CARBAPENEM-RESISTANT-ENTEROBACTERIACEAE - ICU

STRATEGIES IN TREATMENT

Objectives

- Define Carbapenem-Resistant Enterobacteriaceae (CRE) and mechanisms of resistance
- Assess clinical significance of CRE
- Review traditional agents used for CRE
- Discuss recent literature evaluating
- ceftazidime/avibactam (CTZ-AVI) in severe CRE infections and role in current practice
- Highlight potential future agents and concerns

Carbapenem-Resistant Enterobacteriaceae (CRE)

- Enterobacteriaceae include more than 70 different genera and many different mechanisms can lead to carbapenem resistance.
- These gram negative rod bacteria have become resistant to most available antibiotics
- Carbapenemase-producing CRE (CP-CRE) are currently believed to be primarily responsible for the increasing spread of CRE (e.g. Klebsiella pneumoniae carbapenemases(KPC) , oxa48,NDM.
- Implicated in a variety of infections, including bacteremia, ventilator associated pneumonia (VAP), urinary tract infection (UT I), and central venous catheter infection, intra-abdominal infection (IAI).
- Generally of concern in severely ill patients in hospital-acquired infections. Approximately 50% mortality rate with bloodstream infections (BSI): from CRE

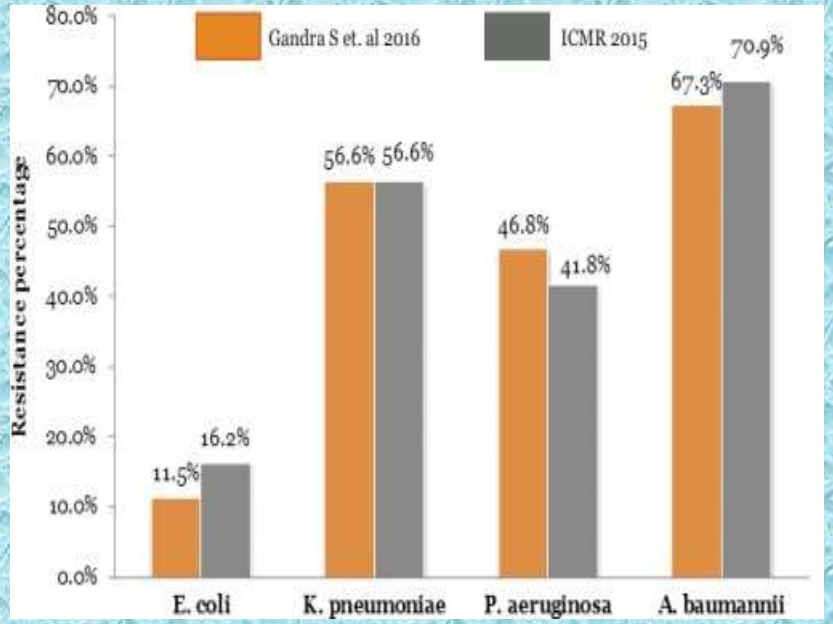
CDC's CRE definition

- **Previous definition (Prior to 1 / 201 5):**
  - **Nonsusceptible to imipenem, meropenem, or doripenem, AND resistant to all third generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftazidime).**
- **Current definition**
  - **Resistant to imipenem, meropenem, doripenem, or ertapenem OR documentation that the isolate possess a carbapenemase**

RESISTANCE SCENARIO IN INDIA

- Carbapenem class of antibiotics is one of the last-resort antibiotics to treat serious bacterial infections
- Resistance to carbapenems among various gram-negative bacteria - extremely high

Carbapenem (meropenem/ imipenem) resistance among various bacteria isolated from blood culture



1.AMR India Scoping Report. Available from http://dbtindia.gov.in/sites/default/files/ScopingreportonAntimicrobialresistanceinIndia.pdf
Last accessed on 08 Oct 2020

THE RISING THREAT OF CRE (CARBAPENEM RESISTANT ENTEROBACTERALES)

- **Excessive reliance on carbapenems for the treatment of piperacillin–tazobactam and cefoperazone–sulbactam- resistant Enterobacterales**
- **Newer threat in the form of colistin-resistant *Klebsiella* spp.**
- **12-59 % of E. coli being extended beta lactamase (ESBL) producers and up to 30% being carbapenemase producers (CP)**

