Clinical review

Recent developments in β lactamases and extended spectrum β lactamases

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Resistance to β lactam antibiotics is an increasing problem worldwide. This review describes the classification and mechanism of action of β lactamases and the options available for detecting, treating, and controlling extended spectrum β lactamases

β lactam antimicrobial agents are the most common treatment for bacterial infections (table 1).[1] Rates of bacterial resistance to antimicrobial agents are increasing worldwide, including in Lebanon.[2] Production of β lactamases is the most common mechanism of bacterial resistance (table 2).[1 3] These enzymes are numerous, and they mutate continuously in response to the heavy pressure of antibiotic use, leading to the development of extended spectrum β lactamases (ESBLs).[4] Examples are the mutated TEM and SHV genes, mainly found in strains of *Escherichia coli* and *Klebsiella pneumoniae* respectively. Infections with ESBL producing bacterial strains are encountered singly or in outbreaks, especially in critical care units in hospitals, resulting in increasing costs of treatment and prolonged hospital stays. We aim to present a simplified review of this highly complex subject, in the hope that it will guide the practising physician in appropriate decisions relating to the use of β lactams in patient care.

Summary points

- β lactamase producing bacteria are increasing in number and causing more severe infections, because of their continuous mutation
- Extended mutation has led to the emergence of extended spectrum β lactamase enzymes, the incidence and types of which vary with geographical location and time
- The functional and molecular classifications are complex for the practising physician who is facing problems in deciding how to treat infections caused by bacteria producing these enzymes
- Awareness and detection of these enzymes are necessary for optimal patient care

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Sources and selection criteria

We examined new information from the most recent relevant literature retrieved from PubMed and the internet.

Groups and mechanisms of action of β lactams

The β lactams are a family of antimicrobial agents consisting of four major groups: penicillins, cephalosporins, monobactams, and carbapenems (table 1). They all have a β lactam ring, which can be hydrolysed by β lactamases. The groups differ from each other by additional rings (thiazolidine ring for penicillins, cephem nucleus for cephalosporins, none for monobactams, double ring structure for carbapenems). The various antibiotics in each group differ by the nature of one or two side chains.

The β lactam antibiotics act on bacteria through two mechanisms targeting the inhibition of cell wall synthesis.[5] Firstly, they are incorporated in the bacterial cell wall and inhibit the action of the transpeptidase enzyme responsible for completion of the cell wall. Secondly, they attach to the penicillin binding proteins that normally suppress cell wall hydrolases, thus freeing these hydrolases, which in turn act to lyse the bacterial cell wall. To bypass these antimicrobial mechanisms of action, bacteria resist by producing β lactam inactivating enzymes (β lactamases) or mutated types of penicillin binding proteins. Here, we will discuss only β lactamases.

P+ *An extra table appears on bmj.com*

Table 1 Groups and examples of β lactam antimicrobial agents

β lactam groups	Examples of antimicrobial agents
Penicillins	Penicillin G, penicillin
	Penicillinase resistant penicillins: methicillin, nafcillin, oxacillin, cloxacillin
	Aminopenicillins: ampicillin, amoxicillin
	Carboxypenicillins: carbenicillin, ticarcillin
	Ureidopenicillins: mezlocillin, piperacillin
Cephalosporins	First generation: cefazolin, cephalothin, cephalexin
	Second generation: cefuroxime, cefaclor, cefamandole, cefamycins (cefotetan, cefoxitin)
	Third generation: cefotaxime, ceftriaxone, cefpodoxime, ceftizoxime, cefoperazone, ceftazidime
	Fourth generation: cefepime, cefpirome
Carbapenems	Imipenem, meropenem, ertapenem
Monobactams	Aztreonam

Table 2 Antimicrobial agents, their modes of action, and the corresponding mechanisms of bacterial resistance

