Extended-spectrum Beta-lactamases

A Brief Clinical Update

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Beta-lactamase enzymes (BLs) have become the most worrisome mediators of antimicrobial resistance expressed by gram-negative bacteria (GNB). The multiple families of BLs have in common the ability to hydrolyze the β-lactam rings of one or more members of the penicillins, cephalosporins, cephamycins, carbapenems, and monobactams. Extended-spectrum β-lactamases (ESBLs) are a subset of BLs that confer resistance to penicillins, cephalosporins, and monobactams and are less efficiently antagonized by β-lactamase inhibitors such as clavulanate, sulbactam, and tazobactam. ESBL-producing GNB ($ESBL^+$ GNB) remain susceptible to the carbapenems and cephamycins (eg, cefoxitin).

BLs produce the majority of antimicrobial resistance in GNB, with >1000 identified and more discovered yearly. The following 2 classification systems are used to categorize BLs: the Ambler molecular classes and the Bush-Jacoby Groups. Ambler classes organize BLs based on amino acid sequence motifs. Bush-Jacoby Groups are based on functional characteristics (ie, spectrum of beta-lactams hydrolyzed).[1]

The first BLs recognized conferred resistance to penicillins and first-generation cephalosporins. Selective pressure from use of second- and third-generation cephalosporins in the 1980s led to emergence of new versions of BLs with new and often broader resistance profiles. ESBLs represent some of these. These BL genes were originally located on bacterial chromosomes, but have become mobilized on plasmids, enabling easy transfer between bacterial species. These plasmids often carry genes conferring resistance to other antimicrobial agents. $ESBL^+$ GNB thus often exhibit simultaneous resistance to fluoroquinolones, aminoglycosides, tetracyclines, and trimethoprim-sulfamethoxazole.

EPIDEMIOLOGY

ESBLs are often produced by *Enterobacteriaceae* family members such as *Escherichia coli* and *Klebsiella pneumoniae*, but also by non–glucose-fermenting bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter* species. Greater resistance in these organisms first appeared in patients with prolonged hospital stays in intensive care settings in Europe.[2] However, $ESBL^+$ GNB soon became a global problem, with isolates identified in Asia, Africa, the Middle East, and the Americas.[3]

ESBLs derived from the original TEM and SHV BLs were the first to be described. More recently, isolates producing CTX-M type ESBLs have become dominant, with the CTX-M-14 and -15 genotypes endemic to Asia, Europe, and South America now common in the United States.[4] The spectrum of activity against different beta-lactam agents can vary among ESBLs within each family. Although ESBLs are a global problem, specific enzymes and genotypes can be associated with geographic regions, hospitals, and individual hospital units, underscoring the importance of knowing local patterns of resistance. GNB also may possess more than 1 type of ESBL as well as induced AmpC beta-lactamase or other BLs.[1,3]

In hospitalized patients, ESBLs have been associated with central venous catheter-related bacteremia, ventilator-associated pneumonia, catheter-associated urinary tract infections, and surgical site infections. Risk factors for $ESBL^+$ GNB infections in adult patients are previous antibiotic use, prolonged hospital stays (particularly in ICU settings), comorbid conditions, indwelling medical devices, invasive procedures, renal replacement therapy, and mechanical ventilation.[5] Few studies have addressed risk fac-

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tors in children, but a study focused on bacteremia caused by ESBL$^+$ GNB found an association with receipt of antibiotics in the 30 days before infection.[6]

ESBL$^+$ GNB used to be infrequent causes of community-acquired infections; however, in the last decade this has changed. The primary site of infection for community-acquired ESBL$^+$ GNB has been the urinary tract in both children and adults.[7,8] A particular clone of CTX-M found in *E. coli* and identified as CTX-M-15 O25b-ST131 was identified in 2008 and subsequently has caused a global pandemic of community-acquired infections, primarily of the urinary tract.[9] As *Enterobacteriaceae* are part of the human intestinal flora, the reservoirs for potential spread, either by fecal-oral or contact routes, include every colonized individual. Human intestinal carriage of ESBL$^+$ GNB is increasingly documented, with carriage for 59 months or longer having been reported.[10]

