

THIS CPD/CEU EXERCISE IS PRESENTED UNDER THE THISTLE QA SERVICE PROVIDER NO : MT00025. IT IS DESIGNED TO TAKE PLACE WITHIN YOUR OWN LABORATORY AS A SMALL GROUP ACTIVITY LASTING APPROXIMATELY ONE HOUR. PLEASE ENSURE THAT YOU KEEP A REGISTER OF THOSE TAKING PART IN THIS EXERCISE AND SUBMIT YOUR APPLICATION FOR 1 CEU POINT ON THE APPROPRIATE HPCSA FORM, ALONG WITH THE RELEVANT THISTLE QA PARTICIPATION CERTIFICATE SENT TO YOUR LAB WITH YOUR EQA KIT AND INSTRUCTIONS.

Cycle 19 Organism 1.

The causative organism was Extended-Spectrum Beta-Lactamase-Producing Isolates

Introduction

The evolution of bacteria since penicillin was introduced into clinical practice in the 1940s clearly indicates that antimicrobial resistance will develop given sufficient time and use of a particular agent or class of agents. β -Lactam antibiotics are among the safest and most frequently prescribed antimicrobial agents in the United States and worldwide; however, emergence of β -lactam resistance in clinically important pathogens has increasingly limited their utility. To treat infections due to β -lactamase-producing bacteria that were resistant to penicillin and early cephalosporin derivatives, new generations of relatively enzyme-stable and broad-spectrum cephalosporin derivatives were introduced in the late 1970s and 1980s. However, over the past decade, antibiotic-resistant mutants producing extended-spectrum β -lactamase (ESBL) emerged among gram-negative bacteria, predominantly *Escherichia coli* and *Klebsiella pneumoniae*.^[1,2]

The emergence of ESBL-producing isolates has important clinical and therapeutic implications. Most bacterial isolates, resistance determinants for ESBL production are carried on plasmids that can be easily spread from organism to organism.^[1] The spread of resistance toward extended-spectrum cephalosporins further limits the utility of the β -lactam class and may lead to increased prescription of more broad-spectrum and expensive drugs such as the carbapenems. These resistant isolates may escape detection with routine susceptibility testing performed by a clinical microbiology laboratory, which can result in adverse therapeutic outcomes.^[3,4] More important, antibiotic selection for treatment of serious infections due to ESBL-producing *E. coli* and *K. pneumoniae* is a clinical challenge due to the complex nature of in vitro susceptibility testing and in vivo correlation. The biggest challenge lies in overcoming widespread unawareness among clinicians regarding these resistant organisms due to underreporting by microbiology laboratories and lack of an obvious marker to indicate production of an ESBL.^[2,5] Ceftazidime or cefpodoxime resistance is the best indicator for most of the TEM- and SHV-derived ESBL types, but cefotaxime resistance is a better indicator for CTX-M type enzymes.^[1] Resistance to ceftazidime, in the absence of resistance to ceftoxitin is strongly indicative of ESBL production.

Mechanism of Resistance

Extended-spectrum β -lactamases are primarily plasmid-mediated enzymes that are frequently derived from either a TEM- or SHV-related enzyme. Both TEM-1 and SHV-1 are parent enzymes that confer resistance to ampicillin.^[5] Ampicillin-resistant isolates producing high levels of enzyme may be resistant to piperacillin and narrow-spectrum cephalosporins such as cefazolin. In the late 1970s through the 1980s, extended-spectrum cephalosporins such as cefotaxime, ceftriaxone, and ceftazidime were introduced to resist the hydrolytic activity of parent TEM and SHV enzymes. However, mutants soon emerged with the ability to produce an extended-spectrum β -lactamase that can

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hydrolyze a broader spectrum of β -lactam antibiotics such as extended-spectrum cephalo-sporins containing an oxyimino group.^[1]

Resistance determinants encoding ESBLs are found on mobile genetic elements, facilitating the spread among Enterobacteriaceae. *Klebsiella pneumoniae* and *E. coli* are most commonly cited in the literature as harboring such resistance determinants.

The ESBL-producing isolates are resistant not only to aminopenicillins, ureidopenicillins, and narrow-spectrum cephalosporins, but all extended-spectrum cephalosporins and aztreonam.^[1] Cephamycins and carbapenems retain stability against these isolates. Over 120 different ESBL types have been identified thus far, with each type conferring a slightly different susceptibility profile, complicating selection of therapy.^[6] Isolates that harbor plasmid-mediated TEM- or SHV- β -lactamases versus AmpC β -lactamases may appear to have similar phenotypes with a notable exception; the latter strains are typically resistant to the cephamycins such as cefotetan or cefoxitin and are not inhibited by β -lactamase inhibitors. Hence, in a strain carrying TEM-, SHV-, and AmpC-derived β -lactamases, the presence of an ESBL may be masked when a confirmatory test is based on lowering the minimum inhibitory concentration (MIC) for ceftazidime or cefotaxime with the addition of clavulanic acid.^[7]

Epidemiology

The ESBL-producing isolates in the U.S. were reported primarily in nosocomial outbreaks in short- and long-term care facilities, and involved *K. pneumoniae* and *E. coli*. Widespread and often indiscriminate administration of extended-spectrum cephalosporins, especially ceftazidime, was strongly implicated. Drastic reduction in administration of ceftazidime coupled with strict implementation of infection-control measures were successful in controlling these outbreaks.^[8] Specific risk factors identified in patients colonized or infected with an ESBL-producing *K. pneumoniae* include prolonged hospital stay, intensive care unit admission, urinary and arterial catheterization, and exposure to antibiotics, particularly extended-spectrum cephalosporins.^[9] A surveillance study conducted across the U.S. indicated that 15% of *E. coli* and 24% of *K. pneumoniae* have elevated MICs of 2 μ g/ml or more to ceftazidime, consistent with an ESBL phenotype among selected isolates.^[10] However, the true prevalence of ESBL production among members of the Enterobacteriaceae family in non-outbreak settings in the U.S. is unknown due to inherent difficulties in laboratory detection.

Conclusion

Carbapenems remain the treatment of choice for ESBL-producing pathogens. These pathogens have been associated with increased mortality when compared with similar infections caused by non-ESBL-producing pathogens. Piperacillin-tazobactam and cefepime should not be routinely administered for treatment of ESBL-producing pathogens. These agents are limited by an inoculum effect and by poor outcomes not predicted by in vitro susceptibility testing. Due to the poor prognosis for patients and the limited number of treatment options available, prevention of ESBL infections remains of primary importance.

References

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CPD Questions.

1. What antibiotics can be used to detect ESBL producing bacteria ?

2. What are the most effective antimicrobial agents used to treat patients with ESBL producing pathogens ?

3. ESBL isolates should be reported as being resistant to what group of antibiotics ?

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