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ISCCM Handbook on COMBATING ANTIMICROBIAL RESISTANCE (The ICCARe Book)

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CHAPTER 3

Treating Extended-spectrum Beta-lactamase and AmpC Producing Gram-negative Bacteria

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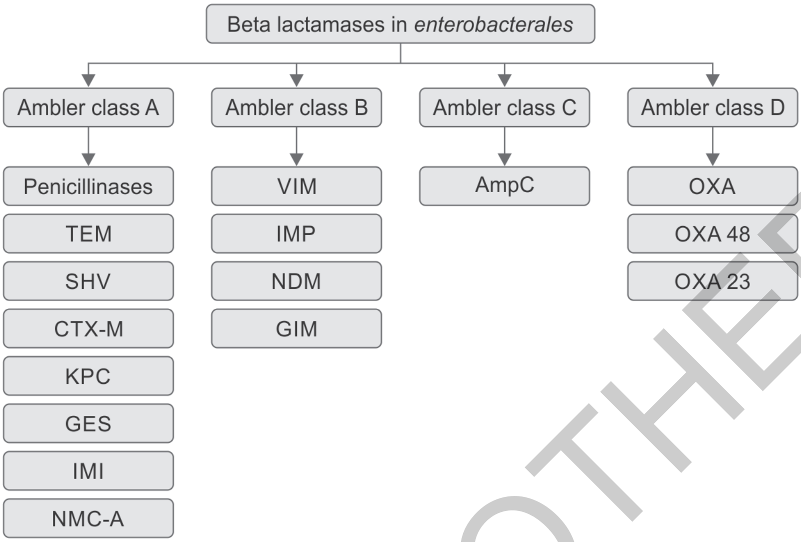
INTRODUCTION

Antibiotic resistance in the intensive care unit is a significant concern as it hampers effective treatment, leading to longer hospital stays, increased healthcare cost, and higher mortality rates.[1] Extended-spectrum beta-lactamase (ESBL) was only the first step on the slippery slope of loss of antibiotic efficacy, and a historical perspective may be useful to understand our "see-saw" battle with the microbes. The third-generation cephalosporins brought new hope for treating broad-spectrum β-lactamases in the 1980s. Unfortunately, soon in 1983, reports of plasmid-encoded β-lactamases capable of hydrolyzing these new third-generation cephalosporin became available.[2] ESBL and AmpC β-lactamases, which belong to ambler class A and C respectively, will be discussed in this chapter.

EXTENDED-SPECTRUM BETA-LACTAMASE

The ESBL enzymes belong to ambler class A of β-lactamases[3] **(Flowchart 1)**. They mediate resistance to all penicillins, third-generation cephalosporins, and monobactam, but not to cephamycins and carbapenems.[4] The organisms carrying ESBL genes often have additional genes or mutations in genes that mediate resistance to a broad range of antibiotics. Commonly encountered varieties of ESBL include TEM, SHV, and CTX-M. ESBL other than plasmid-mediated ESBL, such as *Pseudomonas* extended resistance (PER), Vietnam extended-spectrum β-lactamase (VEB), and Guiana extended-spectrum (GES), are not common and have been found mainly in *P. aeruginosa*. The incidence of common pathogens producing ESBL and their resistance genes in Indian settings is mentioned in **Table 1**. Routine ESBL testing is not performed by most microbiology laboratories and nonsusceptibility to ceftriaxone is often used as a proxy for ESBL production, although this has limitations with low specificity. Detection of ESBL can be done by use of cefotaxime or ceftazidime disks with or without clavulanate in *Klebsiella*, *Escherichia coli*, and *P. mirabilis*. A difference of ≥5 mm between the zone diameters of either of the cephalosporin disks and respective cephalosporin/clavulanate disks is taken as phenotypic confirmation of ESBL production.[5]

Flowchart 1: Ambler classification of β-lactamases.



(GES: guiana extended-spectrum; KPC: klebsiella pneumoniae carbapenemase; OXA: oxacillinase)

TABLE 1: Incidence of resistance in India and their molecular resistance mechanism.[6]

	Resistance up to (%)	*Molecular mechanism of resistance*
E. coli	70	SHV, TEM, OXA-1, and CTX-M
Klebsiella pneumoniae	60	SHV, TEM, and CTX-M
Pseudomonas aeruginosa	25	VEB
Acinetobacter baumannii	70	TEM and PER

(OXA-1: oxacillinase; PER: pseudomonas extended resistance; VEB: vietnam extended-spectrum β-lactamase)