Antimicrobial agents	Mode of action	Resistance mechanisms
β lactams	Cell wall synthesis, cell division	β lactamase, altered penicillin binding proteins
Glycopeptides (azoles, cycloserine)	Cell wall division	Blocking of drug access to pentapeptide
Aminoglycosides (spectinomycin)	Inhibit protein synthesis (bind to 30S ribosome)	Enzymatic inactivation, altered target, impermeability
Macrolides	Inhibit protein synthesis (bind to 50S ribosome)	Altered target, enzymatic inactivation
Tetracycline	Inhibit protein synthesis (affect t-RNA binding to 30S)	Efflux, altered target, impermeability, enzymatic inactivation
Chloramphenicol (lincosamides, streptogramin)	Inhibit protein synthesis (bind to 50S ribosome)	Enzymatic inactivation, impermeability
Quinolones	Replication: inhibit DNA gyrase	Altered target enzymes, impermeability
Rifampin	Transcription: inhibit DNA dependent RNA polymerase	Altered target enzymes, impermeability
Sulfonamides	Folic acid synthesis	Altered target
Trimethoprim	Folic acid synthesis	Altered target, impermeability
Polyenes (nystatin, amphotericin B)	Cell membrane permeability	Ergosterol deficient mutants

β lactamases

Synthesis and mode of transfer

The synthesis of β lactamases is either chromosomal (constitutive), as in *Pseudomonas aeruginosa*, or plasmid mediated (inducible), as in *Aeromonas hydrophila* and *Staphylococcus aureus*. Plasmids are a major cause of bacterial resistance spreading, as they can be transferred between Gram negative bacteria by conjugation and between Gram positive bacteria by bacterial viruses called transducing phages. This transferability is responsible for many outbreaks of resistance, especially when appropriate infection control measures are breached in hospital settings.

Location

In the Gram positive bacteria β lactamases are secreted to the outside membrane environment as exoenzymes. In the Gram negative bacteria they remain in the periplasmic space, where they attack the antibiotic before it can reach its receptor site.[3]

Mechanisms of action

β lactamase enzymes destroy the β lactam ring by two major mechanisms of action. Firstly, most common β lactamases have a serine based mechanism of action. They are divided into three major classes (A, C, and D) on the basis of the amino acid sequences. They contain an active site consisting of a narrow longitudinal groove, with a cavity on its floor (the oxyanion pocket), which is loosely constructed in order to have conformational flexibility in terms of substrate binding (fig 1).[1 3] Close to this lies the serine residue that irreversibly reacts with the carbonyl carbon of the β lactam ring, resulting in an open ring (inactive β lactam) and regenerating the β lactamase. These enzymes are active against many penicillins, cephalosporins, and monobactams. Secondly, a less commonly encountered group of β lactamases is the metallo β lactamases, or class B β lactamases. These use a divalent transition metal ion, most often zinc, linked to a histidine or cysteine residue or both, to react with the carbonyl group of the amide bond of most penicillins, cephalosporins, and carbapenems, but not monobactams.[6]

Table 3 Evolution of functional classification of β lactamases

Year	Author	Basis of classification of β lactamases
1968	Sawai et al	Used cephalosporins versus penicillins as substrates
1973	Richmond and Sykes	Expanded substrate profile and suggested five major groups (Ia-d, II, III, IV, V)
1976	Sykes and Matthew	Differentiated the plasmid mediated β lactamases on the basis of isoelectric focusing
1981	Mitsuhachi and Inoue	Added the category "cefuroxime hydrolysing β lactamase"
1989	Bush	Expanded further the substrate profile, added the reaction with EDTA, correlated between functional and molecular classification
1995	Bush, Jacoby, and Medeiros	Expanded the Bush scheme and used biochemical properties, molecular structure, and nucleotide sequence. Suggested classification into four groups (1-4)* on the basis of the spectrum of activity and other functional characteristics

*Details in text and in table on bmj.com

Classification of β lactamases

Because of the diversity of enzymatic characteristics of the many β lactamases discovered so far, many attempts have been made to categorise and classify them since the late 1960s. These classifications involve two major approaches: the first and older one is based on the biochemical and functional characteristics of the enzyme; the second approach is based on the molecular structure of the enzyme.

Functional classification of β lactamases

Several criteria were used in the functional classification of the β lactamases, including the spectrum of antimicrobial substrate profile, enzyme inhibition profile, enzyme net charge (pI), hydrolysis rate (Vmax), binding affinity (Km), isoelectric focusing, protein molecular weight, and amino acid composition. Since the 1960s several functional classification schemes of β lactamases have evolved, as shown in table 3.[7]

Bush-Jacoby-Medeiros presented, in 1995, the latest classification of β lactamases based on four groups (1-4) and subgroups (a-f) as follows (see table on bmj.com).[7]

