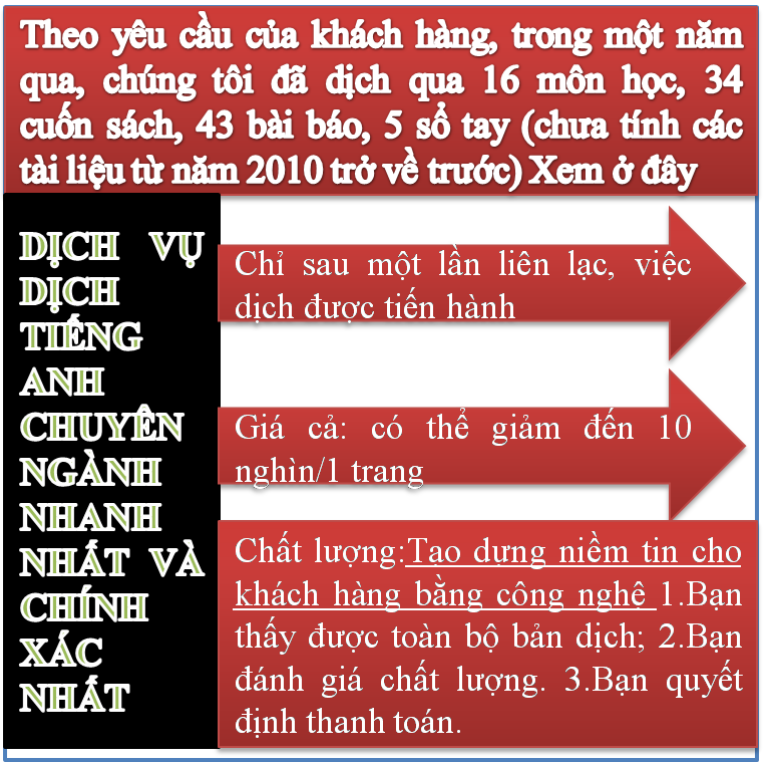

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REVIEW ARTICLE MECHANISMS OF DISEASE The New Beta-Lactamases 8/7 THE Beta-LACTAMASES ARE THE MAJOR DEFENSE OF GRAM-NEGATIVE Bacteria against Beta-lactam antibiotics. Beta-lactamases can be broadly divided into enzymes with a serine residue at the active site, similar to bacterial penicillin-binding proteins, from which they probably evolved,1 and metalloenzymes with zinc ion as a cofactor and with a separate heritage.2 Both arc ancient enzymes. The serine group is estimated from current sequence diversity to have evolved with bacteria over the past 2 billion years.3 Since, bata-lactam antibiotics came into clinical use, Beta-lactamases have coevolved with them.4 Early events were an increase in their prevalence in organisms in which the enzyme was known but uncommon (such as Staphylococcus aureus) and spread to pathogens that previously lacked Beta-lactamase (namely, Haemophilus influenzae and Neisseria gonorrhoetie). Beginning about 20 years ago, agents that shared	BÀI BÁO TỔNG QUAN CÁC CƠ CHẾ GÂY BỆNH Các Beta-Lactamase mới CÁC Beta-LACTAMASE LÀ CÁC ENZYME DO CÁC VI KHUẨN GRAM ÂM TẠO RA ĐỂ CHỐNG LẠI KHÁNG SINH Beta-lactam. Nói chung, các Beta-lactamase có thể được chia thành các enzyme có đơn phân serine ở vị trí hoạt động, tương tự như các protein gắn với penicillin vi khuẩn, mà từ đó chúng đã phát triển, và các enzyme kim loại với ion kẽm đóng vai trò là đồng yếu tố và với một heritage riêng biệt. Cả hai đều là các enzyme cổ. Nhóm serine được ước tính từ sự đa dạng trình tự hiện tại đã tiến hóa với vi khuẩn trong 2 tỷ năm qua. active site: vị trí hoạt động, vùng hoạt động, trung tâm hoạt động, hoạt điểm Kể từ khi kháng sinh Bata-lactam được đưa vào sử dụng lâm sàng, beta-lactamase đã phát triển đồng hành với chúng.4 Diễn biến ban đầu là sự gia tăng mức độ hiện diện của chúng trong các sinh vật trong đó enzyme được biết đến nhưng không phổ biến (chẳng hạn như Staphylococcus aureus) và lây lan sang các mầm bệnh trước đây thiếu Beta-lactamase (cụ thể là, Haemophilus influenzae và Neisseria gonorrhoetie).Do đó,	

the property of resistance to the then-common Beta-lactamases were introduced; they included cephamycins, cephalosporins with an oxyimino side chain, carbapenems, and the monobactam az- treonam. Bacteria responded with a plethora of “new” Beta-lactamases — including extended-spectrum Beta-lactamases (ESBLs), plasmid-mediated AmpC enzymes, and carbapenem-hydrolyzing beta-lactamases (carbapenemases) — that, with variable success, can confer resistance to the latest Beta-lactam antibiotics (Table 1). The properties of these new Beta-lactamases, the ways in which they can be detected, their origins, and options for treating the associated infections are considered in this article; aspects of these topics have been the subject of other recent reviews.5'8	bắt đầu từ khoảng 20 năm trước đây, các tác nhân có khả năng kháng beta-lactamase phổ biến đã được giới thiệu, chúng bao gồm cephamycins, các cephalosporin có một chuỗi bên oxyimino, carbapenems, và monobactam az-treonam. Những vi khuẩn tạo ra nhiều beta-lactamase "mới" - bao gồm beta-lactamase phổ rộng (các ESBL), enzyme AmpC hình thành gián tiếp thông qua thể plasmid, và các beta-lactamase thủy phân carbapenem (carbapenemases) - với mức độ thành công khác nhau, có thể chống lại các kháng sinh beta-lactam mới nhất (Bảng 1). Các tính chất của các beta-lactamase mới này, những con đường dẫn đến phát hiện chúng, nguồn gốc của chúng, và các lựa chọn để điều trị các bệnh nhiễm trùng liên quan được xem xét trong bài báo này, các khía cạnh của các vấn đề này đã là chủ đề của những bài tổng quan gần đây.5 '8 Bacteria responded with a plethora of: dịch theo nghĩa đen là “Những vi khuẩn hưởng ứng sự dư thừa của”, nhưng ở đây để dễ hiểu mình sẽ dịch “Những vi khuẩn tạo ra nhiều”	
CLASSIFICATION OF Beta-LACTAMASES Understanding the new enzymes requires a brief review of Beta-	[redacted]	

