The Explosion of ESBL in the ICU Setting: Conventional and Novel Options

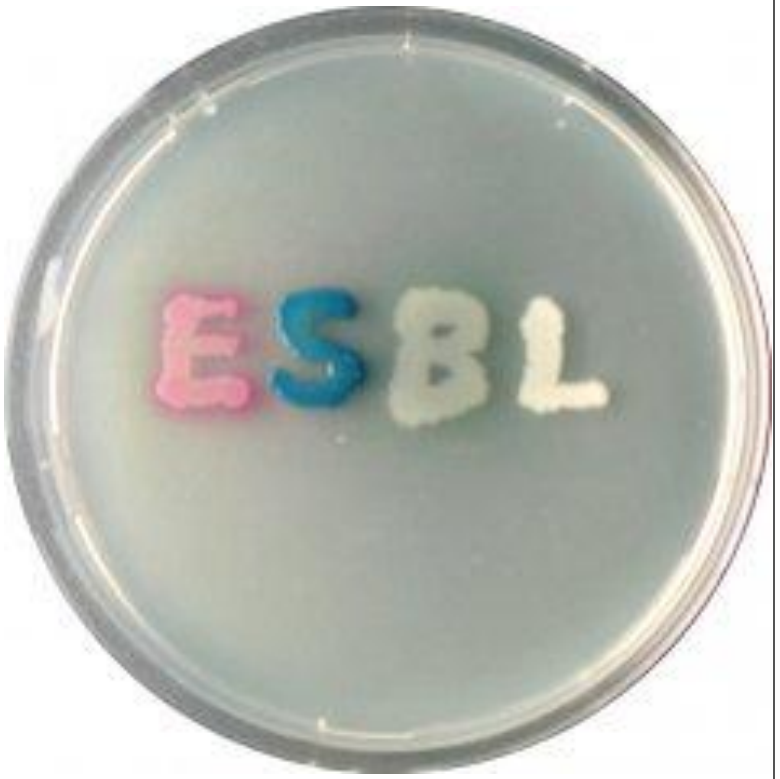
Introduction

- The ever-increasing bacterial resistance to antibiotics is one of the most challenging tasks of all the medical issues which are being faced by us today.
- Increasing prevalence of extremely drug resistant Gram negative bacteria is a major global concern.
- A single mutation in bacteria which leads to a new resistance mechanism against various drugs is like undoing within moments, the great efforts in developing these drugs, of a great mind.
- Extensive usage of carbapenem has resulted in emergence and spread of carbapenem resistant *Enterobacteriaceae, Pseudomonas and Acinetobacter.*

Ghafur *et al . J Microbiol Infect Dis* 2012; 2(1): 5-8

ESBLs

- The first report of plasmid-encoded β-lactamases capable of hydrolyzing the extended-spectrum cephalosporins was published in 1983.
- The resistance to newer β-lactams which are a result of these ß-lactamases, has emerged quickly.
- These new β-lactamases are termed **extended spectrum β-lactamases (ESBLs)**



Dalela G *et al. J Clin and Diag Res.* 2012 April, Vol-6(2): 182-187

Selected β-lactamases of gram-negative bacteria

β-lactamase	Examples	Substrates	Inhibition by clavulanate*	Ambler's class / Bush's class
Broad-spectrum	TEM-1, TEM-2, SHV-1	Penicillin G, aminopenicillins, carboxypenicillins, piperacillin, narrow-spectrum cephalosporins	+++	A / 2b
	OXA family	Broad-spectrum group plus cloxacillin, methicillin, and oxacillin	+	D / 2d
Extended-spectrum	TEM family, SHV family	Broad-spectrum group plus oxyimino-cephalosporins, and monobactam (aztreonam)	++++	A / 2be
	CTX-M family	Expanded-spectrum group plus, for some enzymes, cefepime	++++	A
	OXA family	Same as for CTX-M family	+	D / 2d
	Others (PER-1, PER-2, BES-1, GES/IBC family, SFO-1, TLA-1, VEB-1, VEB2)	Same as for TEM family and SHV family	++++	A

*+, +++ , and ++++ denote relative sensitivity to inhibition.

Peterson DL. Am J Med 2006; 119 (6 Suppl 1):S20-8.

Selected β-lactamases of gram-negative bacteria

β-lactamase	Examples	Substrates	Inhibition by clavulanate*	Ambler's class/ Bush's class
AmpC	ACC-1, ACT-1, CFE-1, CMY family, DHA-2, FOX family, LAT family, MIR-1, MOX-1, MOX-2	Expanded-spectrum group plus cephamycins	0	C / 1
Carbapenemase	IMP family, VIM family, GIM-1, SPM-1 (metallo-enzymes)	Expanded-spectrum group plus cephamycins and carbapenems	0	B / 3
	KPC-1, KPC-2, KPC-3	Same as for IMP family, VIM family, GIM-1, and SPM-1	+++	A / 2f
	OXA-23, OXA-24, OXA-25, OXA-26, OXA-27, OXA-40, OXA-48	Same as for IMP family, VIM family, GIM-1, and SPM-1	+	D / 2d

*+, +++ , and ++++ denote relative sensitivity to inhibition.

Peterson DL. Am J Med 2006; 119 (6 Suppl 1):S20-8.

