Review

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Management of Extended-Spectrum Beta-Lactamase-Positive Gram-Negative Bacterial Urologic Infections

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Extended-spectrum beta-lactamases (ESBLs) are enzymes that confer increased resistance to commonly used antibiotics. The prevalence rates of ESBL producing bacteria are increasing, and the associated increase in morbidity and mortality is becoming a public health concern. ESBL producers are emerging as an important cause of urinary tract infection (UTI) and empirical therapy should therefore be carefully selected for patients with UTI. Fosfomycin or nitrofurantoin would be an appropriate choice for empirical therapy of uncomplicated UTI. Ertapenem or cefepime might be recommended for initial empirical therapy patients suspected of having complicated UTI.

Keywords: Extended-spectrum beta-lactamases; Urinary tract infections; Antibacterial agents

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INTRODUCTION

Extended-spectrum beta-lactamases (ESBLs) are enzymes that induce resistance to most beta-lactam antibiotics such as penicillins, cephalosporins, and monobactam [1]. ESBL producing organisms remain an important cause of therapy failure with beta-lactam antibiotics and have a serious impact on infection control [2]. Therefore, the detection of ESBL producing organisms and the correct choice of antibiotics is important.

Large numbers of outbreaks due to ESBL producing organisms have been reported around the world and their prevalence is increasing [3]. The incidence of urinary tract infection (UTI) caused by ESBL producers is also rising [4]. Because of the increasing importance of ESBL producing bacteria in the community, clinicians should be aware of the potential of treatment failure associated with urinary infections caused by these organisms. In this review, we examine the basis for caution associated with the use of antibiotics for ESBL producing organisms and discuss whether available clinical evidence justifies the choice of antibiotics.

EXTENDED-SPECTRUM BETA-LACTAMASEs

Beta-lactamases (BLs) are enzymes that open the beta-lactam ring and inactivate beta-lactam antibiotics. Production of BL is the essential mechanism of resistance against beta-lactam antibiotics [5]. Historically, these enzymes, such as TEM-1 and TEM-2, were proven to hydrolyze penicillins and narrow-spectrum cephalosporins such as cefazolin or cephalothin, but were shown to be ineffective against higher generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone, or cefepime). Therefore, these higher generation antibiotics were introduced for use against BL producing bacteria. However, shortly after the introduction of

cefotaxime into clinical use, strains of *Klebsiella pneumoniae* with transferable resistance to the third-generation cephalosporins, such as cefotaxime, ceftazidime, and ceftriaxone, were found in Germany [6]. Since then, an increase in the variety of BLs has been reported and ESBL producing bacteria have spread throughout the world. The rapid evolution and spread of BLs is believed to result from the widespread use of antibiotics in human and veterinary medicine [7].

1. Classification of Extended-Spectrum Beta-Lactamases

BLs can be classified according to two general schemes: the Ambler molecular classification and the Bush-Jacoby-Medeiros functional classification system [8,9]. The Ambler scheme divides BLs into four major classes according to protein homology. In contrast, the Bush-Jacoby-Medeiros classification groups BLs into four main groups and multiple subgroups according to functional similarities. The characteristics of these two classification systems are summarized in Table 1 [10]. Although there is no precise definition of ESBLs, the commonly used working definition is that ESBLs are enzymes with hydrolysis capacity for penicillins, first-, second-, and third-generation cephalosporins, and aztreonam, that exhibit susceptibility to BL inhibitor [1]. Most ESBLs are included in group 2be, members of which inactivate penicillins, cephalosporins, and monobactams, and are inhibited by clavulanic acid.

The key characteristic of ESBLs is their ability to inactivate third-generation cephalosporins. A great diversity of ESBLs has been reported and the most frequently encountered ESBLs belong to the TEM, SHV, and CTX-M classes [11]. TEM BLs have amino acid substitutions around the active site of the enzyme that change the configuration to allow hydrolysis of oxymino-beta-lactam substrates [11]. Based on the type of change, hundreds of TEM-type enzymes have been described to date [12]. SHV-type ESBLs also have amino acid changes around the active site [13], and are most commonly found in *K. pneumoniae* [11]. CTX-M BLs that preferentially hydrolyze cefotaxime have low relatedness to TEM or SHV-type ESBLs [14]. They have been found in many different *Enterobacteriaceae* [15], and known as the most common ESBL type in ESBL producing *Escherichia coli* and worldwide [16].