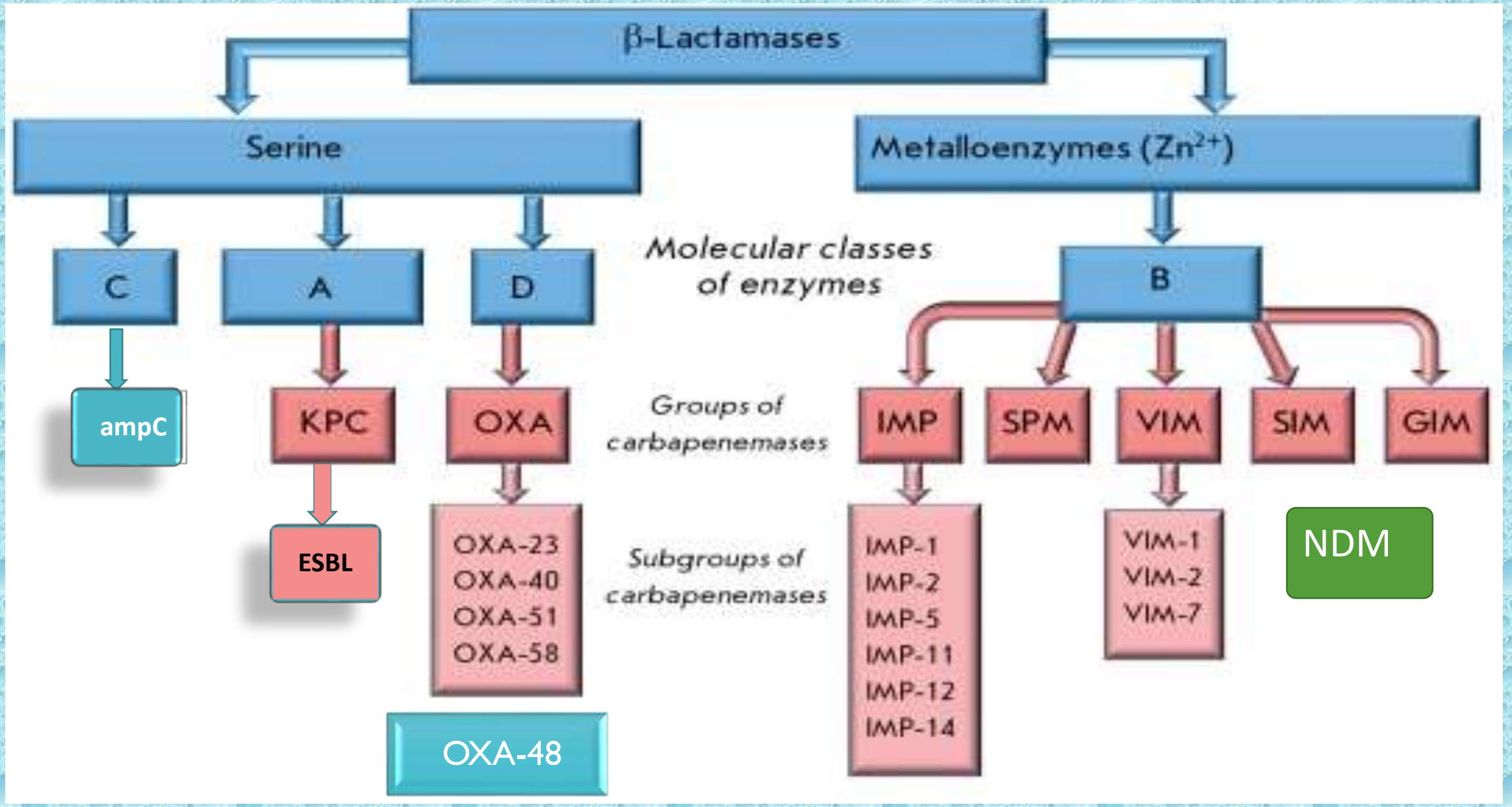
Klebsiella pneumoniae has emerged over the last few years as a highly resistant pathogen with up to 50% resistance to carbapenems and rapidly increasing resistance to polymyxins

- **CRE pneumonia tend to be associated with the highest mortality rate**

Veeraraghavan B, Pragasam AK, Bakthavatchalam YD, Anandan S, Swaminathan S, Sundaram B. Colistin-sparing approaches with newer antimicrobials to treat carbapenem-resistant

organisms: Current evidence and future prospects. Indian J Med Microbiol 2019;37:72-90

Treatment Guidelines for Antimicrobial Use in Common Syndromes. 2nd edition. Indian Council of Medical Research 2019.
Van Duin D. Carbapenem-resistant Enterobacterales: What we know and what we need to know. Virulence. 2017 May 19;8(4):379-382.


β-Lactamases
Serine
Metalloenzymes (Zn^{2+})
Molecular classes of enzymes
C
A
D
B
ampC
KPC
OXA
IMP
SPM
VIM
SIM
GIM
Groups of carbapenemases
ESBL
OXA-23
OXA-40
OXA-51
OXA-58
OXA-48
Subgroups of carbapenemases
IMP-1
IMP-2
IMP-5
IMP-11
IMP-12
IMP-14
VIM-1
VIM-2
VIM-7
NDM

The True Enemy:Carbapenemases

- Carbapenem-hydrolyzing ß-lactamases that confer resistance to a broad spectrum of beta-lactam substrates, including carbapenems.

