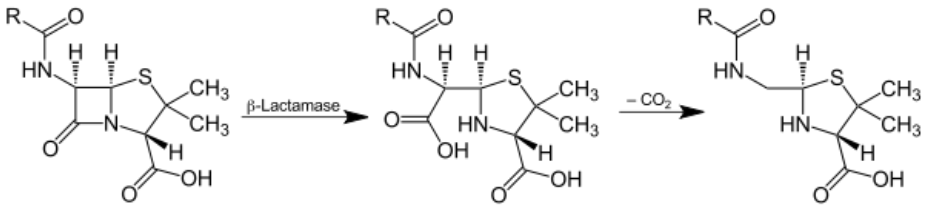
Beta-lactamases

Bacteria can become resistant to penicillins through a number of mechanisms:

- **destruction of antibiotics by β-lactamases** - the most common mechanism;
- **inability to penetrate the outer membrane of G- bacteria**;
- **efflux** across the *outer* membrane of G- bacteria;
- **low antibiotic binding to target PBP.**

Some bacteria may have more than one resistance mechanism, eg. the *mecA* gene in MRSA encodes another PBP (penicillin binding site) and most also produce **beta lactamase.**[1]

β-lactamase



Changes in β-lactam structure under the action of β-lactamases.

β-lactamases are enzymes that covalently bind to the β-lactam ring, hydrolyze it and render the antibiotic ineffective. Resistance to beta-lactam antibiotics began before penicillin was widely available, with the first **β-lactamase** (*penicillinase*) being described in *Escherichia coli* in 1940. Resistance to *S. aureus* due to **plasmid β-lactamase** followed.

Many genera of G- bacteria have naturally occurring **chromosomal β-lactamases** (*AmpC*). The first plasmid β-lactamase in G- bacteria, *TEM-1,* The first plasmid β-lactamase in G- bacteria. Over the years, it has spread worldwide and been found in many different species. Many antibiotics that have been resistant to these β-lactamases have been developed over the last 20 years. However, with each new class of drugs, new β-lactamases appear.

Classification

There are two classification systems for β-lactamases.

Molecular (Ambler)

Four classes (A to D) based on the nucleotide / amino acid sequences of the enzymes:

- classes A, C and D are ***serine β-lactamases;***
- Class B are zinc-dependent enzymes ***(metallo-β-lactamases, MBL),*** that hydrolyze the β-lactam ring by various mechanisms.

Functional (Bush-Jacoby-Medeiros)

Three groups, each with subgroups:

- group 1 - **cephalosporinases that are not inhibited by clavulanic acid;**
- group 2 - **penicillinases and / or cephalosporinases which are inhibited by clavulanic acid;**
- group 3 - **are zinc dependent (MBL) and are not inhibited by clavulanic acid;**

AmpC β-lactamases

These are **chromosomal β-lactamases**, that are active against third-generation cephalosporins (ceftriaxon, cefotaxim) and are not inhibited by clavulanic acid. They belong to molecular group C and functional group 1. They are found in the group of **ESCAPPM** *(Enterobacter spp., Serratia spp., Citrobacter freundii, Acinetobacter spp., Proteus vulgaris, Providencia spp., Morganella morganii.)* Use of third generation cephalosporins for treatment of these infections leads to the selection of mutants that ***hyperproduce AmpC.*** These infections are therefore usually treated with **carbapenems**.[1]

ESBL

Extended spectrum β-lactamases. ESBLs are most common in *E. coli* and *Klebsiella pneumoniae*, but have been described in many other G- bacteria. Most ESBLs are derivatives of TEM and SHV enzymes. Resistance develops to penicillins, cephalosporins of 1st, 2nd and 3rd generation, and aztreonam (monobactam). ESBLs hydrolyze these antibiotics. ESBL may be inhibited by β-lactamase inhibitors.

ESBLs include:

- **TEM β-lactamases** - TEM-1 is the most common β-lactamase in G- bacteria and is able to hydrolyze penicillins and cephalosporins. TEM enzymes are most common in *E. coli* and *K. pneumoniae*, but are increasingly common in other species of G- bacteria.
- **SHV β-lactamases** - SHV-1 β-lactamase is most common in K. pneumoniae.
- **CTX-M β-lactamases** - plasmid β-lactamases that preferentially hydrolyze cefotaxime. They have been found in Salmonella enterica and E. coli.
- **OXA β-lactamases** - these are characterized by high hydrolytic activity against oxacillin. OXA-type ESBLs occur mainly in *P. aeruginosa*, but have also been detected in other G- bacteria.
- Other ESBLs - A number of other ESBLs have been described, eg **PER-1**, **PER-2**, **VEB-1**, **GES**, **BES**, **TLA**, **SFO** and **IBC**.[1]

References

1. *TOROK, E. MORAN, E., COOKE, F.: Oxford Handbook of Infectious Diseases and Microbiology. (Oxford Medical Handbooks). ISBN-10: 019967132X. ISBN-13: 978-0199671328.*