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Original Article

Clinical characteristics and predictive factors for mortality in coryneform bacteria bloodstream infection in hematological patients

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ABSTRACT

Background: We examined the clinical characteristics and predictive factors for mortality in coryneform bacteria bloodstream infection in hematological patients.
Methods: We searched for hematological patients who had positive blood cultures for coryneform bacteria at our center between April 2007 and January 2016. Patients with definite bloodstream infections were included. We started species identification in April 2014.
Results: Twenty of twenty-eight cases with a positive blood culture for coryneform bacteria were regarded as definite infections. Sixteen and two patients were allogeneic and autologous hematopoietic stem cell transplantation (HSCT) recipients, respectively. *Corynebacterium striatum* was identified in all nine of the cases tested and one patient was co-infected with *Corynebacterium amycolatum*. None of the patients died directly due to coryneform bacteria infection. The survival rates at 30, 60 and 180 days were 100%, 73.7% and 51.3%, respectively. Causes of mortality included progression of the underlying disease (n = 6), other infections (n = 4) and HSCT complications (n = 2). Mixed infection (hazard ratio (HR) 5.47, 95% confidence interval (CI) 1.30–23.0), renal impairment (HR 6.31, 95% CI 1.06–37.4) and absence of a central venous (CV) catheter at the onset (HR 6.39, 95% CI 1.04–39.45) were identified as predictive factors for mortality.
Conclusion: Most of the coryneform bacteria bloodstream infections occurred in HSCT recipients. Contamination seemed to be less common when coryneform bacteria were detected in blood in hematological patients. Although coryneform bacteria bloodstream infection seemed to mostly be manageable, the prognosis was not desirable, particularly in patients with mixed infection, renal impairment and absence of a CV catheter.

1. Introduction

Coryneform bacteria are characterized as irregularly shaped, aerobically growing non-spore-forming gram-positive rods, and encompass several genera, such as *Corynebacterium*, *Arcanobacterium*, and *Brevibacteriumis* [1]. Coryneform bacteria other than *Corynebacterium diphtheriae* are considered to be common contaminants of clinical specimens since they are widely distributed in the environment and colonize the skin and mucous membrane of humans [1]. However, there is increasing evidence of their pathogenicity, particularly in immunocompromised patients [2]. Nosocomial infections attributed to coryneform bacteria in the literature include intravascular catheter-related bloodstream infection, endocarditis, urinary tract infection, respiratory tract infection and surgical wound infection [2–6]. Some reports have highlighted the importance of *Corynebacterium jeikeium* as the cause of catheter-related bloodstream infection in hematological patients [7–9]. Nevertheless, there have been few studies on coryneform bacteria infection in hematological patients and their clinical significance is still unclear. Therefore, we examined the clinical characteristics of coryneform bacteria bloodstream infection in hematological

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patients and also evaluated the predictive factors for mortality in these infections.

2. Patients and methods

2.1. Study patients

The Division of Hematology, Saitama Medical Center, Jichi Medical University has 4 individual rooms and 4 quad rooms (20 beds in total) that are equipped with a laminar air-flow (LAF) system with high-efficiency particulate air (HEPA) filters. Most hospitalized patients undergo allogeneic or autologous hematopoietic stem cell transplantation (HSCT), or intensive chemotherapy for acute leukemia. The first allogeneic HSCT in our center was performed in 2007, and 50 to 70 autologous and allogeneic HSCT procedures have been performed per year since then.

We reviewed the charts of hematological patients who had positive blood culture for coryneform bacteria between April 2007 and January 2016. Among these patients, those with definite coryneform bacteria bloodstream infections, defined as detection of the pathogen in at least two separate blood cultures, were included in this study. As parameters of neutropenia, we calculated not only the simple duration of neutropenia but also the D-index, which reflects both the duration and depth of neutropenia, and the cumulative D-index (c-D-index) from the start of neutropenia until the development of infection as described previously [10,11]. Renal and hepatic impairment were graded by Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0). This study was approved by the Institutional Review Board of Saitama Medical Center, Jichi Medical University.

2.2. Blood cultures, species identification and antimicrobial susceptibility

Blood samples were drawn after the skin or catheter hub was swabbed with 70% alcohol and 10% povidone-iodine. In principle, two sets of blood cultures were obtained. When the patient had a central venous catheter, one blood culture set was drawn from the catheter. Blood specimens were processed by a BD BACTEC 9120 Blood Culture System (2007–2008; BD Diagnostics, Sparks, MD, USA) or a BacT/Alert 3D System (2008–2016; bioMérieux, Inc., Marcy-l'Étoile, France) with incubation for 5 days. Coryneform bacteria were determined by Gram staining, colonial morphology and hemolysis.