lactamase classification. Hundreds of beta-lactamases have been described and have been given a bewildering variety of names (see Glossary). Fortunately, the enzymes can be classified on the basis of their primary structure into four molecular classes (A through D),9 or on the basis of their substrate spectrum and responses to inhibitors into a larger number of functional groups.10 Class A and class C /8-lactamases are the most common and have a serine residue at the active site, as do class D /8-lactamases. Class B comprises the metallo-beta-lactamases. Twenty years ago, plasmids mediating resistance to Beta-lactam antibiotics in Escherichia coli and other Enterobacteriaceae most often carried genes encoding class A enzymes such asTEM-1 or SHV-1 or class D enzymes such as OXA-l.11 Class B and C enzymes had a broader spectrum of activity but were almost always encoded by chromosomal genes and hence were confined to particular bacterial species.

THE NEW Beta-LACTAMASES

TEM-TYPE ESBLs (CLASS A)

Amino acid substitutions at many sites in TEM-1 Beta-

lactamases can be created in the laboratory without loss ofactivity.'7 Those responsible for the ESBI. phenotype change the

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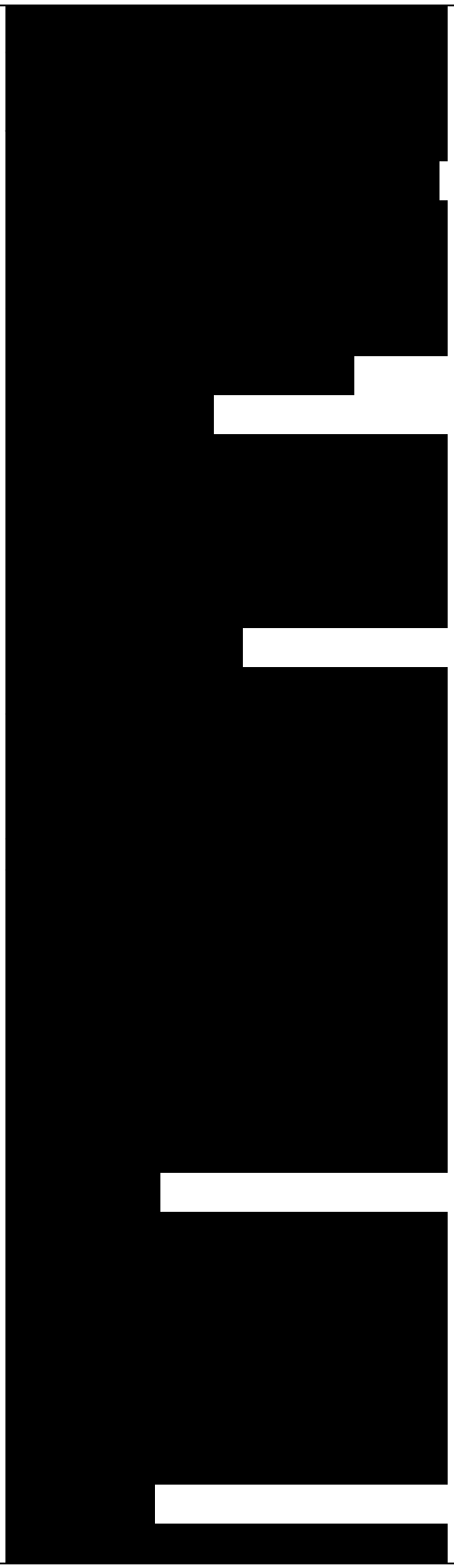
Glossary

AmpC Beta-lactamase: This type of broad-spectrum enzyme, usually encoded on the bacterial chromosome, is active on cephamycins as well as oxyimino-Beta-lactams.

Beta-Latam-Beta-Lactamase inhibitor combinations: Clavulanic acid, sulbactam, and tazobactam are inhibitory beta-lactams that bind to and block the action of class A, and to a lesser extent, class D Beta-lactamases. The inhibitors are available in combinations with otherwise Beta-lactamase-susceptible antibiotics, such as ticarcillin-clavulanic acid, ampicillin- sulbaclam, and piperacillin-tazobactam

Carbapenems: Compounds with a fused Beta-lactam system in which the sulfur atom of the five-member ring is replaced by carbon. Examples include imipenem, meropenem, and ertapenem.

