EDITORIAL

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Third-generation cephalosporin resistance in gram-negative bacteria in the community: a growing public health concern

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The rate of resistance to third generation cephalosporins has increased among gram-negative bacteria (GNB) causing community-onset infections. This is attributed largely to the spread of CTX-M type extended-spectrum β-lactamases (ESBLs) in the community worldwide, especially in *Escherichia coli*. In addition, global expansion of the ST131 clone in *E. coli* is considered a potential cause of the emergence of ESBL-producing *E. coli* in the community [1]. In Korea, ESBL-producing *E. coli* has been increasingly recognized as a cause of community-onset infections since 2007 to 2008, and the proportion of ESBL producers continues to increase at both secondary- and tertiary-care hospitals [2,3]. The proportion of ESBL producers among community-onset *E. coli* isolates increased markedly from 3.6% in 2006 to 14.3% in 2011 at a tertiary-care university hospital in Seoul [3]. Such an increase in the proportion of ESBL-producing *E. coli* was also noted at a secondary-care hospital in Daejeon [2], with the proportion of ESBL producers increasing from 1.2% in 2005 to 10.2% (17/167) in 2010. In Korea, CTX-M14 and -15 were the most frequently identified ESBL types among ESBL-producing *E. coli* isolates, suggesting that the wide spread of these genes is partly responsible for the current increase in the incidence of community-onset infections caused by ESBL-producing *E. coli* [3,4]. While ESBL-producing *E. coli* in the community has been investigated extensively, the clinical and epidemiological features of community-onset ESBL-producing *Klebsiella pneumoniae* have not been well characterized, although a recent study suggested that the number of ESBL-producers appeared to be increasing in *K. pneumoniae* isolates associated with community-onset bacteremia [5]. One study in Korea also showed an increasing trend in ESBL-producing *K. pneumoniae* as a cause of community-onset bacteremia [6]. Nonetheless, the number of cases was small, most were healthcare-associated, and the results could be confounded by selection bias; therefore, the actual prevalence of ESBL-producing *K. pneumoniae* in the community is still considered to be low; further investigation of this issue is necessary.

In this issue of *The Korean Journal of Internal Medicine*, Lee et al. [7] reported the rate of third generation cephalosporin resistance among *E. coli* and *K. pneumoniae* causing community-onset

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bacteremia at a secondary-care hospital in Daegu over a 7-year period from 2003 to 2009. As the authors discussed in their article, most of the epidemiological studies of antibiotic resistance in Korea have been conducted at patients who visit tertiary care hospitals are more likely to have been exposed to healthcare settings, the data from such studies might not fully reflect the current epidemiological change in the community. Therefore, this article, together with the aforementioned study at a secondary-care hospital in Daejeon, can give valuable insight into the recent trend in third generation cephalosporin resistance in GNB in the community. This article reports that the third generation cephalosporin resistance rate was significantly higher in 2009 compared to 2005 (10.6% vs. 4.3%, respectively), which is consistent with Park et al. [2] (10.2% in 2010 vs. 1.2% in 2005). Although the authors did not specify the proportion of ESBL producers, the third generation cephalosporin resistance rate can be regarded as the proportion of ESBL-producing organisms because in this study the vast majority (91.1%) of third generation cephalosporin-resistant bacteria produced ESBL.

However, the authors analyzed third generation cephalosporin-resistant bacteria together, including *E. coli* and *K. pneumoniae*, which made it difficult to understand the antibiotic resistance profiles and risk factors for each pathogen. Instead of the CTX-M type, the SHV type was the predominant *ESBL* gene in ESBL-producing *K. pneumoniae* in the community [6]. Consequently, different antibiotic resistance profiles are expected in *E. coli* and *K. pneumonia*. Moreover, there are clinical and epidemiological differences between *E. coli* and *K. pneumoniae*. As in this article, most of the *E. coli* infections were of the urinary tract, whereas *K. pneumoniae* most commonly infected the abdomen. Despite this limitation, the authors provided data on the third generation cephalosporin resistance rate in GNB in a particular community. From a clinical perspective, this gives a straightforward choice of empirical antibiotic therapy for patients with GNB sepsis presenting at emergency departments.

This changing epidemiology of the antibiotic resistance profiles in GNB poses a great challenge to public health for three reasons: 1) the choice of the optimal empirical antibiotic therapy for patients with gram-negative bacteremia; 2) the potential emergence of carbapenem-resistance among *Enterobacteriaceae*; and 3) the increasing economic burden on the public due to the need for prolonged hospitalization and intravenous antibiotic therapy.