INFECTION CONTROL

ESBL$^+$ GNB are spread through contact with infected or colonized persons and can be disseminated through the hands of healthcare workers. They are also found on equipment and surfaces. Infections spread by contaminated ultrasound gel, bronchoscopes, and glass thermometers have been reported.[3] These outbreaks were resolved by elimination of the source, helping to underscore the importance of identifying the mechanisms for dispersal of the organisms. However, sources of infection can be very difficult to identify. Use of contact isolation, hand hygiene, and active surveillance often interrupts transmission but are not always successful.[11] Accordingly, nosocomial transmission of ESBL$^+$ GNB has required closure of inpatient units or removal of cephalosporins from hospital formularies to interrupt the spread.

LABORATORY TESTING

Conventional antimicrobial susceptibility testing, as standardized by the Clinical and Laboratory Standards Institute (CLSI), can be used as a screen for ESBL production. Briefly, if minimum inhibitory concentrations (MICs) or disk diffusion inhibitory zone diameters for cefpodoxime, ceftazidime, aztreonam, cefotaxime, and/or ceftriaxone are greater than defined MICs or less than defined inhibitory zone diameters, respectively, when testing *E. coli*, *K. pneumoniae*, or *Klebsiella oxytoca*, the isolate is a possible ESBL producer. The same is true for *Proteus mirabilis* when considering cefpodoxime, ceftazidime, and cefotaxime results. Possible ESBL-producing microbes can be confirmed by showing that the ceftazidime and/or cefotaxime MIC is ≥8-fold higher than when the same agent is tested in the presence of clavulanic acid. ESBL production also is considered present when the inhibitory zone diameter around a ceftazidime and/or cefotaxime disk is ≥5 mm smaller than when the same agent is tested in the presence of clavulanic acid.

Because these CLSI ESBL testing guidelines are complicated and difficult for many laboratories to implement, in 2010, CLSI published lower susceptible, intermediate, and resistant breakpoints for cefazolin, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, and aztreonam that obviate the need for ESBL screening and confirmatory testing. However, commercially available, FDA-approved, automated antimicrobial susceptibility testing panels that include the lower concentrations of the antibiotics needed to apply the 2010 breakpoints were not widely available to date. Laboratories that continue to use the older breakpoints must perform ESBL screening and confirmatory testing.

TREATMENT

Based on in vitro and clinical data, carbapenems (meropenem, imipenem, and ertapenem) have the most consistent activity against ESBL$^+$ GNB. As noted, ESBL$^+$ GNB often carry genes encoding additional resistance mechanisms, which can lead to treatment failure when trimethoprim-sulfamethoxazole, fluoroquinolones, or aminoglycosides are empirically prescribed for Gram-negative coverage. A clinical study in adults demonstrated good outcomes with carbapenem monotherapy and suggested that carbapenems may be more effective than quinolone monotherapy.[12]

When multidrug resistant (MDR) ESBL$^+$ GNB cause urinary tract infections, antibiotic selection may be limited to burdensome parenteral options. Favorable outcomes in adults with uncomplicated urinary tract infections caused by ESBL-producing *E. coli* have been achieved with oral fosfomycin,[13] but pediatric experience is limited.

Another potential agent that may be considered for MDR ESBL$^+$ GNB infections in older children and adolescents is tigecycline. A recent in vitro study found that 99% of ESBL- and carbapenemase-producing *E. coli* were susceptible to tigecycline.[14] However, adequate clinical studies of this drug in children have not been completed, and the restrictions on use in children <8 years of age would be the same as for other tetracyclines.

CONCLUSION

ESBL$^+$ GNB have become a global problem necessitating collaborative approaches to antimicrobial surveillance and stewardship. The multidrug resistant nature of many ESBL$^+$ strains often limits therapeutic options to carbapenems, which are steadily becoming empiric therapy in many hospitalized patients. If MDR-ESBL$^+$ GNB become prevalent in community-acquired UTI or other infections, the community practitioner will be faced with managing outpatient IV therapy or closely monitoring patients for clinical improvement while awaiting culture data to ensure that any oral antimicrobial agent selected is appropriate. Increasing use of carbapenems also may further drive antimicrobial resistance, resulting in even more limitation of therapeutic options unless new antimicrobial agents are developed.

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