- Ambler Classification:
  - Class A — KPC , SME, ESBL, , GES
  - Class B — NDM, VIM, IMP (Metallo-enzymes)
  - Class C — ampC
  - Class D — OXA48 and others

Risk Factors for CP-MDROs

Use of broad spectrum cephalosporins and/or carbapenems, especially long-duration

- ❑ **Trauma**
- ❑ **Malignancy**
- ❑ **Organ transplantation**
- ❑ **Mechanical ventilation**
- ❑ **Indwelling urinary or venous catheters**
- ❑ **Overall poor functional status or severe illness**

CURRENT ANTIMICROBIAL SUSCEPTIBILITY PROFILE, MOLECULAR RESISTANCE MECHANISMS (B-LACTAMASES)OBSERVED IN INDIA

Organism	Cephalosporin		Carbapenems		Colistin (among carbapenem resistance)
	% resistance	Mol. Resistance mechanisms	% resistance	Mol. Mechanisms	% resistance
E.coli	Upto 70%	ESBL(SHV,TEM,I OXA-1, CTX-M-15	Upto 10%	NDM, OXA-48 like	8%
K.Pneumoniae	Upto 60%	ESBL(ampC)SHV,TEM, CTX-M-15	Upto 40%	OXA-48 like, NDM	37%

Veeraraghavan B, Pragasam AK, Bakthavatchalam YD, Anandan S, Ramasubramanian V, Swaminathan S, Gopalakrishnan R, Soman R, Abraham O C, Ohri VC, Walia K. Newer β-Lactam/β-Lactamase inhibitor for multidrug-resistant gram-negative infections: Challenges, implications and surveillance strategy for India. Indian J Med Microbiol 2018;36:334-43

INCREASING INCIDENCE OF OXA-48

Isolates of *E.coli* (N=42) and *K. pneumoniae* (n=134) collected during 2013-2015 (South)[1]

Carbapenem resistant gene	E.Coli n(%)	K.Pneumoniae n(%)	Total n(%)
OXA-48 like	8(19%)	48 (36%)	56 (32%)
NDM	20 (48%)	36 (27%)	56 (32%)
NDM + OXA-48 like	2 (5%)	20 (15%)	13 (13%)

Prevalence of OXA-48 like and NDM-1 among clinical isolates of *K. pneumoniae* and *E. coli*[2]

Bacterial	MDR*	CR**	bla_{NDM-1} †	bla_{OXA-48} †	$bla_{NDM-1}bla_{OXA-48}$ †
E. coli	218	64(29.4)	17(26.6)	22(34.4)	10(15.6)
K. pneumoniae	173	75(43.4)	33(44)	22(29.3)	07(9.3)
Total	391	159(40.7)	50(31.4)	44(27.7)	17(10.7)

*Multidrug resistance

**Carbapenem resistance (proportion in % calculated with MDR as n)

†Proportion in % calculated with MDR as n

1. Sharma A, Bakthavatchalam YD, Gopi R, Anandan S, Verghese VP, et al. (2016) Mechanisms of Carbapenem Resistance in *K.pneumoniae* and *E. coli* from Bloodstream Infections in India. J Infect Dis Ther 4: 293
2. Filgona, J., Banerjee, T., & Anupurba, S. (2018). Endemicity of OXA-48 and NDM-1 Carbapenemase Producing Klebsiella pneumoniae and Escherichia coli from a Tertiary Hospital in Varanasi, India. *Journal of Advances in Microbiology*, *12*(3), 1-8.

DETECTING CARBAPENAMASES

When choosing a detection strategy cost, time to results, test performance (accuracy), and the information provided by the test are all factors that need to be considered

Growing evidence suggests early detection of CRE-colonized patients on admission to long-term care facilities may help to prevent institutional outbreaks and limit regional spread of this emerging public health threat

Lutgring JD, Limbago BM. The Problem of Carbapenemase-Producing-Carbapenem-Resistant-Enterobacteriaceae Detection. J Clin Microbiol. 2016 Mar;54(3):529-34.

CARBAPENEM RESISTANCE DETECTION

Genetic methods:

- Xpert Carba-R lessthan-2hrs(after isolation, costR2500)
- BioFire-micro array-lessthan-2hrs,(directly keep sample ,cost Rs 8ooo)
- Multiplex PCR-6-7hrs
- Genome sequencing -2days

Phenotypic methods

- Kirby bauer disc diffusion
- MIC-broth dilution
- Vitek/microscan/phoenix-automation
- E CIM and m CIM (CLSI)
- CARBA-NP test,
- Maldi -Tof

XPERT CARBA-R (GENEXPERT)

- **Xpert Carba-R is an on-demand PCR test that detects and differentiates the most prevalent carbapenemases gene families (KPC, NDM, VIM, IMP-1 and OXA-48) in 48 minutes**

- **Xpert Carba-R provides rapid and accurate detection of CPO; giving you actionable information to help prevent outbreaks and help determine the best patient management pathway**

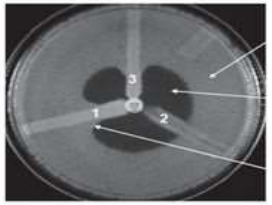

GeneXpert
Xpert® Carba-R
genexpert

BIOFIRE-MICRO ASSAY

PHENOTYPIC METHODS- DETECTION OF CARBAPENEMASES

Modified Hodge Test

A.