Genetics of ESBLs

- *E. coli* and *Klebsiella pneumoniae* often carry genes for TEM-1, -2 and SHV-1 ß-lactamases.
- TEM-1, -2 and SHV-1 are so-called broad-spectrum (but not extended-spectrum) ß-lactamases that are capable of hydrolyzing penicillins but not cephalosporins.
- These TEM- and SHV-derived ESBLs were the commonly observed ESBL types in *E. coli* throughout the 1980s and 1990s.
- Unlike TEM and SHV-type ESBLs, CTX-M-type ESBLs do not have corresponding non-ESBL progenitors.
- Currently, five groups of CTX-M-type ESBLs have been identified: CTX-M-1, -2, -8, -9 and -25 groups. CTX-M-14 (belonging to the CTX-M-9 group) and CTX-M-15 (belonging to the CTX-M-1 group) are particularly associated with community-acquired isolates

Major sources of extended-spectrum β-lactamases

Type	Major sources
TEM, SHV	E. coli, K. pneumoniae
Cefotaxime hydrolyzing (CTX-M)	S. Typhimurium, E. coli, K. pneumoniae
Oxacillin hydrolyzing (OXA)	P. aeruginosa
PER-1 PER-2	P. aeruginosa, A. baumanii, S. Typhimurium S. Typhimurium
VEB-1	E. coli, P. aeruginosa

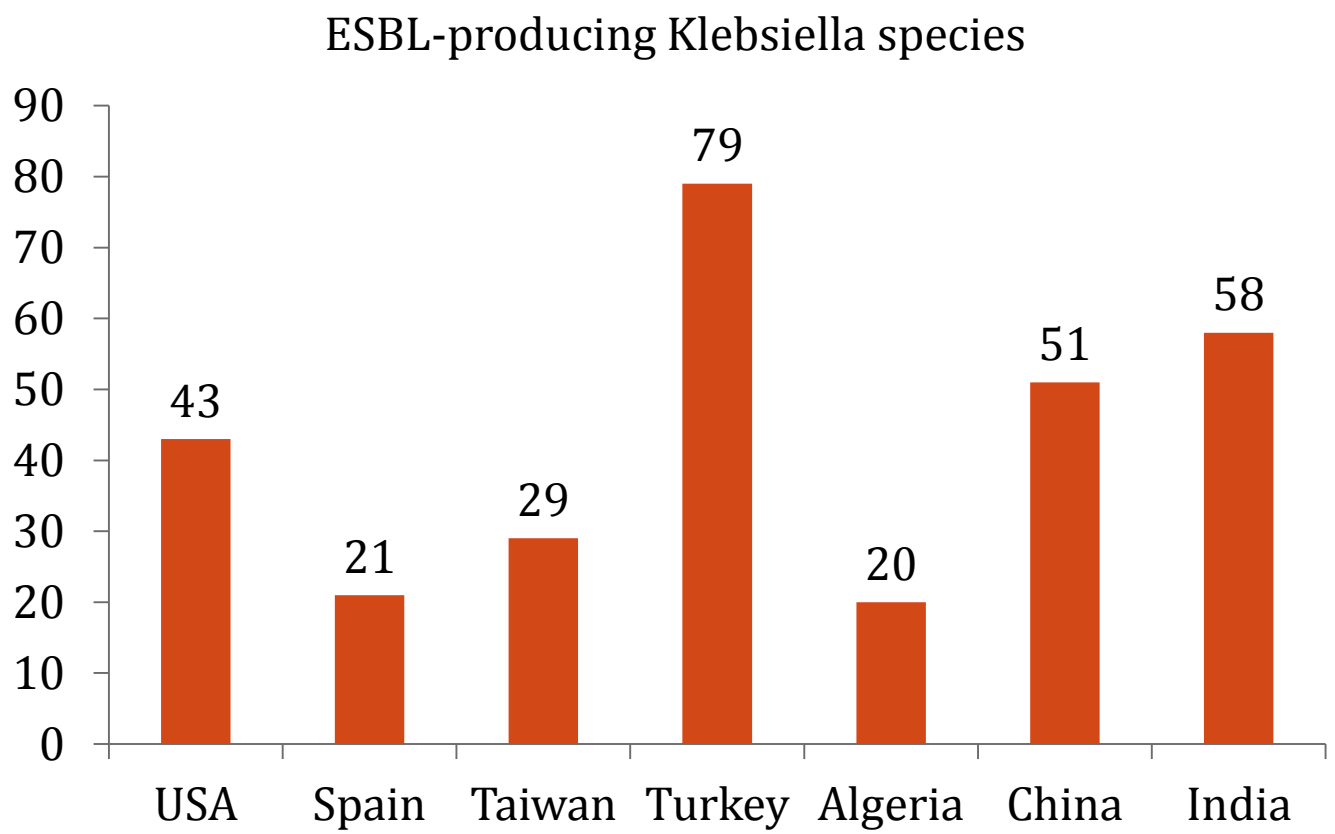
Epidemiology

- Several studies, mostly in adult patients, have demonstrated that infections due to ESBL-producing organisms are associated with
  - increased treatment failure,
  - higher mortality,
  - longer hospital stays, and
  - higher health care costs.
- Although population-based estimates of the prevalence and incidence of this burden exist, the statistics vary widely from continent to continent, and even from center to center, with ranges as low as **6%** and as high as even **70%.**

Benner KW *et al., J Pediatr Pharmacol Ther*. 2014 Apr-Jun; 19(2): 83–90

ESBL Prevalence across Globe

- In the recent years, a significant increase in ESBL-producing Klebsiella species has been reported from across the globe.



Khalid Abdalla Ali Abdel Rahim *Jundishapur J Microbiol.* 2014 Nov; 7(11): e17114.