Cephamycins: Cephalosporins



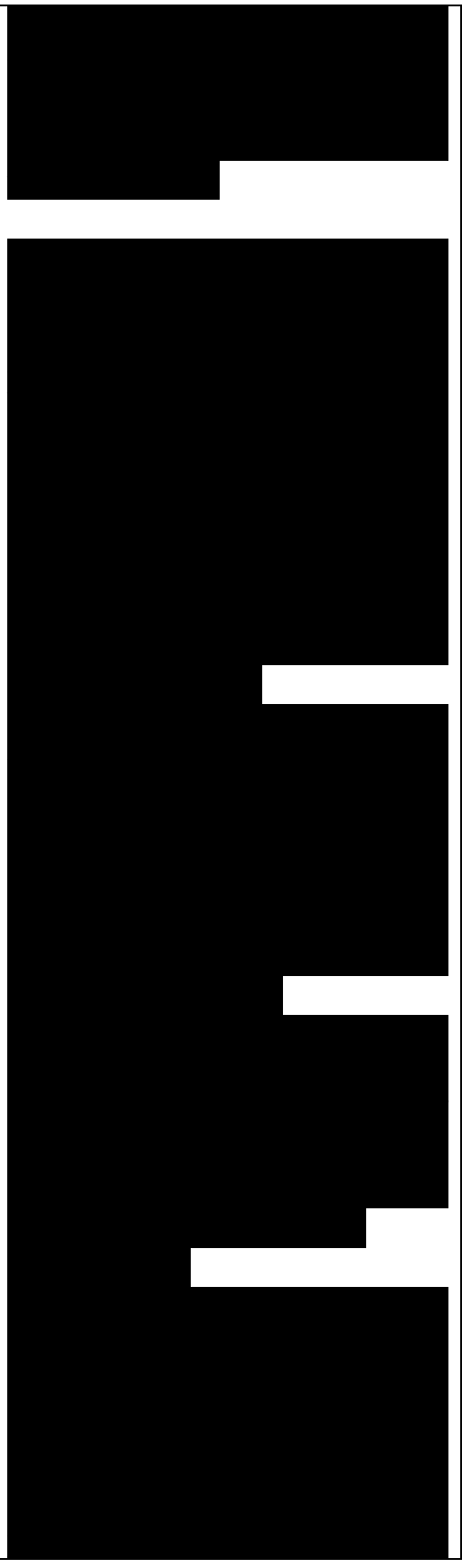
with a 7 anpha-methoxy side chain that blocks hydrolysis by class A and class D Beta-lactamases Examples include cefoxitin, cefotetan, and cefmetazole.

Extended-spectrum Beta-lactamase (ESBL): This name was originally coined to reflect the expanded substrate spectrum of enzymes derived from narrower-spectrum TEM, SHV, or OXA 0-lactamases. The term now also refers to Beta-lactamases, such as those in the CTX-M family, with a similar phenotype but a separate heritage.

Inhibitor-resistant Beta-lactamase: Enzyme variants in the TEM family (and, less often, the SHV family) with reduced sensitivity to clavulanic acid, sulbactam, and tazobactam inhibitors as a result of amino acid substitutions.

Inoculum effect: Increased resistance with increasing numbers of test bacteria. One possible mechanism is increased hydrolysis with larger inocula of Beta-lactamase-producing organisms.

Integron: A unit of DNA containing a gene for a site-specific integrase [intl) and a recombination site (alt/), into which gene cassettes made up of an antibiotic-resistance gene linked to a 59-base clement (or



attC site) can be integrated A strong promoter adjacent to the attl site ensures that the integrated genes will be efficiently expressed. Integrons can be part of a transposon or a defective transposon and thus have an additional potential for mobility. Monobactam: A monocyclic Beta-lactam. The single commercially available example is aztreonam, which has an oxyimino side chain and is therefore also an oxyimino-Beta-lactam. Oxyimino-beta-Lactams: Beta-Lactams with an oxyiminoside chain designed to block the action of beta-lactamase. Sometimes referred to as "third-generation cephalosporins," they include cefotaxime, ceftriaxone, ceftazidime, and cefepime (a "fourth-generation" derivative). Plasmid: An extrachromosomal segment of DNA, usually circular, varying in size from a few kilobases to a 10th or more of the size of the bacterial chromosome. Plasmids larger than 20 kb are often conjugative and can promote their transfer between bacterial hosts. Resistance plasmids carry		

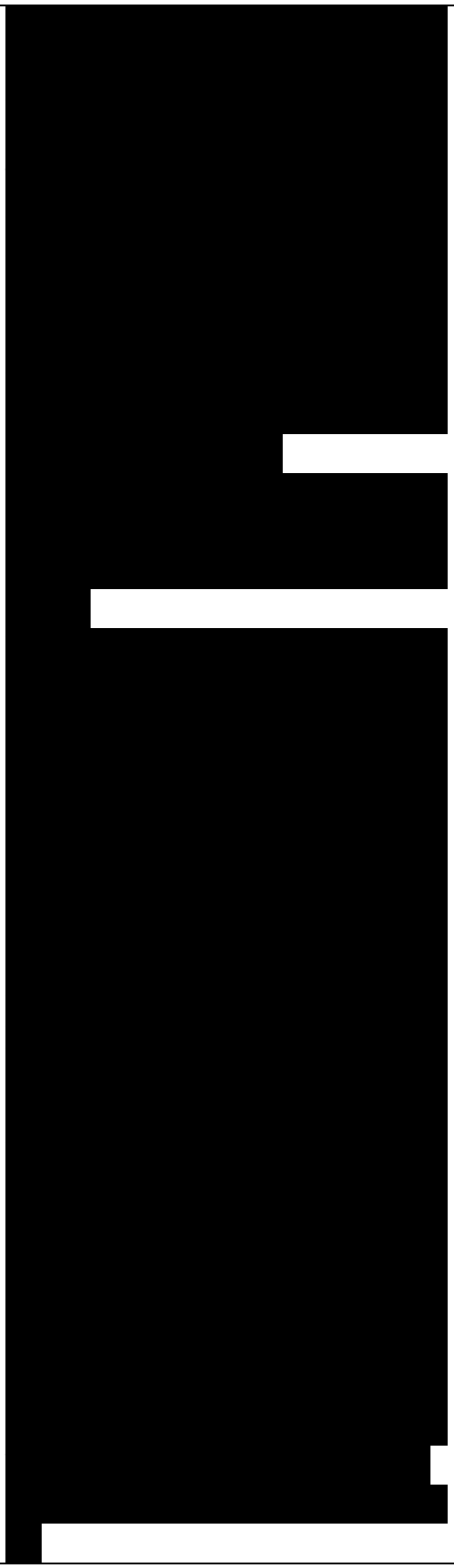
resistance genes, often organized into integrons or carried on transposons. Other plasmids carry metabolic genes or act as sex factors to promote transfer of the bacterial chromosome. SHV, TEM, OXA, IMP, VIM, and KPC: Beta-Lactamase families with members (denoted by numerals, as in SHV-1) that are related by a few amino acid substitutions. Beta-Lactamase nomenclature is not standardized. SHV denotes a variable response to sulfhydryl inhibitors; TEM was named after the patient (Temoneira) from whom the first sample was obtained; CTX-M, OXA, and IMP reflect an ability to hydrolyze cefotaxime, oxacillin, and imipenem, respectively; VIM denotes Verona integron-encoded metallo-beta-lactamase; and KPC is derived from Klebsiella pneumoniae carbapene- mase. The origin of names for other Beta-lactamases is just as variable and arcane. Transposon: A mobile unit of DNA that can jump, or transpose, from one DNA molecule to another — for example, from a plasmid to a chromosome or from a plasmid to a plasmid, usually without site specificity. In class I transposons, a pair of insertion	[redacted]	

