



Risk factors for extended-spectrum beta-lactamase-producing *Enterobacteriales* infection: are they the same in neutropenic and non-neutropenic patients?

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Febrile neutropenia (FN) is one of the most frequent and serious complications of chemotherapy for cancer. Neutropenia is defined by an abnormal reduction of neutrophils usually within 7–12 days after chemotherapy. According to the European Society for Medical Oncology (ESMO), FN is defined as “an oral temperature of > 38.3 °C or two consecutive readings of > 38.0 °C for 2 h and an absolute neutrophil count (ANC) of $< 0.5 \times 10^9/L$, or expected to fall below $0.5 \times 10^9/L$ ” [1]. Neutropenic patients may be less capable of fighting infections due to the reduced levels of neutrophils in circulation. In patients with FN, the prognosis is worst in case of proven bacteremia, with mortality rates of 18% in Gram-negative and 5% in Gram-positive bacteremia [2]. During the last decade, the global increase in the prevalence of extended-spectrum β -lactamase (ESBL)-producing *Enterobacteriales* has also affected immunocompromised patients [3]. ESBLs can hydrolyze many beta-lactams except for carbapenems and oxyimino-monobactam, so making bacteria resistant in particular to broad-spectrum cephalosporins.

Because of unanticipated resistance, patients with infection caused by antimicrobial-resistant bacteria usually experience delays in receiving appropriate antimicrobial therapy and have a worse prognosis because of this delay. A recent meta-analysis concluded that the higher mortality in ESBL infections is likely to be mediated by the increased chance to be treated with inadequate empirical therapy [4]. Although some ESBL isolates remain susceptible in vitro to piperacillin–tazobactam, the MERINO trial recently demonstrated that piperacillin–tazobactam should not be used for the treatment of bloodstream infections due to ceftriaxone-resistant

Escherichia coli or *Klebsiella pneumoniae*. The study reported a higher 30-day all-cause mortality rate in the piperacillin–tazobactam arm in comparison with meropenem [5, 6]. These findings could generate a more extensive use of carbapenems undermining the carbapenem-sparing strategy, which aims to decrease selective pressure for carbapenem-resistant *Enterobacteriales* and other Gram-negative bacteria [7, 8]. In this perspective, predicting when the infection is caused by an ESBL-producing isolate becomes crucial to increase the chance of adequate therapy and obtain a better outcome. However, this goal remains exceptionally challenging. The most frequent clinical factors associated with infection caused by ESBL-producing organisms are a history of ESBL colonization/infection, age ≥ 40 years, indwelling vascular device, recent hospitalization in an ESBL high-burden region, and previous antibiotic exposure [9, 10].

Thus, are we allowed to assume the same ESBL-bacteremia risk factors for neutropenic and non-neutropenic patients? Unfortunately, less information is available for adult neutropenic patients, and direct comparison with non-neutropenic ones is lacking. Results from a recent study conducted in neutropenic patients substantially confirmed that a previous antimicrobial therapy, long-term central venous catheter, and hospital-acquired bacteremia are significantly associated with ESBL-bacteremia [11]. Very recently, Kim et al. put forward the idea of considering profound neutropenia as a stand-alone risk factor for ESBL-bacteremia in patients with FN. In the just-mentioned study, neutropenia was in fact divided into two levels: profound and not profound, where profound was defined as an ANC $\leq 0.1 \times 10^9/L$ [12]. The result obtained was intriguing. It was found that profound neutropenia acted as an independent risk factor for ESBL infection after adjusting for age, the presence of a solid tumor, and the parameters of sepsis severity scores. In such complicated clinical contest, this different approach to neutropenia might lead a promising way to be further deepened by prospective studies, maybe with larger sample size, to collect precise information on the other

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possible confounders for FN, such as kind of chemotherapy and location of the tumor.

Prevalence rates of ESBL organisms vary from country to country and even from hospital to hospital [13, 14]. Therefore, we should not forget that both local prevalence and molecular biology represent cornerstones in the decision-making process to adequate antibiotic treatment. In recent decades, we observed a shift in the most common beta-lactamase genes from TEM and SHV to CTX-M. *E. coli* strains with CTX-M enzymes are responsible for both nosocomial and community-acquired urinary tract, intra-abdominal, and bloodstream infections. Moreover, CTX-M *E. coli* isolates are often co-resistant to other antibiotics, including aminoglycosides, cotrimoxazole, and fluoroquinolones [15, 16]. This modification does not seem to be associated with a worse outcome, but the results are controversial and additional studies are needed [17]. Finally, it is noteworthy to say that, after the recent introduction of two the new antibiotics ceftazidime/avibactam and ceftolozane/tazobactam, we now have more weapons to fight multidrug-resistant bacteria. The available data of these two new antimicrobial agents look promising as carbapenem-sparing therapeutic options for the treatment of complicated urinary tract and intra-abdominal infections caused by ESBL-producing *Enterobacteriales*. The role of these new molecules is not well established, especially in the neutropenic setting which could represent a promising field of research.

Compliance with ethical standards

Conflict of interest The authors state that they have no conflicts of interest.

Statements on human and animal rights The article does not contain any studies with human participants or animals performed by the author.

Informed consent None.

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