AmpC

AmpC β-lactamases are β-lactamase enzymes that are produced at basal levels by several Enterobacterales and glucose nonfermenting gram-negative organisms. The AmpC expression during antibiotic treatment is commonly described for *Enterobacter cloacae complex*, *Klebsiella aerogenes*, and *Citrobacter freundii*.[7] Increased AmpC production by Enterobacterales generally occurs by one of three mechanisms—(1) inducible chromosomal gene expression, (2) stable chromosomal gene derepression, or (3) constitutively expressed *ampC* genes.[6] Detection of AmpC can be done by disk approximation test. Disk flattening of the zone of inhibition between the ceftazidime disk and the inducing substrates such as imipenem, cefoxitin, and amoxicillin-clavulanate disk is considered positive for AmpC production.[8]

DIFFERENCE BETWEEN ESBL AND AmpC

AmpC β-lactamases in a derepressed variant and ESBLs share the hydrolytic activity to the penicillins and cephalosporins and it is difficult to differentiate the mechanisms of resistance. Organisms actively producing AmpC β-lactamases may be resistant to antibiotics such as amoxicillin-clavulanate, ampicillin-sulbactam, and sometimes piperacillin-tazobactam. However, ESBL-producing organisms may or may not be resistant to them, depending on previous antibiotic exposure and ESBL subtype. Also, AmpC β-lactamase-producing organisms will often be susceptible to aztreonam, whereas ESBL-producing organisms will be resistant to it.[9]

TREATMENT OPTIONS FOR ESBL PRODUCING ORGANISMS

Carbapenem

Carbapenems are preferred treatment for serious infections caused by ESBL-producing organisms, which include meropenem, imipenem-cilastatin, and ertapenem.[10] In patients with critical illness and hypoalbuminemia, the free fraction of ertapenem increases, leading to a significant decrease in half-life; hence, other carbapenems should be considered over ertapenem in these patients.

Beta-lactam/Beta-lactamase Inhibitor Combinations

Beta-lactam/β-lactamase inhibitors (BLBLIs) are considered as reliable carbapenem-sparing antibiotics in treatment of ESBL producing organisms. β-lactamase inhibitors, such as tazobactam, clavulanate, sulbactam, and avibactam, have shown efficacy for ESBL enzymes. Their classification and spectrum of activity are discussed in the **Table 2**.

Carbapenem versus Beta-lactam/Beta-lactamase Inhibitors

Treatment of ESBL infection with carbapenem or BLBLI remains a topic of debate. A carbapenem is recommended as the first-line treatment for ESBL-E infections outside of the urinary tract. In MERINO trial patients with *E. coli* or *K. pneumoniae* bloodstream infection and ceftriaxone resistance, treatment with piperacillin-tazobactam compared with meropenem was not noninferior.[11] Piperacillin-tazobactam can fail in treating ESBL because its minimum inhibitory concentration (MIC) may be inaccurate and/or poorly reproducible when ESBL enzymes are present and poor activity with increased bacterial inoculum. However, exclusive use of carbapenems for the treatment of ESBL raises issues of cost and the risk of development of resistance. Few studies have shown the noninferiority of BLBLI over carbapenems.[12] Certain parameters which can be considered for deciding the treatment between BLBLI and carbapenem are discussed in the **Table 3**.

TABLE 2: Classification of beta-lactamase inhibitors and properties.

	Agents	*Activity*
First generation BLI	Clavulanic acid/ sulbactam/ tazobactam	• Cover only the class A β-lactamases • Only sulbactam has intrinsic activity against *A. baumannii*
Newer generation	Vaborbactam	• Boronic acid derivative • Potent inhibitor of class A (KPC) and C β-lactamase
Diazabicyclooctanes (second-generation β-lactamase inhibitor)		
First-generation DBO	Avibactam and relebactam	• Potent inhibitor of class A, C, and D • Not effective against *Acinetobacter* species, producing OXA type carbapenemase • No activity against MBL producers
Second-generation DBO	Zidebactam	• Increased activity to class C β-lactamase than avibactam and relebactam • Intrinsic activity against *P. aeruginosa* and *A. baumannii*

(BLI: beta-lactamase inhibitors; DBO: diazabicyclooctane; KPC: *Klebsiella pneumoniae* carbapenemase; MBL: metallo-β-lactamase; OXA: oxacillinase)

TABLE 3: Considerations for BLBLI versus carbapenem.