2. Detection

The detection methods for ESBLs are divided into two groups: phenotypic methods that detect the ability to hydrolyze different cephalosporins and genotypic methods using molecular techniques that detect the genes responsible for ESBL production. Most clinical laboratories use phenotypic methods because of their convenience and cost effectiveness; however, detection of ESBL by phenotypic methods cannot confirm the specific enzymes involved and molecular methods should be applied for the determination of specific ESBLs.

The Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) have published guidelines for ESBL detection in *Enterobacteriaceae* [17,18]. Previously, the CLSI recommended screening of isolates of *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* by disk diffusion or broth dilution for resistance, followed by a confirmatory test for increased susceptibility in the presence

Table 1. Main features of two general classification schemes [10]

Bush-Jacoby-Medeiros group	Ambler molecular classification	Preferred substrate	Representative enzyme	Resistance or susceptibility to beta-lactamase inhibitor
1	C	Cephalosporins	AmpC	Resistant
2b	A	Penicillins, cephalosporins	TEM, SHV	Susceptible
2be	A	Penicillins, extended-spectrum cephalosporins, monobactams	TEM, SHV	Susceptible
2d	D	Penicillins, cloxacillin	OXA	Resistant
2e	A	Cephalosporins	Inducible cephalosporinases from *Proteus vulgaris*	Susceptible
2f	A	Penicillins, cephalosporins, carbapenems	NMC-A from *Enterobacter cloacae*	Resistant
3	B	Most beta-lactams including carbapenems	L1 from *Stenotrophomonas maltophilia*	Resistant

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of BL inhibitor. In 2010, however, CLSI revised the minimum inhibitory concentration (MIC) and disk diffusion breakpoints for the *Enterobacteriaceae*, and many organisms that were previously classified as susceptible using the former breakpoints were recategorized as intermediate or resistant [19]. EUCAST also changed the breakpoint criteria in 2010, and ESBL confirmatory testing is no longer necessary in both CLSI and EUCAST guidelines.

Molecular tests for specification of ESBLs may be performed for epidemiological studies and infection control purposes. Because of the diversity of different point mutations that can result in ESBLs, genetic methods for the detection of TEM- or SHV-type ESBLs are complex and challenging. As a result, the most commonly used molecular method is target amplification followed by direct sequencing of the bla_{TEM} and bla_{SHV} genes [20]. Several other molecular methods such polymerase chain reaction (PCR) with restriction fragment length polymorphisms and real-time PCR also have been developed to eliminate thbe use of sequencing [21,22]. However, a large number of new mutations within each ESBL have been reported to date; therefore, these techniques have considerable limitations with respect to covering the whole range of variants with different point mutations.

EPIDEMIOLOGY

1. Global Epidemiology

ESBL producers have been reported worldwide, not only in hospital specimens but also in samples from the community. It was also reported that prevalence rates vary from hospital to hospital and from country to country [23]. In the Tigecycline Evaluation and Surveillance Trial, the rates of ESBL producers among *K. pneumoniae* were highest in Latin America, followed by Asia/Pacific Rim, Europe, and North America [24].

High rates of ESBL producing bacteria are present in Asia. In 2002, the prevalence of ESBL-producing clinical isolates in the Asia-Pacific region and South Africa was published by the SENTRY Antimicrobial Surveillance Program. Because of the large geographical area, there was considerable variation in prevalence rates and genotype of ESBL producers [25]. After this report was published, a large number of prevalence reports were published for many Asian countries [26]. National surveillance programs have indicated the presence of ESBLs in 5-8% of *E. coli* isolates from Korea, Japan, Malaysia, and Singapore and 12-24% of isolates from Thailand, Taiwan, Philippines, and Indonesia [1].

