ESBL
Extended-Spectrum B-Lactamase

What is an “extended-spectrum B-lactamase (ESBL)?” ESBL is a type of B-lactamase that hydrolyzes (inactivates) most extended-spectrum B-lactams (but NOT cephamycins, carbapenems, or B-lactamase inhibitor combinations).

Detection and reporting of bacteria that produce extended-spectrum beta-lactamases (ESBLs) present a continuing challenge for the clinical laboratory. This is due primarily to the complex nature of these enzymes and their increasing prevalence. This information should provide a basic review of ESBLs and recommendations for detection and reporting of ESBL-producing gram-negative rods. In addition, it highlights the problems that may occur in the patient if ESBLs are not detected.

What are B-lactams?

B-lactams are a group of antimicrobial agents that have a “B-lactam ring” as a part of their molecular structure. The antimicrobial classes included within the B-lactam group and a few examples of sub-classes and specific agents are:

<table>
<thead>
<tr>
<th>Class</th>
<th>Subclass</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>aminopenicillins</td>
<td>ampicillin</td>
</tr>
<tr>
<td></td>
<td>penicillinase-stable</td>
<td>oxacillin</td>
</tr>
<tr>
<td></td>
<td>penicillins</td>
<td></td>
</tr>
<tr>
<td>B-Lactam/</td>
<td>none</td>
<td>amoxicillin-clavulanate</td>
</tr>
<tr>
<td>B-Lactamase Inhibitors</td>
<td></td>
<td>piperacillin-tazobactam</td>
</tr>
<tr>
<td>Cephems</td>
<td>cephalosporins (1st generation)</td>
<td>cefazolin</td>
</tr>
<tr>
<td></td>
<td>cephalosporins (3rd generation)</td>
<td>cefotaxine</td>
</tr>
<tr>
<td></td>
<td>cephamycins</td>
<td>cefoxitin</td>
</tr>
<tr>
<td>Monobactams</td>
<td>none</td>
<td>aztreonam</td>
</tr>
<tr>
<td>Penems</td>
<td>carbapenems</td>
<td>imipenem</td>
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<tr>
<td></td>
<td></td>
<td>meropenem</td>
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</tbody>
</table>

B-lactams by Definition:

- **Narrow-spectrum B-lactams**
  - Active against gram-positive bacteria, eg. penicillin
- **Broad-spectrum B-lactams**
  - Active against gram-positive & gram-negative bacteria, eg. Ampicillin, 1st generation cephalosporins
- **Extended-spectrum B-lactams**
  - Active against gram-positive and enhanced activity against gram-negative bacteria
What is a B-Lactamase?

B-Lactamase is an enzyme that destroys the B-Lactam ring portion of B-Lactam molecules. The following figure shows a simple B-Lactamase reaction depicting hydrolysis of penicillin to penicilloic acid. Penicilloic acid does not have any antibacterial activity.

![Simple B-Lactamase Reaction](image)

What is an extended-spectrum B-lactamase (ESBL)?

An extended-spectrum B-lactamase is a type of B-lactamase that hydrolyzes (inactivates) most extended-spectrum B-lactams (but NOT cephamycins, carbapenems, or B-lactamase inhibitor combinations).

Important facts about ESBLs

- Primarily found in E. coli, Klebsiella spp., and P. mirabilis but can be found in other gram-negative rods.
- Arise from small mutations in genes (usually located on plasmids) that code for production of common B-lactamases (eg, TEM-1 that codes for ampicillin resistance in E.coli).
- They are inhibited by B-lactamase inhibitors (eg, clavulanic acid).
- They can result in serious infections.
- They can cause nosocomial infections - failure to detect ESBLs has contributed to their uncontrolled spread.
- Are often resistant to agents in other antimicrobial classes (eg, aminoglycosides, fluoroquinolones).
- They are generally susceptible to carbapenems and agents within this class (eg, imipenem or meropenem) which are often used to treat serious infections caused by ESBL producers.
- Many types of ESBLs (approximately 300) have been described, and these contribute to a variety of susceptibility profiles.

Why do ESBL producers sometimes test “S” to drugs and then these drugs do not work in the patient?

In order for an antimicrobial agent to cure an infection, the drug must 1) get to the site of the infection and 2) attain a concentration at the infection site that is greater than the MIC of the infecting bacterium. Standard MIC testing uses 10x5 CFU/mL for testing. Sometimes the concentration of bacteria at the infection site is greater than the amount used in routine testing. The MIC generally increases for an ESBL-producing isolate when challenged with greater
than 10x5 CFU/mL. At the higher concentration of bacteria, the drug cannot overcome the increased concentration of ESBL that is present. Although this is one possible explanation, other factors may contribute to clinical failures, such as concentration of drug at the infection site compared with the MIC of the infecting bacterial and how long that concentration stays above the MIC.

Recommendations

All organisms of the Genus and Species E. coli, Klebsiella spp. and Proteus mirabilis should be tested for ESBL. These are the most common organisms exhibiting ESBL production, however, other organisms have been found to produce ESBL. In monitoring clinical findings and evaluating effectiveness of antimicrobial therapy, consideration should be given to the possibility that ESBL may negatively impact effective treatment and cure of bacterial infections. This could have a direct impact on course of treatment and potential success or failure of therapy.

For example, if ESBL-producing Klebsiella pneumoniae is isolated from a blood culture and the susceptibility test shows that it is “S” to cefotaxime, what could happen if we do not test for, and ignore ESBL reporting and rules and expect the cefotaxime is “S.” In this case, if cefotaxime is used to treat the patient, the patient may fail therapy and die. This is an example where in vitro results may NOT correlate with clinical outcome.