sequences (segments of DNA that can replicate and insert more or less randomly at other sites) flank a resistance gene. In class II transposons, terminal inverted-repeat segments enclose the genes for a transposase (tnpA), a resolvase (tnpR), and one or more antibiotic-resistance genes. Some transposons are conjugative.

configuration of the active site of the enzyme, allowing access to oxyimino-Beta-lactams (Fig. I).14,18

Opening the active site to /6-lactam substrates also typically enhances the susceptibility of the enzyme to Beta-lactamase inhibitors, such as clavulanic acid. Amino acid substitutions distinct from those leading to the ESBL phenotype can confer resistance to inhibitors, but the combination of inhibitor resistance and an extended spectrum of activity seems to be, with rare exceptions,19 incompatible. More than 130 TEM enzymes are currently recognized, and their variety provides a useful way to follow the spread of individual resistance genes.20 TEM-10, TEM-12, and TEM-26 are among the most common in North and South America.21

SHV-TYPE ESBLs (CLASS A)



SHV-1 shares 68 percent of its amino acids with TEM-1 and has a similar overall structure (Fig. 1).22 As with TEM, SHV-type ESBLs have one or more amino acid substitutions around the active site. More than 50 varieties of SHV are currently recognized on the basis of unique combinations of amino acid replacements.20 SHV-type ESBLs currently pre-dominate in surveys of resistant clinical isolates in Europe and America.21’23 SHV-5 and SHV-12 are among the most common members of this family.21

CTX-M—TYPE ESBLs (CLASS A)

The most common group of ESBLs not belonging to the TEM or SHV families was termed CTX-M to highlight their greater activity against cefotaxime than against ceftazidime. More than 40 CTX-M enzymes are currently known.6 Belying their name, some hydrolyze ceftazidime more rapidly than they do cefotaxime. CTX-M-14, CTX-M-3, and CTX-M-2 are the most widespread.6

OTHER CLASS A ESBLs

Other class A ESBLs are uncommon and have been found mainly in Pseudomonas aeruginosa and at a limited

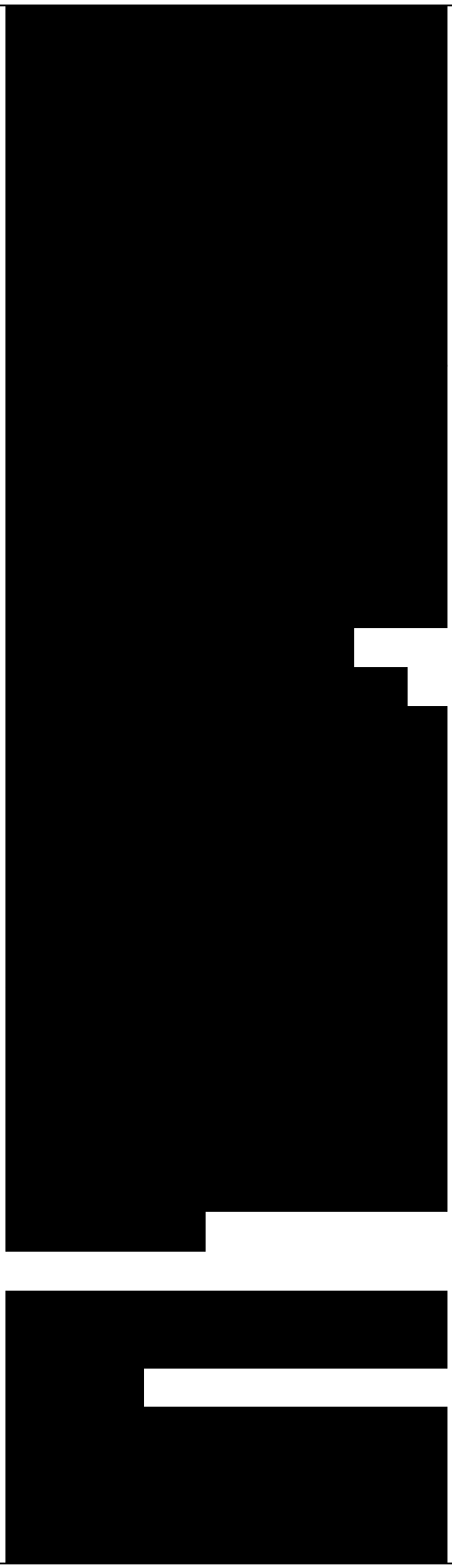
number of geographic sites: PER-1 in isolates in Turkey, France, and Italy; VEB-1 and VEB-2 in strains from Southeast Asia; and GES-l.GES-2, and 1BC-2 in isolates from South Africa, France, and Greece.24 PER-1 is also common in mulliresist antacinetobacter species in Korea and Turkey.25 Some of these enzymes arc found in Enterobacteriaccac as well, whereas other uncommon ESBLs (such as BES-1, IBC-1, SFO-1, andTLA-1) have been found only in Enterobacteriaceae.26'29

OXA-TYPE ESBLs (CLASS D)

Twelve ESBLs derived from OXA-IO, OXA-1, or OXA-2 by amino acid substitutions are currently known.20 They have been found mainly in P. aeruginosa in specimens from Turkey and France.5,30 Most OXA-type ESBLs are relatively resistant to inhibition by clavulanic acid. Some confer resistance predominantly to ceftazidime, but OXA-17 confers greater resistance to cefotaxime and cefepime than it does resistance to ceftazidime.31

PLASMID-MEDIATED AmpC ENZYMES (CLASS C)

AmpC Beta-lactamases, usually inducible by Beta-lactams, are encoded by chromosomal genes in many gram-negative bacilli.