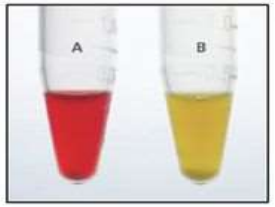
A lawn of carbapenem susceptible *E. coli* ATCC 25922

Zone of inhibition of *E. coli* ATCC 25922 by ertapenem

Indentation of *E. coli* ATCC 25922 growth (clover leaf appearance) around the streak line of the carbapenemase-producing *K. pneumoniae* ATCC BAA-1705.

Carba NP and variants

B.



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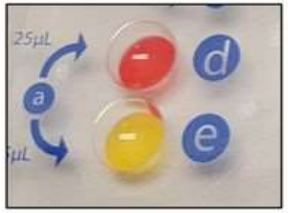

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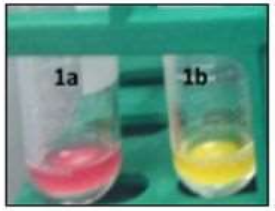
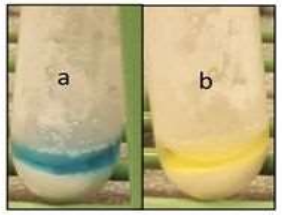


E.



Modified Carbapenem Inactivation Method (mCIM) & EDTA- mCIM (eCIM)

F.

G.

H.

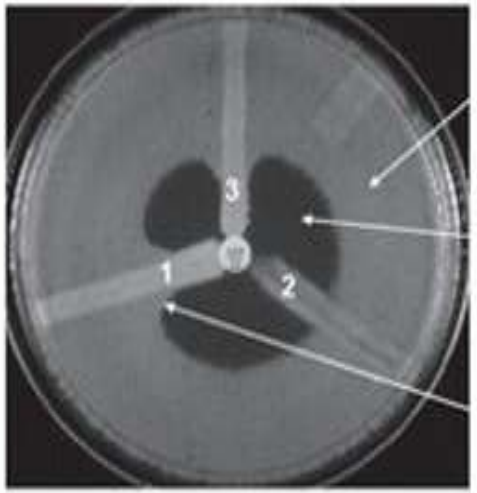
I.

Lateral Flow Immunoassay

J.

Modified Hodge Test

A.



