

Antibiotic-Resistant Gram-Negative Bacteremia in Febrile Neutropenic Children

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Children with malignancy receiving chemotherapy are prone to suffer from bacteremia and sepsis, which may consequently lead to significant neutropenia, loss of mucosal integrity, and the need for an indwelling central venous catheter. Bacteremia reportedly occurs more often in neutropenic than non-neutropenic episodes (20% vs. 3%) [1], and the presence of sepsis or bacteremia confers a 10-fold increase in the risk of death [2]. Further, febrile episodes are observed in 34% of neutropenic periods in pediatric cancer patients, with bacteremia identified in 10-20% of cases; however, up to 79% of episodes of febrile neutropenia are not associated with serious infection [3].

Pathogens associated with bacteremia and the rates of resistance in febrile neutropenic children vary depending on the time and location. Lee *et al.* [4] conducted a single-center pediatric retrospective study in Seoul, Korea, including 336 bacteremia episodes occurring in 186 febrile neutropenic children over 4 consecutive years, to describe the distribution of the causative bacteria and clinical impact of antibiotic-resistant organisms. Even though there is substantial evidence of a significant shift towards more Gram-positive isolates from blood-cultures in febrile neutropenic children [5], more than

50% of bacteremia cases were caused by Gram-negative bacteria in Lee's study [4]. Moreover, the portion of Gram-positive bacteremia in febrile neutropenic children might be overestimated because the normal skin flora, including coagulase-negative staphylococci, were considered true pathogens in cases with indwelling vascular catheters and use of antibiotics [4]. However, coagulase-negative staphylococci, which are generally low-virulent, can cause serious infection in febrile neutropenic children, and may thus need to be regarded as an actual pathogen in these situations if an alternative source of infection is not identified [6].

Multi-drug resistance (MDR), defined as diminished sensitivity to ≥ 3 of the broad-spectrum antibiotic classes, is known to be associated with increased morbidity and mortality in febrile neutropenia [7]. Lee *et al.* [4] concluded that antibiotic-resistant organisms were significantly associated with increased overall mortality in febrile neutropenic bacteremia, although antibiotic-resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus* spp. and vancomycin-resistant *Enterococcus* spp. were not associated with higher morbidity and mortality compared to non-antibiotic-resistant Gram-positive bacteria. However, antibiotic-resistant

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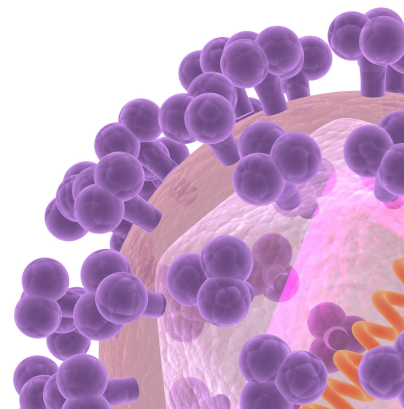
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Gram-negative bacteria, including extended-spectrum β -lactamase producers and carbapenem-resistant organisms, caused significantly higher 7-day mortality compared to non-antibiotic-resistant Gram-negative bacterial infections (25.9% vs. 5.5%; $P < 0.001$). As antibiotic-resistant organisms constituted approximately 30% of Gram-negative bacteria isolated from cases of blood stream infection in febrile neutropenic children in Korea [4], aggressive and prompt management with an appropriate empiric antimicrobial therapy against antibiotic-resistant Gram-negative bacteria can reduce the mortality rates in this population.

Although monotherapy with a broad-spectrum agent covering *Pseudomonas* is recommended as an initial empirical antibiotic in febrile neutropenic patients based on the current guideline [8], a survival benefit was observed when empirical combination therapy was prescribed for children with blood-stream infections caused by MDR Gram-negative bacteria, particularly when receiving agents other than carbapenems [9]. Empirical combination therapy also contributed to the survival of adult patients infected with MDR Gram-negative organisms in another previous study [10]. The emergence of carbapenem-resistant Gram-negative bacteria is of particular concern and children who have risk factors for carbapenem-resistant organisms may benefit from the practice of empirical combination therapy. Because 87% of patients experiencing MDR Gram-negative bacteremia were reportedly previously colonized or infected with MDR Gram-negative organisms [9], screening for MDR isolate carriers would be helpful for making empiric antimicrobial choices.

Well-known risk factors for the emergence of resistant strains include antibiotic pressure as a consequence of prolonged courses of broad-spectrum antibiotics and antimicrobial prophylaxis, and recurrent access to the healthcare setting [7]. Antibiotic therapy should be tailored to individual children, and antimicrobial stewardship is mandatory to prevent the emergence and spread of MDR strains in the healthcare setting. In addition, clinical guidelines to identify low-risk patients who can be managed at out-patient clinics with or without oral antibiotics should be established to reduce the risk of hospital-associated infections and the emergence of multi-drug antibiotic resistance, based on multi-center prospective studies to elucidate the portion of actual bacterial infections in pediatric cancer patients in Korea.

In conclusion, continuous surveillance should be performed to detect changes in the pattern of pathogens and antibiotic resistance among febrile neutropenic children in Korea. Furthermore, modified practice guidelines for the use of anti-

microbial agents adopted from other countries are warranted based on the local pathogen profile.

Conflicts of Interest

No conflicts of interest.

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