ESBL Prevalence In Sub-Continent

- Studies in the sub-continent have reported the prevalence of the ESBL

Location	ESBL-EC %	ESBL-KP %	Reference
Mumbai	20	20	Vaidya[15]
Chandigarh	70	60	Sharma *et al.*[16]
Pondicherry	60.8	39.2	Mohamudha Parveen *et al.*[17]
Amritsar	46.4	52.3	Kaur and Aggarwal[18]
Salem	79.5	50	Priyadharsini *et al.*[19]
Guwahati	43	67	Sarma *et al.*[20]
Ujjain	69	41	Pathak *et al.*[21]
Indore	80.6	86.7	Chitnis *et al.*[22]

EC: *Escherichia coli*, KP: *Klebsiella pneumoniae*, ESBL-EC: ESBL producing *E. coli*, ESBL-KP: ESBL producing *K. pneumoniae*

Sridhar PN Rao *et al.* J Lab Physicians. 2014 Jun; 6(1): 7–13.

Epidemiology of ESBL-producing E. coli in the Community

- Community-acquired ESBL-producing E. coli infections have now been reported from all populated continents.
- While CTX-M-type ESBLs are most frequently encountered in E. coli, they have now spread to K. pneumoniae and other enterobacterial species worldwide as well

	Community-acquired	**Hospital-acquired/healthcare-associated**
Organism	*Escherichia coli*	*Klebsiella pneumoniae, but E. coli* increasingly common
infection	Mostly urinary tract infection; also biliary infection and bacteremia	Bacteremia, pneumonia, intra-abdominal and wound infection
ESBL	CTX-M (especially CTX-M-15)	SHV; CTX-M increasingly common

Sridhar PN Rao *et al.* J Lab Physicians. 2014 Jun; 6(1): 7–13.

What is the clinical relevance of ESBLs?

- *E. coli and Klebsiella spp. are common causes of infection*
- Resistance to all penicillins and cephalosporins
- May be treated with β-lactam- β-lactamase inhibitor combinations, aminoglycosides and carbapenems; fluoroquinolones depending on susceptibility results
- Associated with treatment failure; may have increased mortality if appropriate therapy not started within 3 days
- Associated with nosocomial outbreaks, particularly ICUs, LTCHs
- Clonal outbreaks related to cross infection
- Multi-clonal outbreaks related to selective pressure, i.e., antibiotic use

Screening patients/residents for ESBLs

- Screening patients/residents for ESBLs
- Each health care facility should have a consistent approach to surveillance
- Local epidemiology should govern decision making regarding routine screening for ESBLs e.g. if the local incidence is high, there may be value in screening, particularly ICU admissions
- Screen patients in close proximity to colonized/infected patients, e.g., roommates
- During an outbreak, all patients/residents with common risk factors should be screened
- Flag records of known ESBL carriers; place on Contact Precautions and re-screen on readmission

Laboratory Tests

- The best means of testing for ESBLs is an initial screening for reduced susceptibility to cefpodoxime, cefotaxime, ceftriaxone, ceftazidime, or aztreonam, and then performing the phenotypic confirmatory test by demonstrating a synergistic effect between an indicator cephalosporin and a β-lactamase inhibitor.
- The NCCLS/CLSI have recommended the combined disk method and the MIC method for ESBL confirmation

Multi-drug resistance in ESBL-producing organisms

Table 3
Antibiotic susceptibility patterns of ESBL-producing GNB and non-ESBL-producing GNB.

Antibiotic	ESBL-negative Number susceptible/ total tested isolates (%)	ESBL-positive Number susceptible/ total tested isolates (%)	p-value
Ampicillin	25/197 (12.7%)	1/90 (1.1%)	0.003
Cefazolin	96/195 (49.2%)	2/88 (2.3%)	<0.001
Amikacin	182/241 (75.5%)	64/103 (62.1%)	0.017
Gentamicin	150/241 (62.2%)	29/103 (28.2%)	<0.001
Cotrimoxazole	73/242 (30.2%)	17/102 (16.7%)	0.014
Amoxicillin/clavulanate	81/199 (40.7%)	3/93 (3.2%)	<0.001
Ampicillin/sulbactam	91/199 (45.7%)	8/91 (8.8%)	<0.001
Cefotaxime	122/242 (50.4%)	2/103 (1.9%)	<0.001
Ceftriaxone	122/242 (50.4%)	2/103 (1.9%)	<0.001
Ceftazidime	179/242 (74.0%)	5/104 (4.8%)	<0.001
Sulbactam/cefoperazone	180/239 (75.3%)	44/104 (42.3%)	<0.001
Norfloxacin	35/80 (43.8%)	2/30 (6.7%)	0.001
Ciprofloxacin	123/240 (51.3%)	19/104 (18.3%)	<0.001
Cefpirome	173/237 (73%)	26/104 (25.0%)	<0.001
Cefepime	186/240 (77.5%)	50/104 (48.1%)	0.006
Imipenem	185/240 (77.1%)	94/104 (90.4%)	0.019
Meropenem	181/237 (76.4%)	90/102 (88.2%)	<0.001
Tazobactam/piperacillin	182/240 (75.8%)	54/104 (51.9%)	<0.001

Chayakulkeeree M, et al. Southeast Asian J Trop Med Public Health 2005; 36: 1503-9.