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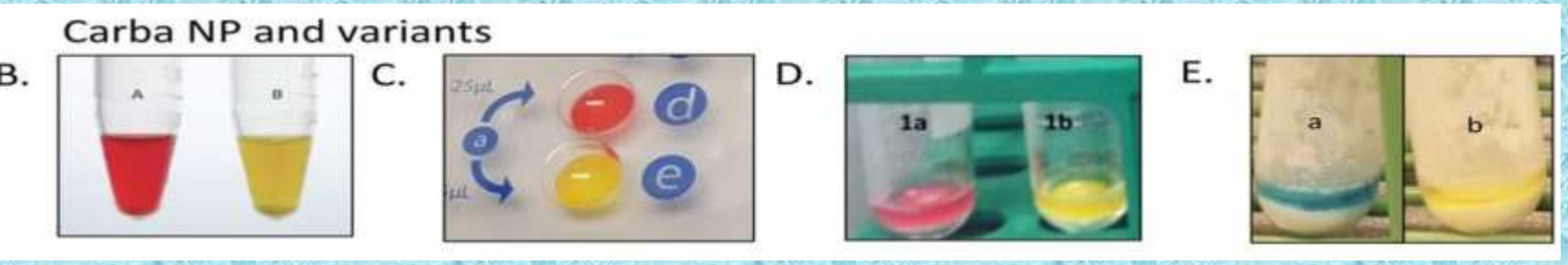
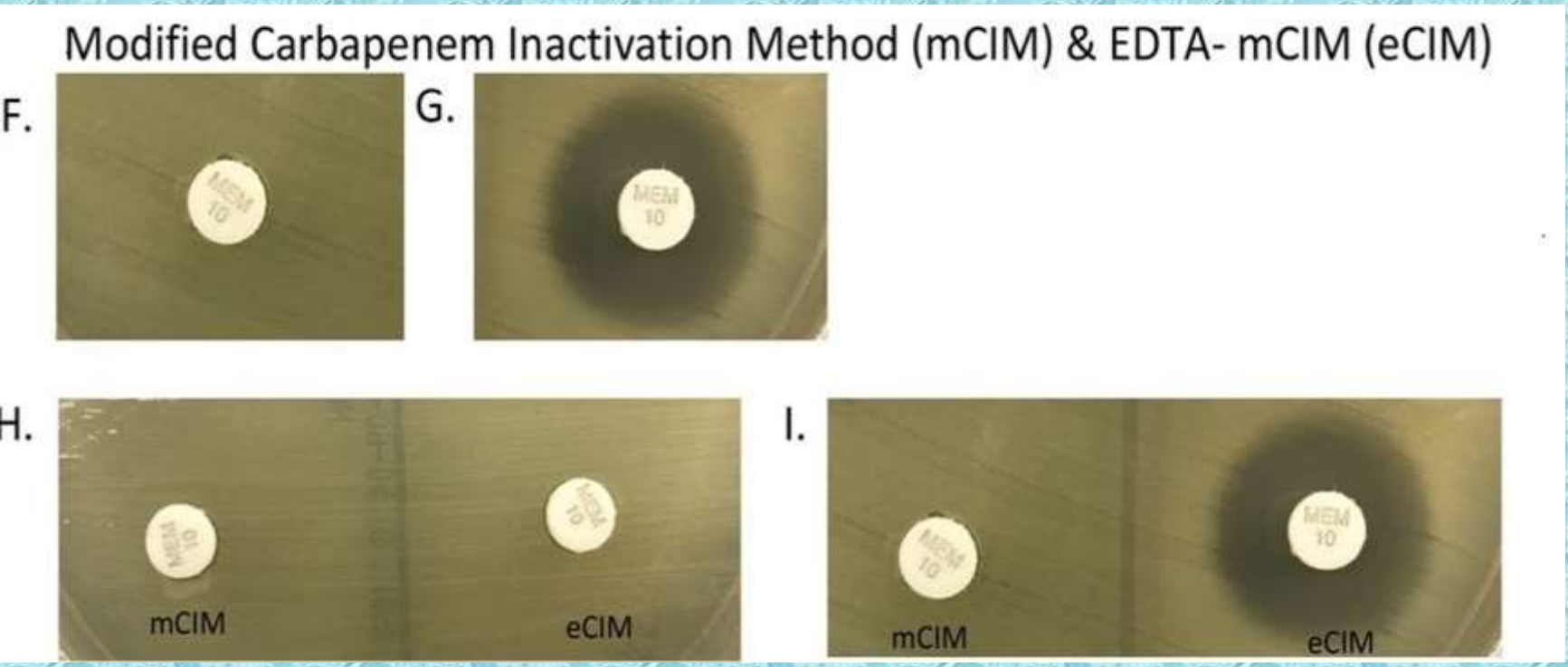
Indentation of *E. coli* ATCC 25922 growth (clover leaf appearance) around the streak line of the carbapenemase-producing *K. pneumoniae* ATCC BAA-1705.

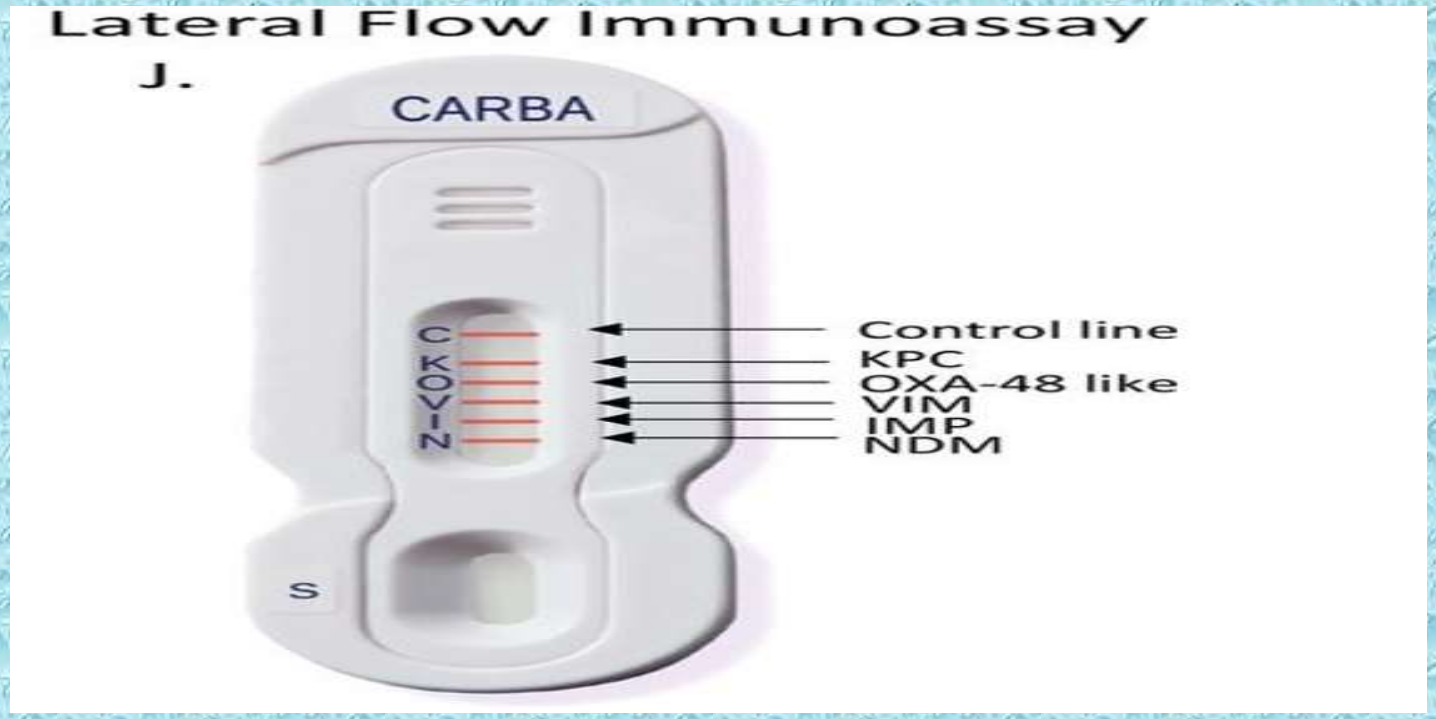
(A) MODIFIED HODGE TEST. 1, KLEBSIELLA PNEUMONIAE ATCC BAA-1705, POSITIVE RESULT; 2, K. PNEUMONIAE ATCC BAA-1706, NEGATIVE RESULT; 3, CLINICAL ISOLATE, POSITIVE RESULT