Third generation cephalosporin resistance leaves us with only limited options for treating patients with gram-negative bacteremia, and carbapenem is considered the treatment of choice. Third generation cephalosporins are used frequently for empirical therapy for patients with suspected gram-negative bacteremia acquired in the community. As we might expect, the initial therapy is more likely to be inadequate for patients with community-onset bacteremia caused by ESBL producers, which could have a detrimental impact on clinical outcomes [8]. However, because of the emergence of carbapenem resistance in GNB, a serious conflict is raised: the need to use carbapenem when ESBL-producing bacteria are suspected versus the need to avoid the overuse of carbapenem to contain resistance. Therefore, empirical antibiotics should be chosen cautiously based on patient risk factors for acquiring third generation cephalosporin resistance and the severity of illness. During the current crisis in new antibiotic development, alternatives to carbapenem continue to be sought among existing antibiotics and their efficacy must be evaluated properly.

Several alternatives to carbapenem have been suggested as empirical and definitive therapy: amikacin, a β-lactam/β-lactamase inhibitor such as piperacillin-tazobactam, fosfomycin, or nitrofurantoin. Previous studies suggested amikacin as adjuvant therapy based on the low rate of resistance (2.9% to 4%) among community-onset ESBL-producing *E. coli* isolates [2,9]. Lee et al. [7] also suggested a combination of a third generation cephalosporin and amikacin as empirical therapy because of the very low resistance rate (< 1%) to this combination among *E. coli* and *K. pneumonia* overall. However, it is concerning that the amikacin resistance rate (13.3%) was relatively high among third generation cephalosporin-resistant bacteria.

Although the use of a β-lactam/β-lactamase inhibitor for treating serious infections caused by ESBL-producers remains controversial, piperacillin-tazobactam was shown to be as effective as carbapenem when used as empirical therapy in a recent observational study

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[10]. It is indeed promising, but remains debatable without randomized controlled clinical trials. That observational study could have been affected by residual confounding even after adjusting for confounding variables by indication; moreover, the size of the study population might have been insufficient to reach statistical power. This could artificially deflate the efficacy of carbapenem and inflate that of piperacillin-tazobactam, failing to reject the statistical difference. Consequently, randomized clinical trials are necessary to evaluate the clinical efficacy of alternatives to carbapenem in the future. Despite such need, it is difficult to randomize patients with serious infections and clinical experience with piperacillin-tazobactam for patients with serious infections caused by ESBL producers remains insufficient to strongly support their use [8]. Therefore, further clinical experience, together with pharmacokinetic/pharmacodynamics studies, is needed for more appropriate use of piperacillin-tazobactam against ESBL producers. More importantly, it is essential to obtain up-to-date knowledge regarding the resistance profiles of local isolates in the community. Recent data showed regional differences in the resistance to piperacillin-tazobactam among ESBL producers, ranging from 74% for ESBL-producing *K. pneumoniae* to 13% for ESBL-producing *E. coli* [10]. Fortunately, the resistance rate for piperacillin-tazobactam among ESBL-producing *E. coli* was relatively low in Korea, ranging from 12% to 21% [2,9]. Lee et al. [7] demonstrated that the piperacillin-tazobactam resistance rate was 20% (9/45) among third generation cephalosporin-resistant isolates in Daegu. These data suggest no marked regional differences in Korea at present. However, these data represent an only minute faction of the overall epidemiology of antibiotic resistance profiles in Korea at one point in time. To implement treatment in a timely manner, an ongoing epidemiological study of antibiotic resistance regionally, as well as nationwide, is needed.

In summary, the results reported by Lee et al. [7] helped us to better understand the antibiotic resistance profiles of GNB in the Korean community. The rate of third generation cephalosporin resistance has increased dramatically in *E. coli* and *K. pneumoniae* causing community-onset bacteremia community-onset bacteremia at a secondary-care, community-based hospital in Korea. Given that this study included only bacteremic patients, who accounted for a small proportion of bacterial infections, the true burden of third generation cephalosporin resistance among GNB in the community appears to be greater than expected. Furthermore, antibiotic resistance profiles change continuously over time and resistance is positively selected by current antibiotic-prescribing practices. In this regard, systematic nationwide population-based surveillance of antibiotic resistance should be conducted, including in the primary care sector, and the implementation of appropriate antibiotic stewardship is advised to minimize application of inadequate antibiotic therapy without increasing adverse health outcomes.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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