Mutations that increase their expression are responsible for the ready emergence of broad-spectrum cephalosporin resistance in Enterobacter cloacae.32 The AmpC enzyme in E. coll is poorly expressed and the AmpC gene is missing from the chromosome of klebsiella and salmonella species, but plasmid-mediated AmpC enzymes can give these organisms the same resistance profile as a Beta-lactam-resistant enterobacter isolate. More than 20 different AmpC beta-lactamases have been found to be mediated by plasmids.7 Some, like the parental chromosomal enzymes, are accompanied by regulatory genes and are inducible, but most are not. Characteristically, AmpC Beta-Iactamases provide resistance to cephamycins as well as to oxyimino-Beta-lactams and are resistant to inhibition by clavulanic acid.

CARBAPENEMASES (CLASSES A, B, AND D)

Carbapenemases are a diverse group of enzymes. They arc currently uncommon but are a source of considerable concern because they are active not only against oxyimino-cephalosporins and cephamycins but also against carbapenems.

8 Plasmid- mediated IMP-type carbapenemases, 17 varieties of which are currently known, became established in Japan in the 1990s in both enteric gram-negative organisms and in pseudomonas and acinetobacter species. IMP enzymes spread slowly to other countries in the Far East, were reported from Europe in 1997, and have been found in Canada and Brazil.

A second growing family of carbapenemases, the VIM family, was reported from Italy in 1999 and now includes 10 members, which have a wide geographic distribution in Europe, South America, and the Far East and have been found in the United States.33 A few class A enzymes, notably the plas-

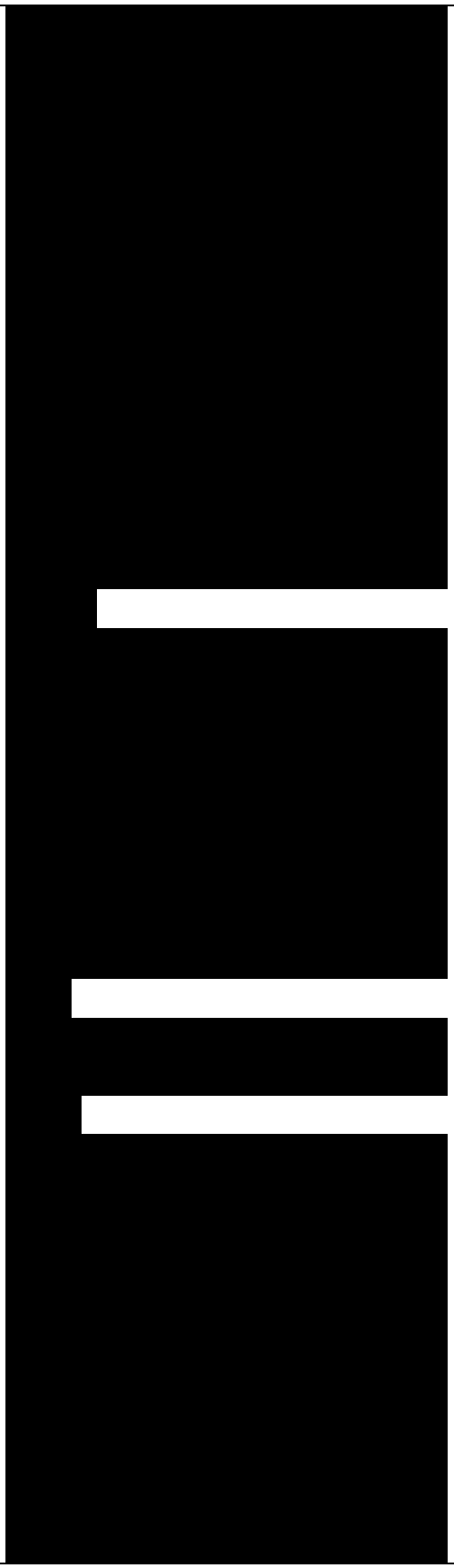


Figure 1. Schematic Diagrams of TEM and SHV Beta-Lactamases.

In these ribbon diagrams of TEM Beta-lactamases13 (Panel A) and SHV /2-lactamases (Panel B),14 the critical serine residue at position 70 is shown in ball-and-stick mode (at the center of each molecule) and the atoms of residues in which amino acid substitutions yield an extended-spectrum Beta-lactamase (ESBL) phenotype are shown in

stick mode. Colors are used to highlight the molecule's secondary structure: yellow indicates a-helixes, pink Beta-strands, and gray turns. Amino acid substitutions at positions 104, 164, 238, and 240 in TEM Beta-lactamases lead to the ESBL phenotype, but ESBLs with the broadest spectrum of activity usually have more than a single substitution. Many TEM ESBLs confer greater resistance to ceftazidime and aztreonam than to cefotaxime, but those with a serine substitution at position 238 may enhance resistance to cefotaxime as well. In the SHV family, substitutions at position 238 or at positions 238 and 240 are the most common and are associated with resistance to ceftazidime, cefotaxime, and aztreonam.15 Less commonly, an alteration at position 146 or 179 provides selective ceftazidime resistance; the change at position 146 causes a moderate decrease in susceptibility to imipenem as well.16,17 mid-mediated KPC enzymes, are effective carbapencmases as well. Finally, some OXA-type Beta-lactamases have carbapenemase activity, augmented in clinical isolates by additional resistance mechanisms, such as impermeability or efflux.8'34	[redacted]	

FACTORS INFLUENCING 0-LACTAMASE EXPRESSION

As if the variety of enzymes were not enough, further complications arise because expression of resistance is affected by additional factors. The same enzyme may express different resistance phenotypes, depending on the bacterial host and the test conditions. For ESBLs of the TEM and SHV families, the expanded spectrum is accompanied by a loss of intrinsic hydrolytic activity.35,36This loss can be compensated for by an increase in gene dosage (through gene duplication or carriage on a multicopy plasmid) or the presence of a promoter with increased activity (through a mutation or insertion- sequence substitution).