2. Epidemiology in Korea

One of the earliest studies on the prevalence of ESBL phenotypes in Korea reported that 7.5% of *E. coli* and 22.8% of *K. pneumoniae* isolates were identified as ESBL-positive in 1994 [27]. Since then, several reports on the prevalence of bacteria with ESBLs in Korea have been published and suggest increasing prevalence rates. A survey conducted from 2005 to 2008 in Gwangju reported that 12.6% (196/1,550) of *E. coli* isolates and 26.2% (294/1,210) of *K. pneumoniae* isolates produced ESBLs [28]. The most prevalent ESBLs were CTX-M (93.5%) and SHV (12.9%) in *E. coli* isolates, and SHV (73.2%) and CTX-M (46.3%) in *K. pneumoniae* isolates. For UTI, Lee et al. [29] reported the total prevalence of UTI due to ESBLs was approximately 13%. It was suggested that increasing trends of ESBL-positive isolates were associated with spread of ESBLs throughout communities [30]; however, the lack of a population-based study limits estimation of the exact prevalence of ESBL producing organisms in Korea.

MANAGEMENT OF INFECTIONS CAUSED BY ESBL PRODUCERS

The choice of appropriate antibiotics is extremely important because failure to successfully treat with antibiotics against an ESBL producer is associated with lack of an adequate response and increased mortality [31,32]. The treatment outcome of this effect was described in a review of 85 patients with ESBL-producing *K. pneumoniae* infection from 12 hospitals in 7 countries, among which 20 patients (24%) died [31]. In this study, multivariate analysis with other predictors of mortality showed that administration of a carbapenem alone or with other antibiotics was associated with a significantly lower mortality than treatment with other antibiotics. Similar efficacy of carbapenem was noted in a smaller study of 10 patients. Endimiani et al. [33] reported the treatment outcome of bacteremia caused by *K. pneumoniae*. Of 10 patients treated with imipenem, 2 patients failed to respond. In contrast, only 2 of 7 cases had a partial response to ciprofloxacin, and the other 5

cases failed to respond [33].

1. Carbapenem

The carbapenem family (imipenem, meropenem, and doripenem) is regarded as first-line therapy for severe infections caused by ESBL producing organisms. Treatment with imipenem or meropenem has demonstrated the best outcome in terms of survival and bacteriologic response rates, and no clear differences in efficacy between these two carbapenems were shown [34]. More recently, doripenem was approved by the US Food and Drug Administration and introduced as a relatively new carbapenem. Although clinical data for infections with ESBL producers are limited, they suggest that the efficacy against ESBL producers is equivalent to that of meropenem or imipenem [35]. The drawback of these carbapenems is very their short half-life and the need for injection by intravenous infusion every 6 to 8 hours. Ertapenem demonstrates an extended serum half-life and has the advantage of once-daily dosing [36]. It also has good in vitro activity [37], and clinical data suggesting its usefulness are accumulating.

However, increased use of carbapenems creates selection pressure for carbapenem resistance and the emerging challenge of carbapenem resistance mediated by the efficient spread of carbapenemases. In response to these concerns, well designed, prospective, and randomized trials have recently recruited participants to demonstrate the efficacy of alternative treatment strategies replacing carbapenems for serious ESLB infections, and the choice of alternative antibiotics will be powered by evidence from these trials in the near future.

2. Cephalosporin

ESBLs have an ability to hydrolyze the oxymino-beta-lactams such as cefotaxime, ceftazidime, ceftriaxone, or cefepime. Although some ESBL producers may show in vitro susceptibility [32,38], treatment of severe infections caused by ESBL producers with these drugs is likely to result in treatment failure. This could be explained by the inoculum effect, in which an increase in MIC is proportional to the increased inoculum [39]. Cefepime may be potentially effective against ESBL producing bacteria if administered in high doses [40]. However, there are still debates over the use of cefepime for treatment of infections because of ESBL-producing pathogens [41,42], and one study showed trends between empirical cefepime therapy and increased risk of mortality, and between carbapenem therapy and decreased risk of mortality [43].