Considerations		*BLBLI*	*Carbapenem*
Severity	Mild to moderate	✓	
	Severe		✓
Immune status	Immunocompetent	✓	
	Immunocompromised		✓
Site of infection	Urine, SSTI, and IAI with source control	✓	
	Blood stream infections and pneumonia		✓
Organisms	*E. coli*	✓	
	Klebsiella and *Enterobacter*		✓
MIC to Piperacillin tazobactam	<8 considering EUCAST break point	✓	
	>16 considering EUCAST break point		✓
If high dose prolonged infusions are used		✓	
For de-escalation		✓	

(BLBLI: Beta-lactam/beta-lactamase inhibitor; EUCAST: European Committee on Antimicrobial Susceptibility Testing; IAI: intra-abdominal infection; MIC: minimal inhibitory concentration; SSTI: skin/soft tissue infection)

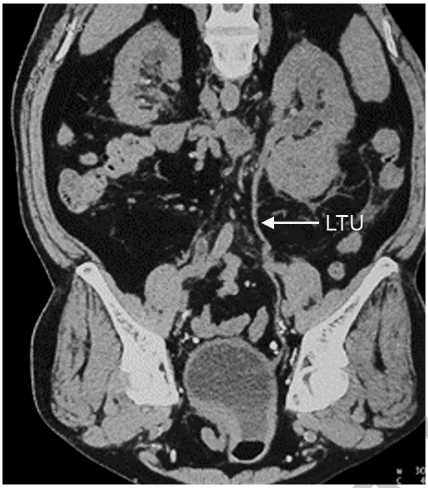


Fig. 1: CT KUB showing left bulky kidney with air pockets suggestive of emphysematous pyelonephritis.

CASE VIGNETTE

A 55-year-old male, with uncontrolled diabetes, was admitted in intensive care unit with sepsis, anuria, and acute kidney injury (creatinine 4.5). Computed tomography of the kidneys, ureters, and bladder (CT KUB) was suggestive of emphysematous pyelonephritis **(Fig. 1)**. Patient had history of urinary tract infection (UTI) 3 months earlier and was catheterized that time. Previous urine culture which was collected from the bag had shown carbapenem-resistant *Klebsiella pneumoniae* for which he was treated with oral antibiotics elsewhere.

What can be considered as empiric choice of antibiotic?
- Ceftazidime avibactam plus aztreonam
- Polymyxin
- Colistin
- Meropenem.

Urine collection from bag is associated with higher chances of contamination and false positive result, hence should be avoided. Emphysematous pyelonephritis is serious infection and the most common cause is *E. coli*. Empiric pathogen coverage of 80% for mild and 90% for severe sepsis is physician-accepted thresholds.[13] It is also necessary to know the local epidemiology before considering empiric antibiotic treatment. Polymyxin has low urinary concentrations and as patient had acute kidney injury, colistin was avoided. Meropenem was avoided as empirical treatment considering previous culture report, although it was understood that previous sample was collected inappropriately.

Patient was started empirically with ceftazidime avibactam plus aztreonam in renal modified doses. Blood culture showed ESBL *E. coli* but urine was sterile. He underwent DJ stenting and proximal urine grew *E. coli* with similar sensitivity compared to blood isolate. Although broad spectrum antibiotics are used in empirical treatment in patients with serious infection, de-escalation to appropriate antibiotics based on culture sensitivity report should be considered. In this case, antibiotics were deescalated to meropenem and patient responded well to treatment.

NEWER BETA-LACTAM/BETA-LACTAMASE INHIBITOR

Ceftolozane-tazobactam

Ceftolozane-tazobactam is a fifth-generation cephalosporin/β-lactamase inhibitor combination. Ceftolozane acts by inhibition of transpeptidase (penicillin binding protein) leading to bacterial cell wall inhibition.[14] Ceftolozane-tazobactam is active against ESBL but does not cover AmpC β-lactamases. It is approved for treatment of complicated intra-abdominal infections, complicated UTIs, and hospital-acquired pneumonia in adults.

Ceftazidime/Avibactam

Ceftazidime-avibactam is combination of ceftazidime, a third-generation cephalosporin and a novel β-lactamase inhibitor avibactam. Ceftazidime acts by binding to transpeptidase and it is inactivated by different β-lactamases and carbapenemases. Combination with avibactam broadens the spectrum of activity against a number of β-lactamases such as ESBL, AmpC, *Klebsiella pneumoniae* carbapenemase (KPC), as well as oxacillinase-48 (OXA-48).[15] It is approved for the treatment of adults with complicated UTI, complicated intra-abdominal infection and hospital-acquired pneumonia, including ventilator-associated pneumonia.