(B) CLSI Carba NP positive result. Tube A, no imipenem added, red; tube B, imipenem added, yellow.
(C) Rapidec Carba NP (bioMérieux, Inc.) positive result. Well d, no imipenem added, red; well e, imipenem added, yellow.
(D) Neo-Rapid Carba screen (Rosco Diagnostica) positive result. Tube 1a, no imipenem added, red; tube 1b, imipenem added, yellow (67). (
E) Rapid Carb Blue Screen (Rosco Diagnostica) positive result. Tube a, no imipenem added, blue; tube b, imipenem added, yellow.





- **(F) Modified carbapenem inactivation method (mCIM) positive result. (G) mCIM negative result.**
- **(H) mCIM and EDTA-mCIM (eCIM) results that are positive for a serine carbapenemase producer, as there is no inhibition of carbapenemase activity in the presence of EDTA.**
- **(I) mCIM and eCIM results that are positive for a metallo-beta-lactamase producer, as there is inhibition of carbapenemase activity in the presence of EDTA**



(J) NG-Test Carba 5 (NG Biotech) lateral flow immunoassay results for the different carbapenemases detected.

CURRENT OPTIONS FOR TREATING MDR GRAM NEGATIVE INFECTIONS

Aminoglycosides

- Rising resistance among CRE
- Toxicity
- Pneumonia?

Colistin

- Last resort, used despite toxicity
- Nephrotoxicity & neurotoxicity
- Optimizing dosage?
- Promotion of resistance- suboptimal dosages
- Narrow therapeutic window

Tigecycline

- No activity against P.aeruginosa
- Limited to cIAI

Fosfomycin

- Approved by FDA for the treatment of uncomplicated urinary tract infection (UTI)
- Hypokalemia and hypernatremia
- No RCTs are available on the clinical efficacy and safety as compared to other antimicrobials

Veeraraghavan B, Pragasam AK, Bakthavatchalam YD, Anandan S, Swaminathan S, Sundaram B. Colistin-sparing approaches with newer antimicrobials to treat carbapenem-resistant organisms: Current evidence and future prospects. Indian J Med Microbiol 2019;37:72-90

Satlin M. Languid Uptake of Ceftazidime-Avibactam for Carbapenem-Resistant Gram-Negative Infections and Continued Reliance on Polymyxins. [published online ahead of print, 2020 Feb 20]. Clin Infect Dis. 2020;ciaa065.

ROLE OF CEFTAZIDIME-AVIBACTAM IN TREATING CRE

CEFTAZIDIME-AVIBACTAM

- Ceftazidime-avibactam is combination of ceftazidime and a novel β-lactamase inhibitor Avibactam
- Avibactam is active against:
  - Ambler class A (ESBLs & KPC)
  - Class C (AmpC), and
  - Some class D β–lactamases (OXA- 48 like)
- Avibactam restores the activity of ceftazidime against most multidrug-resistant *Enterobacterales* and *Pseudomonas aeruginosa*
  In case of group B combination avibactam and aztreonem