3. Beta-Lactam-Beta-Lactamase Inhibitors

By definition, ESBLs can be inactivated by clavulanic acid. Theoretically, beta-lactam-beta-lactamase inhibitors (BLBLIs) such as amoxicillin-clavulanate, ticarcillin-clavulanate, and peperacillin-tazobactam might be effective for ESBL producing organisms. ESBL producers frequently showed susceptibility to BLBLIs in vitro, yet the role of BLBLIs in the clinical treatment of ESBL producers is uncertain [20]. The most important issue concerning the use of BLBLIs for infections caused by these pathogens is the possibility of decreased efficacy with high bacterial load [44]. It is thought that high inoculum infection might overwhelm the effect of BL inhibitors as demonstrated by time-kill studies [39,45]. Some reports and meta-analysis data have suggested that BLBLIs are not inferior to carbapenems for serious infections [46,47], but controversies about the use of BLBLIs for ESBL producers still exist.

MANAGEMENT OF UTI SECONDARY TO ESBL-PRODUCING BACTERIA

1. General Treatment Strategy

The treatment of serious infections with ESBL producers requires carbapenem-based therapy; however, the management of patients with infections in the ambulatory setting is different. Because of the increase in resistance among gram-negative bacteria and the lack of oral treatment options, management of UTI is not a simple issue. If a UTI is suspected, the patient should be evaluated for risk factors of multidrug-resistant bacterial infection. These risk factors include age older than 60 years, prior UTI history or chronic medical conditions, recent hospitalizations or antibiotic treatment, and recent travel [48]. Next, whether the patient is colonized or has a clinical infection should be considered. If the patient is infected with ESBL producers, inappropriate treatment will increase the risk of drug resistance. Moreover, treatment has additional risks of increasing resistance at the community level and narrowing future treatment options for the affected patient. For these reasons, caution is needed when treating patients with asymptomatic bacteriuria because of the possibility of

carrying an ESBL producer.

The treatment approaches for infections with ESBL producers require additional clinical considerations such as the choice of appropriate antibiotics, the combination of therapies, and the time of switching to intravenous antimicrobial treatment for closer observation. Because the treatment of UTI in an outpatient setting is usually empirical, it is likely that patients will be treated with a drug that does not have in vitro activity against the uropathogen [49]. This requires acceptance between clinicians and patients that initial empirical antibiotics may be incorrect and a switching therapy may be needed based on antimicrobial susceptibility results and the clinical response [50].

A number of guidelines reviewing the diagnosis and treatment of UTI were published and the selection of initial empirical therapy was emphasized [49,51]. For acute uncomplicated UTI caused by ESBL producing organisms, UTI-specific antibiotics such as fosfomycin or nitrofurantoin would be good treatment options and convenient in the outpatient setting. However, complicated UTI is associated with an underlying condition such as structural or functional abnormality of urinary tract [52], and potential of treatment failure and serious complications such as the development of antimicrobial resistance or systemic infection is more common than uncomplicated UTI [53]. Therefore, if empirical therapy is needed, antibiotic agent that can cover the most relevant pathogens should be considered and a suggested guide to potential therapeutic agents for ESBL producers is presented in Table 2 [50]. Due to limited systemic absorption, fosfomycin and nitrofurantoin could not be used in this case [53].

2. Fosfomycin

Fosfomycin is a broad-spectrum antibiotic produced by certain *Streptomyces* species [54]. It is an inhibitor of bacterial cell wall synthesis and has excellent bactericidal activity in the urinary tract. Falagas et al. [55] performed a meta-analysis of randomized controlled trials and reported no difference between fosfomycin and comparators in clinical outcomes such as microbiological success, relapse, and reinfection. It is also known that resistance to fosfomycin is uncommon. Given these advantages, fosfomycin will be a useful choice for empirical treatment of UTI secondary to ESBL producing organisms [50]. Recently, a trial comparing outcomes between fosfomycin and carbapenems in UTI caused by ESBL producing *E. coli* was launched. The fosfomycin versus meropenem or ceftriaxone in bacteriemic infections caused by multidrug resistance in *E. coli* (FOREST) study is a phase III, randomized, controlled, multicentric clinical trial designed to prove the non-inferiority of fosfomycin versus meropenem in UTI caused by ESBL producing *E. coli* [56]. This study is approved until August 2017, and it is expected that the results will have a major impact on the use of fosfomycin in UTI.