In some organisms (P. aeruginosa in particular), an active efflux system can reduce the intracellular accumulation of antibiotic and allow an enzyme with only limited hydrolytic capacity to inactivate the drug before it can reach its target; in other organisms, this effect is achieved by diminished expression of an outer-membrane porin required for Beta-lactam uptake. In Klebsiella pneumoniae,

decreased expression ofouter-membrane porins often accompanies ESBL production and may allow a TEM- or SHV-type ESBL to express resistance to cefepime or allow an AmpC Beta-lactamase to express resistance to imipenem.37’38

GENETICS OF Beta-LACTAMASES

Plasmids are responsible for the spread of most of the new Beta-lactamases, but the genes encoding these enzymes may also be located on the bacterial chromosome. The genes encoding some Beta-lactamases are carried by transposons.39 Genes for many of the new Beta-lactamases are found in integrons, which often include genes conferring resistance to other antibiotics. For this reason, the new Beta-lactamases are usually produced by organisms that are resistant to multiple antimicrobial agents.

Occasionally, the ESBL phenotype emerges in an organism isolated from a patient treated for multiple episodes of bacteremia, but much more often an ESBL-producing plasmid or strain disseminates to multiple patients, so that in hospital outbreaks one type of ESBL often predominates. Particular TEM-type ESBL varieties seem to have a fixed geographic distribution, whereas at least

some SHV types have been found all over the world, suggesting that they have a multifocal origin. For example, TEM-3 is common in France and has been reported in a few other European countries but has not been reported in the United States, whereas SHV-5 and SHV-12 have been detected worldwide.

The genes encoding the TEM-1 and TEM-2 Beta-lactamases are carried by transposons, as are the genes encoding some TEM-type ESBLs (Fig.

The gene encoding SHV-1 is found on the chromosome of most strains of K. pneumoniae."""'7 SHV genes also occur on transmissible plasmids; for example, one has been found on a 7.5-kb block of DNA apparently captured from the klebsiella chromosome.48 Genes encoding the remaining types of Beta-lactamase are often found incorporated into integrons (Fig. 2) but have their origin elsewhere. For example, the genes for CTX-M-type enzymes are found on the chromosome of kluyvera, a genus of rarely pathogenic commensal organisms. Rather than evolving from a progenitor with a more limited spectrum of activity, the CTX-M group appears to have emerged in multiple places by plasmid

acquisition of Beta-lactamase genes from such a widespread environmental reservoir.6

Integrons are also involved in the acquisition of AmpC-type Beta-lactamases by plasmids. Many of these plasmid-mediated enzymes can be related to chromosomal AmpC enzymes of particular species: thus, ACC-1 is related to the enzyme produced by Hafnia alvei; ACT-1 and MIR-1 to enzymes of enterobacter species; some CMY enzymes as well as LAT-1 and LAT-3 to enzymes of citrobacter species; other CMY enzymes and the FOX and MOX families to enzymes of aeromonas species; and DHA-1 to the enzyme of Morganella morganii.7 Carbapenemases of the IMP and VIM families are also found within integrons (Fig. 2), but the origin of their genes is not yet known.

PREVALENCE

Despite worldwide use of Beta-lactam antibiotics, the distribution of the enzymes responsible for resistance to oxyimino-cephalosporins and carbapenems is far from uniform. Some hospitals in the United States seem to have no ESBLs, whereas in other hospitals as many as 40 percent of K. pneumoniae isolates have

been reported to be ceftazidime-resistant as a result of ESBL production.49 ESBLs are most likely to be found in K. pneumoniae, K. oxytoca, and E. coli but have been reported in eitrobacter, enterobacter, proteus, salmonella, serratia, and other genera of enteric organisms50 and in such nonenteric organisms as Acinetobacter baumanmisi,s2 and P. aeruginosa.24Their prevalence is higher in isolates from intensive care units than in isolates from other hospital sites. In a sample of more than 4700 K. pneumoniae isolates obtained during the period from 1997 through 1999, the percentage expressing an ESBL phenotype was highest in isolates from Latin America (45.4 percent), the Western Pacific (24.6 percent), and Europe (22.6 percent) and lowest in strains from the United States (7.6 percent) and Canada (4.9 percent).” In more than 13,000 isolates of E. coli, the percentages expressing the ESBL phenotype were as follows: in Latin America, 8.5 percent; in the Western Pacific, 7.9 percent; in Europe, 5.3 percent; in the United States, 3.3 percent; and in Canada, 4.2 percent.53	[redacted]	

In another large data set from the United States collected from 1998 through 2001, ceftazidime resistance was present in 9.6 percent of K. pneumoniae isolates from intensive care units and 6.6 percent of isolates from other hospital locations.54 The higher the apparent frequency in a particular hospital, the more likely a single ESBL is involved. Out-breaks have been due both to a single ESBL-producing strain and to a single ESBL plasmid carried by unrelated strains. A resistant strain or plasmid may cause problems in several hospitals locally or involve a large geographic area.23t55,56 Community clinics and nursing homes have also been identified as potential reservoirs for ESBI.-producing K. pneumoniae and E. coli.57,58

In 1989, nontyphoid salmonella strains producing CTX-M-2 began to spread among neonatal units in Argentina and to neighboring South American countries, and by 2002 this enzyme was present in about 75 percent of ESBL-producing Enterobacteriaceae in Buenos Aires.59 CTX-M enzymes, which are also common in Japan, China, Korea, Taiwan, Vietnam,

and India, are a rapidly emerging problem in the United Kingdom60 and have been reported in Eastern Europe, Germany, France, and Spain and recently in the United States.6,61 It is estimated that in the United States, 3 to 4 percent of clinical K. pneumoniue and K. oxytoca isolates carry plasmid-mediated AmpC enzymes.62

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Integron In60 Containing CTX-M-9 Beta-Lactamase

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Figure 2. Schematic Diagrams of Genetic Units Encoding Various beta-Lactamases.