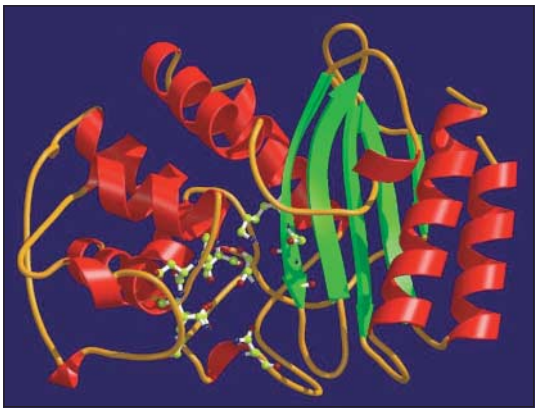

Fig 1 Molecular structure of β lactamase. Adapted from http://biosafety.ihe.be/AR/betalactamase.html

- Group 1 are cephalosporinases not inhibited by clavulanic acid, belonging to the molecular class C
- Group 2 are penicillinases, cephalosporinases, or both inhibited by clavulanic acid, corresponding to the molecular classes A and D reflecting the original TEM and SHV genes. However, because of the increasing number of TEM and SHV derived β lactamases, they were divided into two subclasses, 2a and 2b. The 2a subgroup contains just penicillinases, whereas 2b are broad spectrum β lactamases, meaning that they are capable of inactivating penicillins and cephalosporins at the same rate. Furthermore, new subgroups were segregated from subgroup 2b:
  - Subgroup 2be, with the letter "e" for extended spectrum of activity, represents the ESBLs, which are capable of inactivating third generation cephalosporins (ceftazidime, cefotaxime, and cefpodoxime) as well as monobactams (aztreonam)
  - The 2br enzymes, with the letter "r" denoting reduced binding to clavulanic acid and sulbactam, are also called inhibitor resistant TEM derivative enzymes; nevertheless, they are still susceptible to tazobactam
  - Later, subgroup 2c was segregated from group 2 because these enzymes inactivate carbenicillin more than benzylpenicillin, with some effect on cloxacillin
  - Subgroup 2d enzymes inactivate cloxacillin more than benzylpenicillin, with some activity against carbenicillin; these enzymes are poorly inhibited by clavulanic acid, and some of them are ESBLs
  - Subgroup 2e enzymes are cephalosporinases that can also hydrolyse monobactams, and they are inhibited by clavulanic acid
  - Subgroup 2f was added because these are serine based carbapenemases, in contrast to the zinc based carbapenemases included in group 3
- Group 3 are the zinc based or metallo β lactamases, corresponding to the molecular class B, which are the only enzymes acting by the metal ion zinc as discussed above. They are able to hydrolyse penicillins, cephalosporins, and carbapenems. Thus, carbapenems are inhibited by both group 2f (serine based mechanism) and group 3 (zinc based mechanism)
- Group 4 are penicillinases that are not inhibited by clavulanic acid, and they do not yet have a corresponding molecular class.

Molecular classification

The molecular classification of β lactamases is based on the nucleotide and amino acid sequences in these enzymes. To date, four classes are recognised (A-D), correlating with the functional classification (see table on bmj.com). Classes A, C, and D act by a serine based mechanism, whereas class B or metallo β lactamases need zinc for their action.[8]

Extended spectrum β lactamases

The persistent exposure of bacterial strains to a multitude of β lactams has induced a dynamic and continuous production and mutation of β lactamases in these bacteria, expanding their activity even against the third and fourth generation cephalosporins such as ceftazidime, cefotaxime, and cefepime and against aztreonam. Thus these new β lactamases are called extended spectrum β lactamases.[9]

The incidence of ESBLs varies with geographical location and time. In Lebanon, the incidence of ESBLs increased approximately twofold at a major tertiary hospital, the American University of Beirut Medical Center, between 1998 and 2002, for both *E coli* (3% *v* 5 %) and *K pneumoniae* (6.4% *v* 13%).[2] In the USA the incidence in *Enterobacteriacae* ranges from zero to 25%, and in Europe the incidence is 23-25% for *Klebsiella* spp and 5.4% for *E coli*.[4]