Management of patients/residents with ESBLs

- In acute care: many hospitals use Contact Precautions for known patients
- In non-acute care: residents with AROs, including ESBLs, should be managed using Routine Practices and adding Contact Precautions (gown and gloves) for "direct care"
- Routine Practices:
  - Hand hygiene
  - Use of PPE dependent on risk assessment
  - Cleaning of all equipment used for multiple patients/residents between each patient/resident
- "Direct care: providing hands-on care, e.g., bathing, washing, turning resident, changing clothes, continence care, dressing changes, care of open wounds/lesions, toileting."

Control measures

- Control measures include
  - the judicious use of antibiotics,
  - antibiotic cycling,
  - the implementation of appropriate infection control measures and
  - formulate strategies to detect and prevent the emergence of ESBL producing strains for the effective treatment of infections which are caused by them.

Role of Cefepime + Tazobactam

- Cefepime, a 'fourth-generation' cephalosporin is bactericidal in action against Gram-negative and Gram-positive pathogens and is stable against both AmpC and OXA but lacks activity against ESBLs.
- Tazobactam inactivates ESBLs.
- **Thus Cefepime/tazobactam should effectively cover all the three mechanism of resistance** (Amp C & OXA by cefepime, ESBLs by tazobactam).

Ghafur A *et al.* Antimicrobial Resistance and Infection Control 2012, 1:29

Role of Cefepime + Tazobactam

- Excessive use of carbapenems has resulted in emergence of newer and dangerous bugs like NDM1and MBL producers. The need of the hour is to reduce use of Carbapenems.
- The combinations of β lactams and β lactamase inhibitors is a therapeutic option to treat moderately severe infections due to ESBL producers.
- Cefepime/tazobactam is a new promising β- Lactam/β-Lactam inhibitor combination (BL/BLI) for the treatment of moderate-to-severe infections

Hawser SP, Antimicrob Agents and Chemother 2009, 53, 3280-3284.

Zwitterions

- Cefepime exert bactericidal activity by interfering with bacterial cell wall synthesis and inhibiting cross-linking of the peptidoglycan. These cephalosporins are also thought to play a role in the activation of bacterial cell autolysins which may contribute to bacterial cell lysis.
- Cefepime, which is a zwitterion, has a net neutral charge that allows it to penetrate the outer membrane of Gram-negative bacteria faster than third generation cephalosporins. It is more stable against beta-lactamases because of the lower affinity of the enzymes for cefepime when compared with third generation cephalosporins.

Cefepime's superior activity is attributed to

1. More rapid penetration into bacteria: Allows for the higher concentration of the antibiotic in the periplasmic space of Gram negative bacteria; this ultimately increases the access to PBPs
2. Targeting of multiple penicillin-binding proteins
3. Lower affinity for several β-lactamases and is stable against many of the common plasmid- and chromosome-mediated beta-lactamases. As a result, it retains activity against Enterobacteriaceae that are resistant to third-generation cephalosporins, such as derepressed mutants of Enterobacter spp
4. Decreased propensity to induce beta-lactamases compared with other beta-lactam antibiotics.

Indications

Cefepime + Tazobactam is used parenterally for the treatment of moderate to severe infections caused by or suspected of being caused by susceptible beta lactamases producing bacteria when cefepime alone would be ineffective.

1. Moderate Nosocomial Infection
2. Hospital Acquired Pneumonia
3. Ventilator Associated Pneumonia

Clinical Studies

Clinical Studies

AmpC β-lactamases in nosocomial isolates of Klebsiella pneumoniae from India

- Gupta V *et al. e*valuated for both extended spectrum β-lactamases (ESBL) and AmpC β-lactamases in Klebsiella pneumoniae clinical isolates
- **100** consecutive, non-duplicate clinical isolates of K. pneumoniae collected over a period of one year (June 2008 - June 2009) were included in the study.
- An antibiotic susceptibility method was used with 10 antibiotics for Gram-negative infections which helped in screening for ESBL and AmpC β-lactamases and also in confirmation of ESBL production.