Diagrams of transposons and integrons encoding TEM-1.41 CTX-M-9,'12 and VIM-2[43],beta-lactamases are shown. IR denotes inverted repeat, bla beta-lactamase gene, dfr dihydrofolate reductase gene, qac gene conferring resistance to qua ternary ammonium compounds, delta deletion derivative, intl site-specific integrase gene, aad aminoglycoside adenylyltransferase gene, sul dihydropteroate synthetase gene, ORF open-reading frame, ottl recombination site, 59be 59-base element, aac aminoglycoside acetyltransferasc gene, and IS insertion sequence.

One particular plasmid-mediated AmpC enzyme, CMY-2, has been responsible for increasing resistance to ceftriaxone and other oxyimino-Beta-lactams in salmonella isolates from the United States.63’64 In Japan, IMP-type carbapcnemascs, first detected in Serratia marcescens and P. aeruginosa, have spread to other gram-negative bacilli,65 but the prevalence of this resistance mechanism is surprisingly low:

1.3 percent in P. aeruginosa and less than 0.5 percent in E. coli and K. pneumoniae.06,07 Considering the broad resistance to beta-lactam antibiotics that is conferred by carbapcnemases and considering their presence in Japan for more than a decade, their limited occurrence is surprising and somewhat reassuring considering the potential for future spread. Worldwide, 99.9 percent of Enterobacteriaceac remain susceptible to carbapenems. Carbapenemases can, however, be associated with lethal infections. In Greece and Italy, outbreaks due to carbapenem-resistant P. aeruginosa producing VIM-1 carbapcncmasc were identified in separate hospitals and associated with a high mortality rate.69’70 In Brazil, a

strain of A. baumannii resistant to imipenem and meropenem due to an OXA-type carbapenemase infected eight patients in two hospitals; five of the patients died, despite therapy with multiple antibiotics, including polymyxin B.71 K. pneumoniae strains with reduced susceptibility to carbapenems due to KPC-2 or KPC-3 has been found recently in several hospitals in New York City.72

DETECTION

Detection of the new Beta-lactamases is less straightforward than implied by the properties listed in Table 1 because of the heterogeneity of the enzymes, their variable activity against potential substrates, their coexistcnce with other Beta-lactamases, and the confounding factors that modify their expression. The procedure currently recommended by the Clinical and Laboratory Standards Institute (CLSI) to detect ESBL-producing K. pneumoniae, K. oxytoca, and E. coli involves an initial disk-diffusion or broth- dilution screening test with one or more oxyimino- Beta-lactams, followed by a confirmatory test to measure susceptibility to

ceftazidime and to cefotaxime alone and in combination with clavulanic acid. Automated procedures have also been developed.	[redacted]	
Currently there are no CLSI-recommended tests for detecting AmpC Beta-lactamases or carbapenemases, nor are there recommended tests for detecting ESBLs in P. aeruginosa or in enteric bacteria other than E. coli and klebsiella species. Cefoxitin or cefotetan resistance along with oxyimino-beta-lactam resistance raises the suspicion of an AmpC-type enzyme, although there are other possibilities.7 Car- bapenem resistance in an enteric gram-negative organism is currently rare enough to ensure that such an isolate would receive special attention. Unfortunately, with so many different ESBLs and other new Beta-lactamases, no test is completely reliable73; better tests continue to be proposed, and recommendations continue to evolve.	[redacted]	
Success in identifying these mechanisms of resistance in clinical laboratories is rather poor, suggesting that patients are at risk for receiving	[redacted]	

inappropriate treatment and that the prevalence of ESBLs and AmpC Beta-lactamases is underreported. In a study published in 1,999, before the current CLSI detection criteria were widely known, ESBL- and AmpC-producing K. pneumoniue and E. coli were sent as “unknown” specimens to 38 hospital-affiliated and commercial clinical laboratories in Connecticut. Six laboratories failed to test for resistance to any oxyimino-beta-Lactam, and only nine included both ceftazidime and cefotaxime in their evaluation. Depending on the strain tested, between 24 and 32 percent of laboratories incorrectly reported it as susceptible. 74 In a recent evaluation of the ability of rural laboratories in the United States to identify specific resistance mechanisms, only 5 of 60 laboratories screened K. pneumoniae isolates for ESBL production.75 In a proficiency test of 129 laboratories outside the United States, 7 misreported a highly resistant ESBL-producing K. pneumoniae strain as susceptible to all cephalosporins, and only 2 specifically reported the strain as an ESBL producer.76	[redacted]	

RISK FACTORS FOR INFECTION

Risk factors for colonization or infection by ESBL- producing organisms are little different from the risk factors for other nosocomial infections.77 Reported risks, many of which are linked, include an increased length of stay in the hospital 78,79 an increased length of stay in the intensive care unit,80,81 increased severity of illness,82'84 the use of a central venous or arterial catheter, the use of a urinary catheter, ventilatory assistance,al,82,8f' hemodialysis,87 emergency abdominal surgery,81 the use of a gastrostomy or jejunostomy tube,84 gut colonization,80,88 prior administration of an oxyimino-Beta-lactam antibioticic,84,88-92 and prior administration of any antibiotic.84,85,93 Similar risk factors are emerging for infection with P. aeruginosa producing IMP-type carbapenemases.94