These ESBLs enzymes are plasmid borne and have evolved from point mutations altering the configuration of the active site of the original and long known β lactamases designated TEM-1, TEM-2, and SHV-1. The activity of these enzymes is limited to ampicillin, penicillin, and carbenicillin. The original TEM was first discovered in *E coli* in a patient named Temoniera in Greece, but it spread rapidly to other bacteria. Although TEM-type β lactamases are most often found in *E coli* and *K pneumoniae*, they are also found in other genera of *Enterobacteriacae* and in other penicillin or ampicillin resistant Gram negative bacteria such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*. The SHV enzymes, named after the "sulfhydryl variable" active site, are commonly associated with *K pneumoniae*. At first these bacteria contained a single ESBL gene, but now multiple ESBL genes are commonly present

Table 4 Laboratory tests for detection of extended spectrum β lactamases

Tests	Method and interpretation
Screening tests	
Double disk approximation or double disk synergy	Disk of third generation cephalosporin placed at 30 mm distance from amoxicillin-clavulanic acid. Enhanced inhibition indicates ESBL
Combination disk	Uses two discs of third generation cephalosporin alone and combined with clavulanic acid. An increase in the zone inhibition of >5 mm with the combination disk indicates ESBL
Microdilution test	Growth in a broth containing 1 μg/ml third generation cephalosporin indicates ESBL
Confirmatory tests	
MIC broth dilution	MIC of third generation cephalosporin alone or combined with clavulanic acid. A decrease in the MIC of the combination of ≥3 twofold dilutions indicates ESBL
E test (MIC ESBL strips)	Two sided strip containing ceftazidime on one side and ceftazidime-clavulanic acid on the other. The ratio of the MIC of the combination to that of ceftazidime alone of >8, or the presence of a phantom zone (or both) indicates ESBL
Automated instruments (for example, Vitek)	Measures MICs and compares growth of bacteria in presence of ceftazidime *v* ceftazidime-clavulanic acid
Molecular (DNA probes, PCR, RFLP)	Targets specific nucleotide sequences to detect different variants of TEM and SHV genes

ESBL=extended spectrum β lactamases; MIC=minimum inhibitory concentration; PCR=polymerase chain reaction; RFLP=restriction fragment length polymorphism.

in a single strain, further complicating the process of detecting them and identifying an appropriate treatment regimen.[10] To date, more than 90 TEM-type and more than 25 SHV-type β lactamases have been identified. Other recently recognised genes with similar activity include PER-1 β lactamases, first discovered in *Pseudomonas aeruginosa* in Turkey, and the VEB-1 and TLA-1 from single *E coli* isolates from Vietnam and Mexico respectively.[4]

The ESBL producing bacteria are typically associated with multidrug resistance, because genes with other mechanisms of resistance often reside on the same plasmid as the ESBL gene.[10] Thus some ESBL producing strains also show resistance to quinolones, aminoglycosides, and trimethoprim-sulfamethoxazole.[11] β lactamase inhibitors such as β lactam-β lactamase inhibitor combinations could show higher in vitro susceptibility results against bacterial strains with ESBL production than their original parent. However, their in vivo activity remains to be validated.[12]

Infections with ESBL producing bacteria can result in avoidable failure of treatment and increased cost in patients who have received inappropriate antibiotic treatment. Nosocomial outbreaks of this form of resistance are most often associated with intensive care units and oncology, burns, and neonatal wards. They can result in prolongation of hospital stay, as well as devastating or even fatal consequences.[13]

Methods of detecting ESBLs

The increasing prevalence of ESBL producing bacterial strains has caused many outbreaks. This has warranted the establishment of rapid and reliable laboratory methods for screening and confirmation (table 4, fig 2).[14–18]

Generally, an isolate is suspected to be an ESBL producer when it shows in vitro susceptibility to the second generation cephalosporins (cefoxitin, cefotetan) but resistance to the third generation cephalosporins and to aztreonam. Moreover, one should suspect these strains when treatment with these agents for Gram negative infections fails despite reported in vitro susceptibility. Once an ESBL producing strain is detected, the laboratory should report it as "resistant" to all penicillins, cephalosporins, and aztreonam, even if they test as susceptible.[19 20] Other antimicrobial agents can be reported as they are tested.

