majority of antibiotics, including 52% resistance to ceftriaxone, 43% to ticarcillin/clavulanic acid, and 40% to ciprofloxacin. Gram-positive bacteria including *S. aureus*, *S. epidermidis*, *S. pneumoniae*, and viridans streptococci were all susceptible to vancomycin, teicoplanin, and linezolid, but demonstrated relatively high resistance rates to

other common agents. Two MDR isolates exhibited resistance to aminoglycosides, -lactams, and cephalosporins.

2.5 Relationship Between Peripheral Blood Neutrophil Count and Infection

All 55 patients were in a state of severe neutropenia when infection occurred in the early post-transplant period. However, peripheral white blood cell counts at the time of infection control were significantly higher than before infection ($t=3.616$, $P=0.00$). No significant differences were observed in the timing or duration of infection between patients receiving peripheral blood stem cell transplantation alone versus those receiving combined peripheral blood and cord blood stem cell transplantation ($P>0.05$, Table 3).

2.6 Occurrence of GVHD

Upon close observation, 8 of the 55 children with sepsis developed acute GVHD in the early post-transplant period, manifesting as skin rejection. Following treatment, the skin rash resolved rapidly. No patients with severe GVHD were identified.

2.7 Treatment and Outcome of Infection

All 55 patients recovered following antimicrobial therapy. Eight patients showed no significant improvement after combination antibiotic therapy and were treated empirically with antifungal agents including caspofungin, voriconazole, and liposomal amphotericin B despite negative fungal cultures, resulting in infection control. Fifty-four patients achieved successful engraftment. One patient who underwent sibling bone marrow plus peripheral blood stem cell transplantation experienced graft failure on day +24 and was discharged after discontinuing treatment. No early transplant-related deaths or deaths due to severe infection or sepsis occurred in this cohort.

Discussion

HSCT is now widely used for the treatment of severe thalassemia [14]. The conditioning regimen involves high-dose chemotherapy and immunosuppressive agents that suppress the immune system and damage gastrointestinal mucosa. In the early post-transplant period, hematopoietic function has not yet recovered, leaving the marrow in a essentially "barren" state with extremely low immunity, making patients highly susceptible to infection. Infection represents the most common complication of HSCT and a frequent cause of mortality in these patients. During the early post-transplant period before hematopoietic recovery, prompt empirical administration of antimicrobial agents is crucial and represents one of the key measures for improving transplant success rates [15].

The early pre-engraftment phase generally spans 2-4 weeks after stem cell infusion, with neutropenia and mucosal damage representing the primary predisposing factors [16]. Neutrophils constitute the main cellular component of the defense system against invading microbial pathogens and play a vital role in anti-infective processes. The faster the neutrophil decline and the longer the duration of neutropenia, the higher the risk of concurrent infection and sepsis. Neutrophil dynamics closely correlate with the occurrence and duration of infection [17]. The skin and gastrointestinal mucosal barriers form the body' s natural defense system. The high-dose chemotherapy used in pre-transplant conditioning regimens damages barrier integrity, while intestinal flora dysbiosis and bacterial translocation increase the risk of bloodstream infection [18-19]. In our cohort, sepsis occurred between 0-9 days post-transplantation, with oral mucosa being the predominant infection site (65.5%), followed by respiratory tract, gastrointestinal tract, and perianal skin. The proportion of oral mucosal and gastrointestinal infections was significantly higher than other sites, underscoring the importance of enhanced nursing care, strict aseptic awareness among patients, families, and healthcare staff, and maximal reduction of infection sources during the early post-transplant period. For patients with slow neutrophil engraftment and prolonged neutropenia, subcutaneous G-CSF administration was used to enhance neutrophil chemotaxis, phagocytosis, and pathogen clearance, thereby shortening hospital stays and reducing financial burden on families.

Pathogens causing bloodstream infection in the early post-transplant period include bacteria, viruses, and fungi, with bacteria remaining predominant while fungi and viruses are relatively uncommon. Gram-negative bacteria constitute the main bacterial pathogens, with traditional reports highlighting *E. coli* and *P. aeruginosa*. In our cohort, Gram-negative bacteria represented 67.3% of positive isolates, predominantly *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. Among these, 6 isolates produced ESBL, and 2 each were MRSA and MDR. Drug susceptibility testing revealed high average resistance rates. Our treatment experience for infections occurring before complete hematopoietic recovery involves prompt selection of carbapenems with coverage against most Gram-negative and Gram-positive bacteria, with antimicrobial therapy adjusted according to susceptibility results. This study validates our therapeutic approach. Based on this experience, our center has achieved no early transplant-related deaths from infection, reducing the incidence of severe infection and infection-related mortality with favorable outcomes.

Poutsiaka et al. [11] suggested an association between post-transplant bloodstream infection and acute GVHD, proposing that early conditioning regimen-induced damage to skin and intestinal barriers allows pathogenic microorganisms, particularly lipopolysaccharides on their surface, to enter the systemic circulation and activate donor T cells through antigen-presenting cells, predisposing to aGVHD. However, further research is needed to confirm this hypothesis. In our cohort, 8 cases (14.5%) developed grade I-II acute GVHD in the early post-transplant period, with no severe GVHD observed. The incidence of aGVHD was consistent with reports from other transplant centers domestically

and internationally for other diseases. Our study did not find a close correlation between sepsis and GVHD occurrence, possibly due to the small sample size, observation period limited to one month post-transplant, and the fact that GVHD and infection generally interact in the early post-engraftment period (2-3 months post-transplant) [16].

Invasive fungal infections following HSCT are characterized by insidious onset, often lacking specific signs and symptoms, making early diagnosis difficult. Invasive fungal disease, particularly invasive aspergillosis, has become the leading cause of infection-related mortality after transplantation [20]. Large prospective studies from the United States and Europe have reported that despite reduced invasive fungal mortality over the past decade with the use of third-generation azoles (fluconazole, itraconazole, posaconazole, voriconazole), invasive fungal infection-related mortality can still reach 50% [21]. Our pediatric thalassemia transplant center has achieved favorable results using routine itraconazole prophylaxis beginning 3-5 days after stem cell infusion until neutrophil engraftment. In our cohort, one case of candidemia was identified. Notably, 6 patients with sepsis showed no improvement after 96 hours of potent broad-spectrum antibiotics. Empirical antifungal therapy with caspofungin, voriconazole, and liposomal amphotericin B achieved infection control despite negative fungal cultures. Two of these patients had imaging findings suggestive of fungal infection and were cured after adding caspofungin. Carlos Solano et al. [22] and Yuqian Sun et al. [23] both reported that prophylactic itraconazole reduces invasive fungal infection incidence. Prophylactic use of broad-spectrum antifungal agents during transplantation has become standard practice across transplant centers.

In conclusion, early sepsis after HSCT for severe -thalassemia in children is predominantly caused by Gram-negative bacilli with high average drug resistance rates, with oral mucosa being the most common infection site. Rational antimicrobial use, empirical antifungal therapy, and enhanced care of susceptible sites including oral cavity, lungs, and perianal region represent important measures for preventing and managing early infections in children undergoing HSCT for severe -thalassemia.

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