Gupta V *et al.* Indian J Med Res 136, August 2012, pp 237-241

AmpC β-lactamases in nosocomial isolates of Klebsiella pneumoniae: A Study

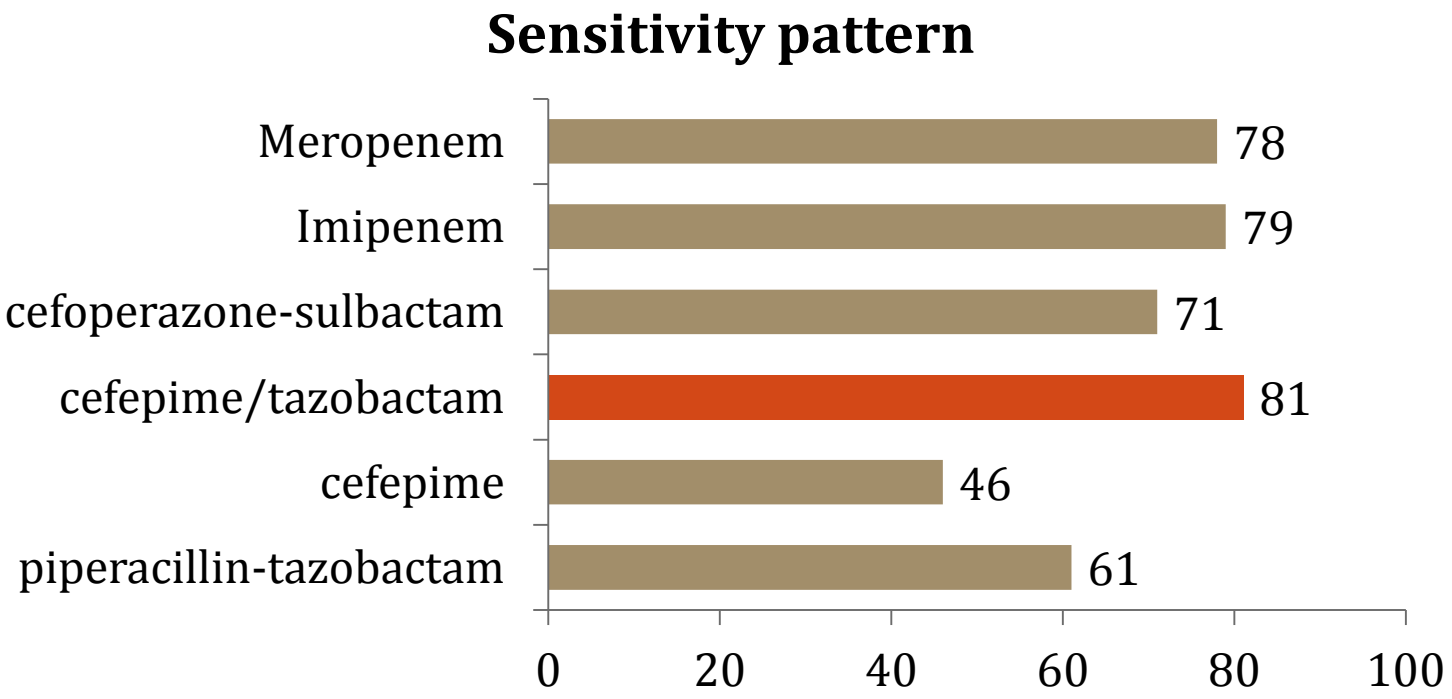
- The detection of AmpC β-lactamases was done based on screening and confirmatory tests. For screening, disc diffusion zones of cefoxitin <18 mm was taken as cefoxitin resistant.
- Tazobactam was the best β-lactamase inhibitor for detecting ESBL in presence of AmpC β-lactamase as this is a very poor inducer of AmpC gene.
- **Cefepime was the best cephalosporin in synergy with tazobactam for detecting ESBL production in isolates co-producing Amp C β-lactamases.**

Gupta V *et al.* Indian J Med Res 136, August 2012, pp 237-241

Sensitivity pattern of Gram negative bacteria to the inhibitor Cefepime/tazobactam combination

- Ghafur *et al* .conducted retrospective analysis of the sensitivity pattern of Gram negative bacterial isolates in Apollo Speciality Hospital; a 300 bedded, tertiary care Oncology, and Orthopaedic Centre in South India.
- Out of the 1003 Gram negative, non-repetitive isolates collected over a period of one year; 80.4% were sensitive to cefepime/tazobactam.
- Addition of tazobactam increased the susceptibility of cefepime from 46.2% to 80.4% in gram negative isolates in general; from 34.4 to 87.9% in E. coli, from 42.3 to 81.0% to Klebsiella, from 72.0 to 81.4% in Pseudomonas and 17.2-54.5% to Acinetobacter.

Sensitivity pattern of Gram negative bacteria to the inhibitor Cefepime/tazobactam combination



Ghafur *et al* . J Microbiol Infect Dis 2012; 2(1): 5-8

Sensitivity pattern of Gram negative bacteria to the inhibitor Cefepime/tazobactam combination

- **Cefepime/tazobactam** provided a better *in vitro* sensitivity profile than other BL-BLI combinations.

Microorganisms	PIP/TAZ No (%)	CEF No (%)	CEF/TAZ No (%)	CFP/SUL No (%)	IMP No (%)	MER No (%)	ERT No (%)
Total Gram Negative Bacilli (n=1003)	607 (60.5)	464 (46.2)	807 (80.4)	716 (71.3)	794 (79.1)	785 (78.2)	513 (87.6)
E. coli (n=316,)	183 (57.9)	109 (34.4)	278 (87.9)	254 (80.3)	297 (93.9)	297 (93.9)	286 (90.5)
K. pneumoniae (n=269)	158 (58.7)	114 (42.3)	218 (81.0)	195 (72.4)	249 (92.5)	247 (91.8)	227 (84.3)
P. aeruginosa (n=308)	242 (78.5)	222 (72.0)	251 (81.4)	227 (73.7)	218 (70.7)	213 (69.1)	
A. baumannii (n=110)	24 (21.8)	19 (17.2)	60 (54.5)	40 (36.3)	30 (27.2)	28 (25.4)	