ACTIVITIES OF AVIBACTAM, AND OTHER BETA-LACTAMS INHIBITORS

	ESBL (class A)	AmpC (class C)	KPC (class A)	OXA (class D)	IMP/VIM (class B)
Clavulanic acid	Yes	No	No	No	No
Tazobactam	Yes	No	No	No	No
Avibactam	Yes	Yes	Yes	Yes	No

- Zasowski EJ, Rybak JM, Rybak MJ.The β-Lactams Strike Back: Ceftazidime-Avibactam. *Pharmacotherapy*. 2015;35(8):755-770. doi:10.1002/phar.1622

CEFTAZIDIME – AVIBACTAM (ZAVICEFTA). SPECTRUM OF ACTIVITY

Complicated urinary-tract infections:[1]
Escherichia coli Klebsiella pneumoniae Proteus mirabilis Enterobacter cloacae Pseudomonas aeruginosa

Complicated intra-abdominal infections:[1]
Citrobacter freundii Enterobacter cloacae Escherichia coli Klebsiella oxytoca Klebsiella pneumoniae Pseudomonas aeruginosa

Hospital-acquired pneumonia, including VAP:[1]
Enterobacter cloacae Escherichia coli Klebsiella pneumoniae Proteus mirabilis Serratia marcescens Pseudomonas aeruginosa

Non-susceptible bacteria include[1]

- ***Staphylococcus aureus*** **(methicillin-susceptible and methicillin-resistant)**
- ***Anaerobes***
- ***Enterococcus spp.***
- ***Stenotrophomonas maltophilia***
- ***Acinetobacter spp.***

VAP, ventilator-associated pneumonia.
Ceftazidime-avibactam (Zavicefta). Local product document. Version LPDZAV102020

POSOLOGY AND METHOD OF ADMINISTRATION OF CEFTAZIDIME-AVIBACTAM

Type of infection	Dose	Frequency	Infusion time	Duration of treatment
Complicated IAI	2 g/0.5 g	8 hours	2 hours	5–14 days
Complicated UTI, including pyelonephritis	2 g/0.5 g	8 hours	2 hours	5–10 days
Hospital-acquired pneumonia, including VAP (with susceptible gram negative organism)	2 g/0.5 g	8 hours	2 hours	7–14 days

- IAI, invasive intra-abdominal infection; UTI, urinary tract infection;VAP, ventilator-associated pneumonia.

Ceftazidime-avibactam (Zavicefta). Local product document. Version LPDZAV102020

RECOMMENDED DOSING FOR RENALLY COMPROMISED

Estimated C_rCL (mL/min)	Dose regimen[2]	Frequency	Infusion time
31-50	1 g/0.25 g	Every 8 hours	2 hours
16-30	0.75 g/0.1875 g	Every 12 hours	2 hours
6-15	0.75 g/0.1875 g	Every 24 hours	2 hours
ESRD including on	0.75 g/0.1875 g	Every 48 hours	2 hours

No dosage adjustments in elderly patients and in patients with CrCL>51ml/min

No dosage adjustments required in patients with hepatic impairment

Ceftazidime-avibactam (Zavicefta). Local product document. Version LPDZAV102020

WARNINGS AND PRECAUTIONS

1. Hypersensitivity reactions
2. *Clostridium difficile*-associated diarrhoea
3. Nephrotoxicity
4. Renal impairment
5. Limitations of clinical data
6. Spectrum of activity of ceftazidime/avibactam
7. Non-susceptible organisms
8. Interference with laboratory tests
9. Controlled sodium diet
10. Direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of haemolytic anaemia

Ceftazidime-avibactam (Zavicefta). Local product document. Version LPDZAV102020

CEFTAZIDIME/AVIBACTAM FOR TREATMENT OF INFECTIONS DUE TO OXA-48 CARBAPENEMASE-PRODUCING

- 57 pts with OXA-48 positive Enterobacterales
- Isolates were **OXA-48- producing *K. pneumoniae*** in 54 cases, ***Escherichia coli*** in 2 cases and ***Enterobacter cloacae*** in 1 case
- **Source of infection:** intra-abdominal in 28%; pulmonary in 26% & urinary in 25%
- **Primary outcome- 14 day all cause mortality**
- Most (81%) received C/A as **monotherapy**
- **Clinical and microbiological cure** were achieved in 77% and 65% of patients respectively
- **All-cause mortality rates** assessed at **14 and 30 days- were 14% and 22%,** respectively
- Development of resistance to ceftazidime/avibactam was not detected in any patient during the whole follow-up period
- Only two patients developed adverse events related to treatment.

CEFTAZIDIME–AVIBACTAM COMPARED TO COLISTIN

- **Prospective multicenter cohort**
- **137 patients with CRE infection[1]**
  - **38 received ceftazidime–avibactam** first (monotherapy n=14 [37%])[1]
  - **99 received colistin** first (monotherapy n=6 [6%])[1]
- Baseline characteristics were similar
  - Median Charlson comorbidity score 3 (IQR: 1–5)[1]
  - Median Pitt bacteremia score 4 (IQR: 2–6)[1]
- Types of CRE infection included:
  - BSI (n=63)[1]
  - Respiratory tract infection (n=30)[1]
  - UTI (n=19)[1]
- Pathogens included: *K. pneumoniae* (n=133), *Enterobacter* spp. (n=4)[1]

BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacterales; IQR, interquartile range; UTI, urinary tract infection.