Since April 2014, we have sent the coryneform bacteria strains to an outsourcing laboratory (BML Inc., Tokyo, Japan) for species identification. Species were identified by a mass spectrometry microbial identification system (VITEK® MS, bioMérieux, Inc., Marcy-l'Étoile, France).

Antimicrobial susceptibility testing was performed by the Kirby Bauer disk diffusion method. Although the Clinical and Laboratory Standards Institute (CLSI) released standards for susceptibility testing for coryneform bacteria in 2010 [12], we continued to use the breakpoint for antimicrobial agents for *Staphylococcus* during the study period, which was the conventional method until the release of the defined standard by CLSI. In principle, antimicrobial susceptibility tests were performed not only in cases of definite bloodstream infection but also in cases with a single positive set.

2.3. Statistical considerations

Kaplan–Meier curves were used to estimate survival probabilities. The cumulative incidence of mortality was estimated and compared using the logrank test. Factors with at least borderline significance ($P < 0.15$) were subjected to a multivariate analysis by a Cox proportional hazard model. The cut-off P-value was set at 0.05. All statistical analyses were performed with EZR [13], which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.2.2, Vienna, Austria).

3. Results

3.1. Patient characteristics

Twenty-eight hematological patients showed a positive blood culture for coryneform bacteria during the study period. All of them were being hospitalized. Twenty-three (82%) episodes occurred after 2012. In 20 (71.4%) patients, the pathogen was detected in at least two separate blood cultures, and these were considered definite bloodstream infections.

The clinical characteristics of these 20 patients are shown in Table 1. Sixteen (80%) and two (10%) patients were allogeneic and autologous HSCT recipients, respectively. Five allogeneic HSCT recipients were in the post-engraftment phase. The remaining two (10%) patients were undergoing chemotherapy. Most of the patients had neutropenia (75%) and had a central venous (CV) catheter (85%) at the onset of coryneform bacteria bloodstream infection. The median values of the total duration of neutropenia, the cumulative duration of neutropenia from the start of neutropenia until the development of bloodstream infection, the D-index and the c-D-index were 22.5 days, 7.5 days, 9457 and 2702.5, respectively. CV catheter tip cultures were also positive for coryneform bacteria in four patients. Inflammation at CV catheter insertion site was observed in two patients. Oral mucositis (>=grade 3 by CTCAE v4.0) and anal infection (etiology unknown) were observed in seven and two patients, respectively. Culture of pleural effusion was positive for coryneform bacteria in one patient. Three patients without a CV catheter had peripheral venous catheters, and showed uncontrolled underlying diseases and suffered from skin or mucosal damage. All patients had been receiving broad-spectrum antibiotics prophylactically or therapeutically. Corticosteroid had been used in five (25%) patients. Six (30%) patients showed co-infection with bacteria other than coryneform bacteria. One of two patients with septic shock was co-infected with *Escherichia coli*.

3.2. Clinical course

The clinical course in the 20 patients is summarized in Table 2. Susceptible antibiotics for coryneform bacteria were started in all patients at a median of 2.5 days after the onset of infection. In principle, vancomycin was used as the first-line therapy for coryneform bacteria infection. However, other antimicrobials such as teicoplanin, daptomycin and linezolid were selected in cases of renal impairment or allergy toward vancomycin. The disappearance of coryneform bacteria in blood culture was confirmed in all patients and none of them died directly due to coryneform bacteria bloodstream infection. CV catheters were removed within seven days in approximately half of the patients. New abnormal findings on chest computed tomography (CT) were observed in four patients, including multiple small nodules ($n = 2$) and localized consolidation ($n = 2$) at a median of 5.5 days (range, 4–8) after the onset of infection, although the causative pathogens ware not definitive. One patient developed eruption which was pyemid with a high probability.

Breakthrough infections due to gram-negative bacteria and fungi were seen in three patients at a median of 20 days after the development of coryneform bacteria bloodstream infection, which led to poor outcomes. The median survival was 183 days at a median follow-up of 124.5 days (range, 30–874 days). Survival rates at 30, 60, 180 and 365 days were 100%, 73.7%, 51.3% and 38.5%,