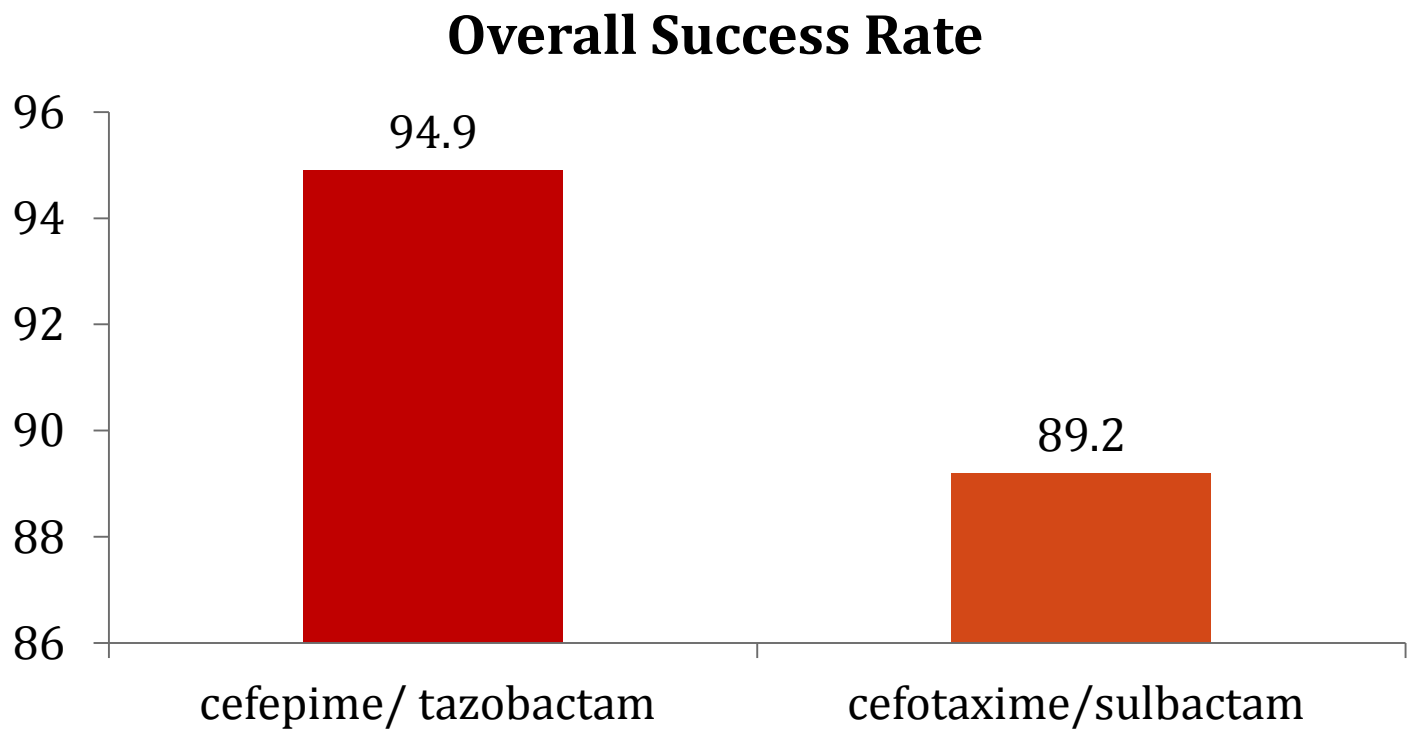
Ghafur *et al* . J Microbiol Infect Dis 2012; 2(1): 5-8

Cefepime and Tazobactam in Patients of Urinary Tract Infection

- Kamalpreet Kaur *et al.* evaluated efficacy and safety of third generation cephalosporin combined with beta-lactamase inhibitors compared with fourth generation cephalosporin.
- Open, randomised, parallel group comparative study includes 60 patients of urinary tract infection.
  - **Group A** :Cefotaxime and sulbactam (0.5-2 gm IV/IM BD) and
  - **Group B** :Cefepime and tazobactam (0.5-1 gm IV/IM BD) depending upon urine culture and sensitivity pattern of causative agent and condition of the patient.
- Bacteriological cure rate, clinical cure rate was assessed for efficacy and adverse drug reaction (ADR) recorded for evaluating safety

Journal of Clinical and Diagnostic Research. 2014 Nov, Vol-8(11): HC05-HC08

	cefotaxime/sulbactam	cefepime/tazobactam
Bacteriological cure rate	86.5%±6.5	**93.3%±6.7**
Clinical cure rate post five days of therapy	79.03%±2.82	**87% ± 2.11**
Clinical cure rate post ten days of therapy	98.57±0.03	**100%**



Journal of Clinical and Diagnostic Research. 2014 Nov, Vol-8(11): HC05-HC08

Clinical profile of patients treated with cefepime/tazobactam: An Indian Study

- Ghafur *et al.* conducted a retrospective observational study on the efficacy and safety of cefepime/tazobactam was conducted at a tertiary care hospital, South India.
- Patients who had a clear source of infection, having a single organism as the causative agent and being treated with cefepime/tazobactam alone were analyzed for efficacy and those cases who had a clear source of infection but either had multiple organism grown or cultures being negative or those patients who received a combination of antibiotics were analyzed for the safety analysis.

J Microbiol Infect Dis 2012; 2(3): 79-86

Clinical profile of patients treated with cefepime/tazobactam: An Indian Study

- 32 patients satisfied study criteria. All patients in the efficacy group had complete clinical cure, with microbiological cure in cases where a repeat culture was indicated.
- There were no significant side effects in any of the evaluable 32 patients assessed for safety.
- **Cefepime/tazobactam is a safe and effective agent to treat patients with nonlife threatening sepsis due to Gram negative bacteria.**