TREATMENT

IN VITRO DATA

ESBL-producing organisms vary in their susceptibility to different oxyimino-Beta-lactams, and despite resistance to some they may appear sensitive to others. For organisms producing TEM and SHV- type ESBLs, apparent in vitro sensitivity to cefepime and to piperacillin-tazobactam is common, but both drugs show an inoculum effect, with diminished susceptibility as the size of the inoculum is increased from 105 to 107 organisms.95'97 Strains with some CTX-M-type and OXA-type ESBLs are resistant to cefepime on testing, despite the use of a standard inoculum.0,30 Strains producing only ESBLs are susceptible to cephamycins and carbapenems in vitro and show little if any inoculum effect with these agents.96'98 AmpC-producing strains are typically resistant to oxyimino-Beta- lactams and to cephamycins and are susceptible to carbapenems; however, diminished porin expression can make such a strain carbapenem-resistant as well.38 Strains with IMP-, VIM-, and OXA-type carbapenemases usually remain susceptible to aztreonam.8 Resistance to non-Beta-lactam antibiotics is common in strains making any of these enzymes,	[redacted]	

such that alternative options for non-beta-lactam therapy need to be determined by direct susceptibility testing. Resistance to fluoroquinolones and aminoglycosides is especially high.99,100

STUDIES IN HUMANS

No randomized, controlled trials have evaluated various treatments for infections caused by organisms producing the new Beta-lactamases. Most reports present a compilation of a small number of cases in the setting of an outbreak, with treatment consisting of a particular antibiotic, often given in combination with other agents and followed by other infections.

Furthermore, the outcome may be specific to the particular enzyme involved, suggesting that caution is warranted in generalizing the results.

For infections caused by ESBL-producing E. coli or klebsiella species, treatment with imipenem or meropenem has been associated with the best outcomes in terms of survival and bacteriologic clearance.101'106 Cefepime and piperacillin-tazobactam have been less successful. Ceftriaxone, cefotaxime, and

ceftazidime have failed even more often, despite the organism's susceptibility to the antibiotic in vitro.107 Several reports have documented failure of cephamycin therapy as a result of resistance due to porin loss.108,109 Some patients have responded to aminoglycoside or quinolone therapy, but in a recent comparison of ciprofloxacin and imipenem for bacteremia involving an ESBL-pro- ducing K. pneumoniae, imipenem produced better outcome.106 There have been few clinical studies to define the optimal therapy for infections caused by ESBL- producing P. aeruginosa strains.24 There are also insufficient data to evaluate the benefit of combination therapy with a Beta-lactam plus a quinolone or aminoglycoside for infections due to ESBL-positive organisms. The data that are available concerning the treatment of infections caused by AmpC-type Beta-lactamase-producing K. pneumoniae indicate a much better response to carbapenem than to cephalosporin therapy.110 Data on treatment for carba-penemase-producing organisms are also very limited. Although these enzymes may fail to hydrolyze aztrconam, some	[redacted]	

clinical isolates have been aztreonam-resistant, presumably because of porin loss, suggesting that caution should be exercised in assuming that the antibiotic can be used successfully for treatment.

OUTBREAK CONTROL

In outbreak situations, successful control has usually involved both restriction of the use of oxyimi-no-beta-lactams and the institution of barrier precautions (hand washing, gloves, and gowns) for patients with infection or colonization.s8,111,112

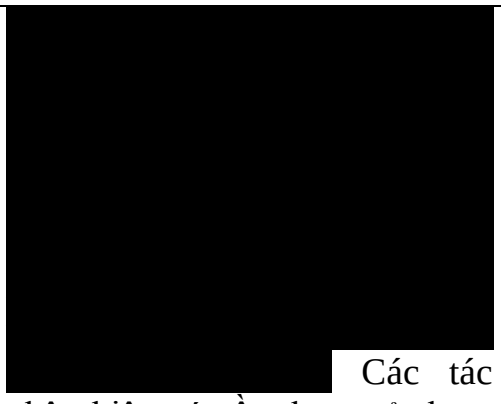
Successful control with the use of strict isolation procedures without limitations on antibiotic use has also been reported.113 Substitution of imipenem,112 piperacillin-tazobactam,114 or cefepime- amikacin115 as die antibiotic of choice for empirical therapy has been followed by decreased isolation of ESBL-producing organisms.

Antibiotic substitutions can, however, have unintended consequences. In an outbreak of infection with K. pneumoniae resistant to other Beta-lactam antibiotics, increased use of imipenem was followed by the emergence of imipenem-resistant K. pneumoniae that produced an AmpC enzyme (ACT-1) and was

missing an outer-membrane porin.37,116 At the same hospital, increased use of imipenem also led to the emergence of imipenem-resistant A. baumannii.117

CONCLUSIONS

Gram-negative bacteria have adapted to broad- spectrum Beta-lactam antibiotics by modifying the substrate spectrum of common plasmid-mediated Beta-lactamases and by mobilizing resistance-promoting chromosomal Beta-lactamase genes into plasmids, allowing their spread to new hosts. Currently, the most common new Beta-lactamases are ESBLs in the TEM, SHV, and CTX-M families. These enzymes confer resistance to ceftazidime, cefotaxime, ceftriaxone, aztreonam, and other oxyimino-Beta-lactams and are found most often in klebsiella species and E. coli, although they also have been detected in many other gram-negative pathogens. Their prevalence is probably underestimated because detection in clinical laboratories is imperfect. Carbapenems are the surest agents for therapy, but the variety of Beta-lactamases that confer resistance to carbapenems is increasing, and overuse of any single class of antibiotic is likely to be followed

by the selection of pathogens resistant to that agent. There are no Beta-lactams in development that can treat infections with organisms producing some of the new Beta-lactamases. Available agents need to be used judiciously and infection-control measures implemented in outbreak situations to prevent the further spread of pathogens with these all-too-successful mechanisms of resistance.	 Các tác nhân hiện có cần được sử dụng khôn ngoan và các biện pháp chống nhiễm trùng được thực hiện trong các tình huống bùng phát dịch để ngăn chặn sự mở rộng các mầm bệnh với các cơ chế kháng quá thành công này.	