Imipenem/Cilastatin/Relebactam

Imipenem/cilastatin/relebactam is a novel BLBLI combination. Addition of relebactam to imipenem/cilastatin can enhance its activity against AmpC, ESBL, and KPC producing Enterobacterales and *P. aeruginosa*. It is approved for the treatment of patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, complicated UTIs including pyelonephritis, and complicated intra-abdominal infections with limited treatment options.[16]

Meropenem/Vaborbactam

Meropenem/vaborbactam is a carbapenem and novel β-lactamase inhibitor combination. Meropenem has activity against various β-lactamases,

TABLE 4: Activity of newer BLBLI against ESBL and AmpC producing Enterobacteriaceae and *Pseudomonas*.[6]

	Enterobacteriaceae			*Pseudomonas*	
BLBLI	***ESBL***	***AmpC***	***ESBL + AmpC***	***ESBL***	***AmpC***
Ceftazidime/avibactam	✓	✓	✓	✓	✓
Ceftolozane/tazobactam	✓	±	±	✓	✓
Imipenem/relebactam	✓	✓	✓	✓	✓
Meropenem/vaborbactam	✓	✓	✓	✓	✓

(ESBL: extended-spectrum beta-lactamase; BLBLI: beta-lactam/beta-lactamase inhibitor)

including ESBL. Vaborbactam enhances meropenem's stability against carbapenemases like KPC, expanding its coverage. This combination has good activity against AmpC and ESBL β-lactamase. It is approved for treatment of cUTI.[17] Activity of newer BLBLI against ESBL and AmpC producing Enterobacteriaceae and *Pseudomonas* is mentioned in **Table 4**.

Aminoglycosides

Aminoglycosides are effective against gram-negative bacteria including ESBL pathogens. The advantage of aminoglycosides is their high urinary concentration; therefore, they can be carbapenem-sparing treatment option in ESBL UTI. Plazomicin is a newer aminoglycoside antibiotic which acts by targeting the 30S ribosomal subunit, and inhibiting bacterial protein synthesis. It has activity against ESBL-producing organisms and some carbapenemases.[18] Aminoglycoside-induced nephrotoxicity is major concern especially for patients in intensive care, shock, older age, and pre-existing renal disease.

Tigecycline

Tigecycline is not affected by ESBL production. It is approved for the treatment of complicated skin and soft tissue infections and intra-abdominal infections but not a good option for UTIs due to poor concentration in urine. Eravacycline is a novel tetracycline antibiotic that exhibits against various gram-positive and gram-negative pathogens, including those with TET-specific acquired resistance mechanisms. Eravacycline is approved for the treatment of complicated intra-abdominal infections in adults.[19]

Fosfomycin

Fosfomycin has activity against many ESBL-E and multidrug-resistant enterobacteriaceae. Its main limitation is the development of resistance during treatment. Fosfomycin is not suggested as empiric treatment of infections caused by *K. pneumoniae* and other gram-negative organisms which carry fosA hydrolase genes that may lead to clinical failure.

TREATMENT OPTIONS FOR AmpC-PRODUCING ORGANISMS

Cefepime is relatively stable against AmpC enzymes and it also has low AmpC induction potential hence treatment with cefepime can be considered in infection due to AmpC producing organisms.[10] Carbapenems remain stable against AmpC β-lactamases and can be considered as treatment option for severe infections caused by these organisms. Newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam, are effective in treatment of AmpC-E but these agents should be reserved for treating infections caused by organisms exhibiting carbapenem resistance. Trimethoprim–sulfamethoxazole (TMP-SMX), fluoroquinolones, aminoglycosides, tetracyclines, and other non-β-lactam antibiotics do not induce AmpC and are also not substrates for AmpC hydrolysis hence these agents can be considered treatment if susceptibility to an appropriate agent is demonstrated.

CONCLUSION

The ESBL and AmpC appear like docile doves today in comparison to carbapenemases. However, they were the harbingers of the latest generation of resistance mechanisms. Organisms frequently have a combination of old and new resistance mechanisms that are being discovered every week. Genotyping and machine learning algorithms rather than phenotypic drug susceptibility testing (DST) and real-time therapeutic drug monitoring (TDM) in blood and tissues, along with closed-loop AI-supported dosing, may help move the field forward.

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Salient Features

- Addresses the most important bacterial infections encountered in Indian intensive care units (ICUs)
- Focuses on understanding the mechanisms of resistance and microbiological aspects of bacterial infections
- Guides the clinicians regarding the therapeutic options for these complex situations
- Also addresses the PK/PD aspects of antimicrobial therapy.

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Printed in India

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ISBN 978-93-5696-985-8

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