J Microbiol Infect Dis 2012; 2(3): 79-86

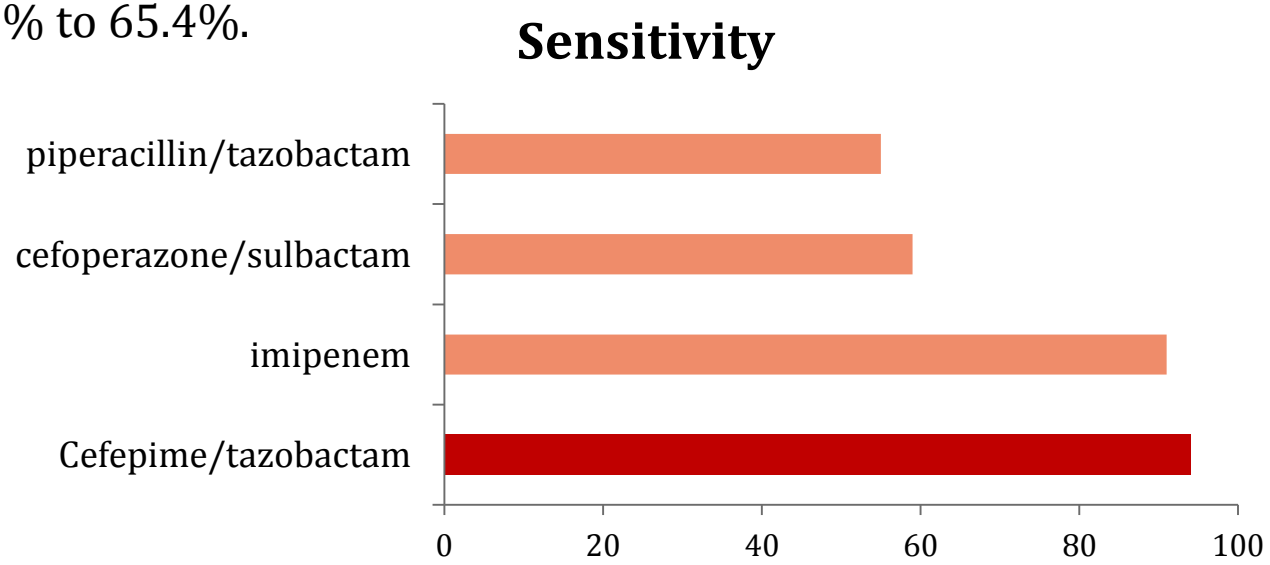
Cefepime/tazobactam-a promising BL-BLI combination against multidrug resistant Gram negative bacteria

- Mudshingkar *et al.* compared the sensitivity pattern of gram-negative bacteria to Cefepime/tazobactam as compared to cefepime, imipenem and other BL/BLI combination like Piperacillin/tazobactam, cefoperazone/ sulbactam. They also analysed whether Cefepime/ tazobactam combination can be used as an alternative to carbapenems.
- Out of 480 clinically significant non-repetitive gram negative isolates tested 122(25.4%) were E.coli, 113(23.5%) were K. pnuemonae , 119 ((24.8%) were other enterobacteriacae (Citrobacter spp., enterobacter spp., & Proteus spp.) followed by Pseudomonas spp. 75(15.6%) and Acinetobacter spp. 51(10.6%).

Mudshingkar, et al. *International J. of Healthcare and Biomedical Research* 2.3 (2014): 127-128.

Cefepime/tazobactam-a promising BL-BLI combination against multidrug resistant Gram negative bacteria

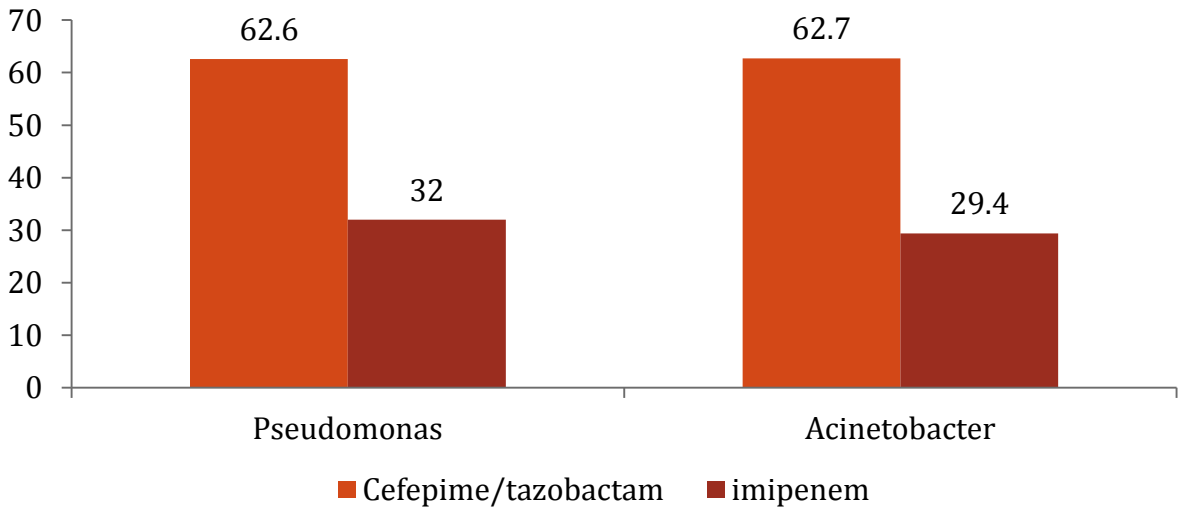
- Amongst enterobacteriaceae 219 (62 %) were ESBL producers. Gram negative bacteria showed maximum sensitivity to Cefepime/ tazobactam (65.4%), followed by imipenem (53.7%), piperacillin/tazobactam(33.5%) and cefoperazone/sulbactam (29.7%).
- Amongst the ESBLs excellent sensitivity was seen with Cefepime/tazobactam (94.1%). Addition of tazobactam increased the susceptibility of GNB to cefepime from 12.8% to 65.4%.