3. Other Antibiotics

The bactericidal drug nitrofurantoin can achieve sufficient urine and bladder concentrations, but not serum or tissue levels [50]. Therefore, this antibiotic is not in use for pyelonephritis, prostatitis, or other severe diseases and is contraindicated in pregnancy and patients with renal failure. Other oral antibiotics, such as fluoroquinolones and trimethoprim-sulfamethoxazole, can be used according to antimicrobial susceptibility results and when local resistance patterns are known [49]. If considering parenteral therapeutic

Table 2. Suggested treatment regimens[a] for UTIs secondary to ESBL producing organisms [50]

Uncomplicated UTI
Fosfomycin, 3 g by mouth sachet in 90-120 ml of water
Nitrofurantoin, 100 mg by mouth twice a day
Cefdinir, 300 mg by mouth twice a day, and amoxicillin/clavulanic acid, 875 mg by mouth twice a day (in vitro data only)
When susceptibilities are known or local antibiogram is supportive:
Trimethoprim/sulfamethoxazole 1 double-strength tablet by mouth twice a day
Fluoroquinolones (500 mg by mouth twice a day for ciprofloxacin or 500 mg by mouth daily levofloxacin)
Complicated UTI
Cefepime, 2 g IV every 12 hours
Ertapenem, 1 g IV per day (other carbapenems also acceptable)
Aminoglycosides IV (amikacin, 15-20 mg/kg per day; gentamycin, 4-7 mg/kg per day)

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UTI: urinary tract infection, ESBL: extended-spectrum beta-lactamases, IV: intravenous.
[a]Doses are based on normal renal function and may need adjustment for reduced glomerular filtration rate.

options for outpatient urinary infections caused by ESBL producers, carbapenems could be considered [57]. Because of the once-a-day dosing schedule, injection with ertapenem would be the most convenient treatment option for outpatient parenteral antimicrobial therapy [58].

4. New Therapeutic Approaches

Several new treatment options are being tested to establish non-carbapenem therapy of UTI caused by ESBL producing organisms. In a retrospective cohort study, Beytur et al. [59] achieved 84.7% (39 out of 46 patients) treatment success with amoxicillin-clavulanic acid treatment for UTI secondary to ESBL producers. However, some strains with high MICs for amoxicillin-clavulanic acid developed resistance during therapy, especially *Klebsiella* species [59]. Other reports showed that alternatives to carbapenems, especially piperacillin-tazobactam, seem to be good treatment options for non-bacteremic UTI [60]. Recently, several novel agents were evaluated for the indication of complicated UTI [61]. These regimens include plazomicin monotherapy and combination of ceftolozane with tazobactam, and revealed good coverage for ESBL-carrying organisms in several clinical trials.

CONCLUSIONS

The conventional therapy for UTI is administration of antibiotics for 3 to 10 days. However, empirical treatment of these infections is sometimes problematic as a result of the emergence of ESBL producing organisms among common pathogens including *E. coli* and *K. pneumoniae*. Because of their excellent activity against ESBL producing bacteria, carbapenems have been suggested as the most reliable antibiotics for the treatment of infections caused by these pathogens. However, the disadvantages of carbapenems, such as intravenous administration and selection pressure for carbapenem resistance, complicate the selection of antibiotics for uncomplicated UTI caused by ESBL producers, especially in an outpatient setting.

When choosing appropriate antibiotics, no matter which antibiotics were selected as empirical therapy for UTI, clinicians must keep in mind that antimicrobial susceptibility should be the most important parameter guiding their choice. During the treatment of UTI, switching antibiotics should be always considered according to antimicrobial resistance and clinical response.

Generally, fosfomycin or nitrofurantoin would be an appropriate choice for empirical therapy of uncomplicated UTI. In patients suspected of having complicated UTI, ertapenem or cefepime might be recommended for initial empirical therapy.

Coupled with the fact that prevalence rates of UTI caused by ESBL producers are increasing globally, including in Korea, and the limited knowledge of effective antimicrobial therapy, further research into the epidemiology and effectiveness of therapy is required to develop the most active and cost-effective empirical therapy for UTI.

CONFLICT OF INTEREST

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

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