Fig 2 Double disk approximation, or double disk synergy, test to detect ESBL producing bacteria

Additional educational resources

www.cdc.gov/ncidod/hip/Lab/FactSheet/esbl.htm—information on laboratory detection of extended spectrum β lactamases (ESBLs)

www.phppo.cdc.gov/dls/master/qa-arc02.asp—answers the question of why only *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*, and not other Enterobacteriaceae, are screened for ESBL production

biosafety.ihe.be/AR/betalactamases.html—Belgian biosafety server: antibioresistance archive on β lactam resistance

www.ncbi.nlm.nih.gov—national center for biotechnology information

www.cdc.gov/ncidod/eid/vol7no2/pdfs/thomson.pdf—*Emerging Infectious Diseases*: special issue on ESBLs

Treatment of ESBLs

Essentially, the choice of drug for treating ESBL producing bacteria is limited to carbapenems—for example, imipenem. Alternatively, fluoroquinolones and aminoglycosides may be used if they show in vitro activity. Although clinical data for their use are absent, a β lactam-β lactamase inhibitor combination such as amoxicillin-clavulanate or piperacillin-tazobactam may also be a further option to consider. All these agents should be used with caution, however, as their susceptibility varies among ESBL producers. Cefamycins, such as cefoxitin and cefotetan, although active in vitro, are not recommended for treating such infections, because of the relative ease with which these strains decrease the expression of outer membrane proteins, rendering them resistant.[21]

Control measures

Proper infection control practices and barriers are essential to prevent spreading and outbreaks of ESBL producing bacteria. The reservoir for these bacteria seems to be the gastrointestinal tract of patients.[22] Alternative reservoirs could be the oropharynx, colonised wounds, and urine. The contaminated hands and stethoscopes of healthcare providers are important factors in spreading infection between patients.[23] Essential infection control practices should include hand washing by hospital personnel, increased barrier precautions, and isolation of patients colonised or infected with ESBL producers. Other practices that have minimised the spread of such organisms include clinical and bacteriological surveillance of patients admitted to intensive care units and antibiotic cycling, as well as policies of restriction, especially on the empirical use of broad spectrum antimicrobial agents such as the third and fourth generation cephalosporins and imipenem.[24]

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Good medical practice

I was appointed as a senior house officer in general surgery at a remote district general hospital. The post would have suited someone with more surgical experience, but my career prospects depended on this job. On occasions, there was no middle grade cover, and I had to manage all the surgical emergencies and take consultant advice as necessary.

Having worked for years in orthopaedics, my thoughts were often focused on bones, even while examining a patient's abdomen. As a general surgical trainee, I had performed a couple of appendicectomies and a few other supervised operations, but I was certainly not ready to do anything as major as opening the abdomen without supervision.

Late one evening, I was called to see a young woman admitted with right sided abdominal pain, vomiting, and fever. Tenderness at McBurney's point, rebound, and leucocytosis made me certain that I was dealing with appendicitis. Now I faced a real dilemma. Should I take her to the theatre and remove the appendix myself? It would be a golden chance to tell my wife and friends of my solo exploits—an achievement every trainee craves. Pride was trying to overpower me. On the other hand, I was afraid of complicating things and being struck off the medical register. I was also afraid that calling my consultant for such a routine operation would block my chances of independent surgery, at least in that job. That was how things worked in the surgical world.

"After all, missing one opportunity is not the end of the world," I told myself. I rang the consultant and told him about the case.

"Can you do it?" he asked.

I was forced to acknowledge the truth: "No, I have done it before, but I am not confident enough to perform without supervision."

My boss soon arrived to see the patient. "Looks like appendicitis, doesn't it. Let's take her to theatre," he remarked. As soon as the peritoneum was opened, there was a gush of bloodstained fluid. "I think we are dealing with a ruptured ovarian cyst here, my friend," said the consultant. My spirits sank. Not only had I lost an opportunity to operate, but my certain diagnosis had just been proved wrong. Anyway, the emergency was soon dealt with efficiently. My boss, after doing the initial few steps, asked me to finish the operation. As I was closing the wound, my boss asked, "Do you think your diagnosis was correct?"

"No, Mr Mullan, I am sorry," I reluctantly replied.

"I'm afraid you are wrong. You did all the right things tonight. 'Good medical practice,'" my boss commented. I was confused. He continued, "You diagnosed an acute abdomen correctly. Then you understood the seriousness of the situation and informed me promptly. Finally, you were honest in admitting you couldn't operate alone and avoided putting the patient at unnecessary risk." My face twitched behind the facemask. I did not have words to express my feelings to the angel who had guided my decisions.

We soon developed a strong trainee-trainer relationship, and I was ultimately trained to be a confident surgeon. Sadly enough, those six months were both the beginning and the end of my general surgical career, and I was soon back to my cosy orthopaedic world.

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