Mudshingkar, et al. *International J. of Healthcare and Biomedical Research* 2.3 (2014): 127-128.

Cefepime/tazobactam-a promising BL-BLI combination against multidrug resistant Gram negative bacteria

- Amongst the non-fermenters like Pseudomonas and Acinetobacter, Cefepime/tazobactam proved an excellent drug showing a higher sensitivity.



- Cefepime/tazobactum is an effective theurapeutic option to carbapenems for treatment of moderately severe infections due to ESBLs and nonfermenters.

Mudshingkar, et al. *International J. of Healthcare and Biomedical Research* 2.3 (2014): 127-128.

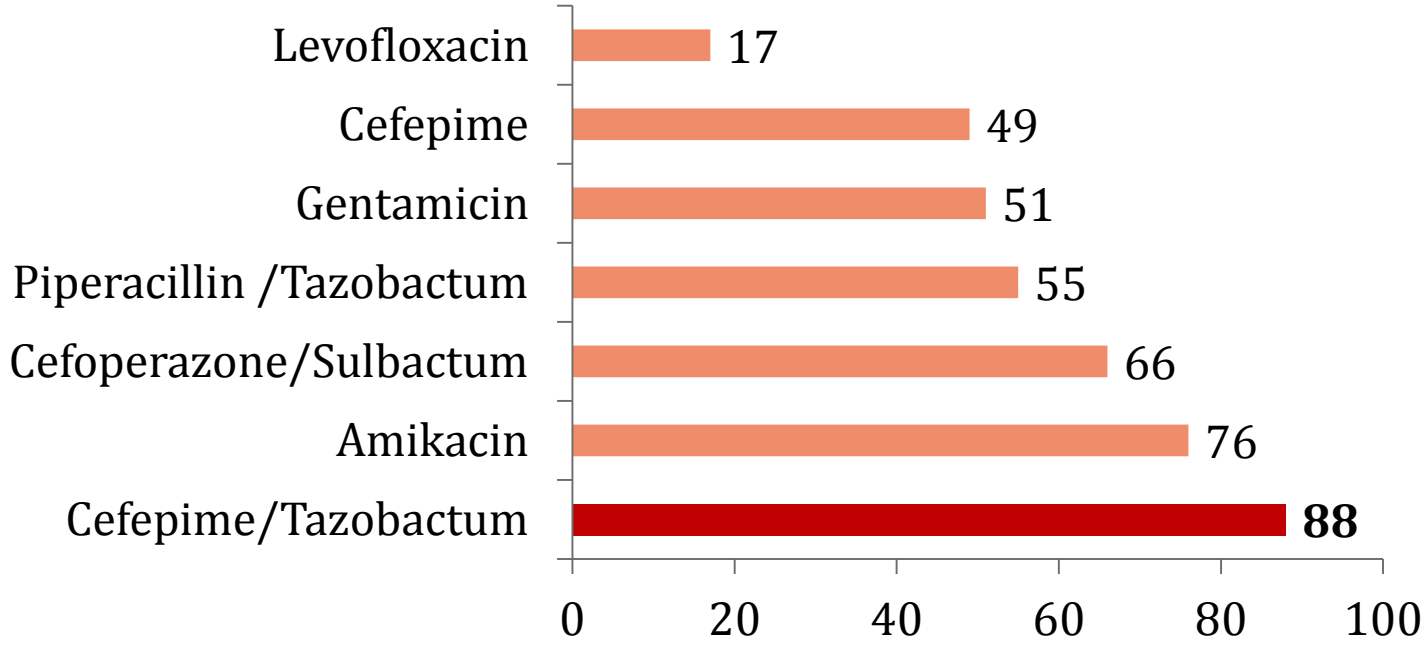
Carbapenem sparing options for the treatment of ESBL and AmpC producing Enterobacteriaceae

- An in- vitro prospective study by Amreliwala *et al.* looked into options that would be carbapenem sparing, for treatment of MDR gram negative Enterobacteriaceae in hemodynamically stable patients.
- Out of 400 MDR isolates studied, 210 (52.5%) were ESBL producers, 89 (22.25%) were Amp C producers, and 101 (25.25%) produced both types of enzymes.

Amreliwala et al. Int J Curr Microbiol App Sci; 2015, 4(2): 513-521

Carbapenem sparing options for the treatment of ESBL and AmpC producing Enterobacteriaceae

- Among the MDR Enterobactericeae, the highest susceptibility observed with CPT 88%,.



Amreliwala et al. Int J Curr Microbiol App Sci; 2015, 4(2): 513-521

Summary

- Serious bacterial infections with their high bioburden are often difficult to treat.
- Emergence of drug-resistant bacteria has worsened the situation, and management of these cases has become a therapeutic challenge.
- Prompt institution of appropriate antibiotic is vital in order to decrease complications and fatalities.
- Cefepime is a new fourth generation parenteral cephalosporin and Tazobactam, β-Lactam inhibitor holds promise for management of these severe infections.

Summary

- The combined power of Cefepime and Tazobactam is the effective in the infection management **against *E. coli* and *Klebsiella pneumoniae.***
- Cefepime and Tazobactam achieves high rates of clinical and bacteriological response among patients with Moderate Nosocomial Infection, Hospital Acquired Pneumonia, Ventilator Associated Pneumonia and Non Life Threatening Sepsis.
- **Cefepime and Tazobactam has an acceptable safety profile and well tolerated.**