1. van Duin D, et al. Clin Infect Dis 2018;66:163–71.

CEFTAZIDIME–AVIBACTAM COMPARED TO COLISTIN

CEFTAZIDIME–AVIBACTAM COLISTIN

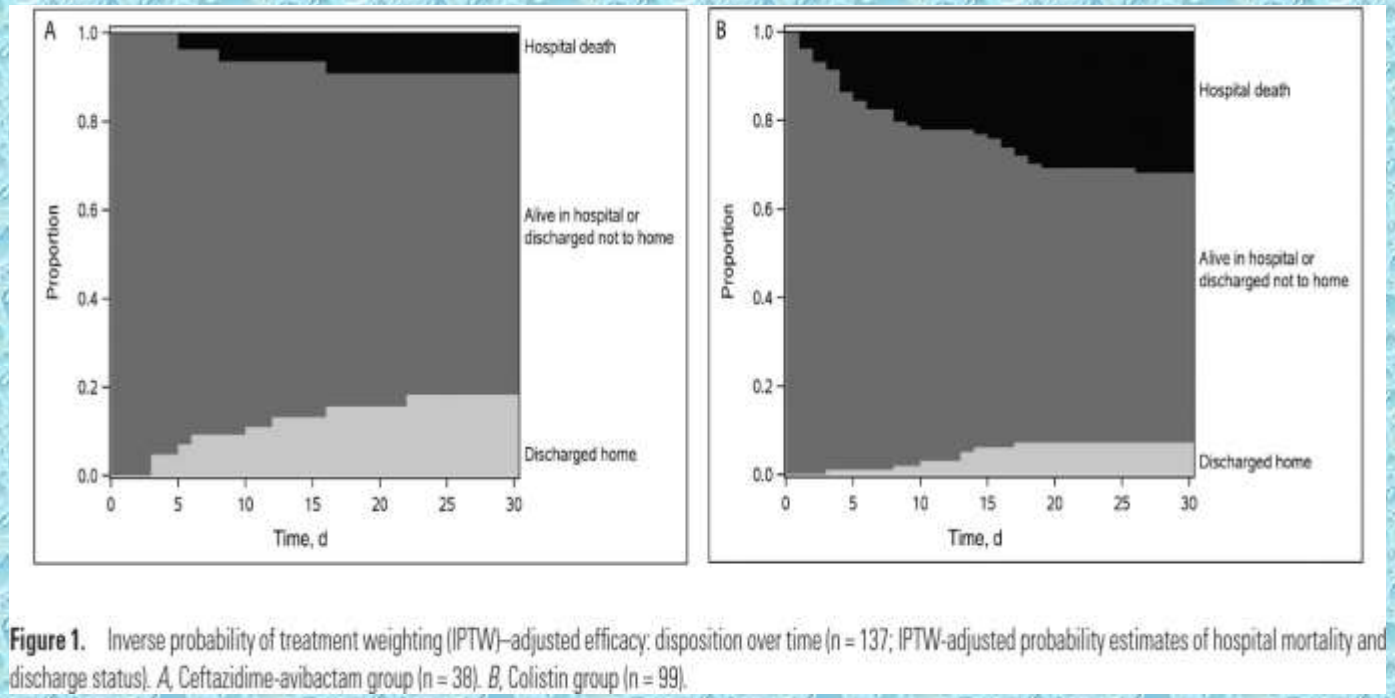


Figure 1. Inverse probability of treatment weighting (IPTW)–adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A*, Ceftazidime-avibactam group (n = 38). *B*, Colistin group (n = 99).

Death rate evaluated at Day 30 after therapy[1]

3/38 (8%) in CAZ–AVI patients versus 33/99 (33%) in colistin group difference 23% (CI95% 9–35%), P=0.001

At Day 30[1]

+ 64% adjusted probability of a better prognosis with CAZ–AVI than colistin (CI 95% 57–71%)

CAZ–AVI, ceftazidime–avibactam; CI, confidence interval; IPTW, inverse probability of treatment weighting.

1. van Duin D, et al. Clin Infect Dis 2018;66:163-71.

The Future Agents of CRE?

- Other medications in the pipeline t'
  - IV Fosfomycin coming to the U.S.A
  - Plazomicin
  - Eravacycline
  - Carbapenem/BLI combinations
    - Meropenem/vaborbactam
    - Imipenem-relebactam
  - Avibactam/aztreonam

- ***Fosfomycin*** **-is a bactericidal antibiotic interfere with cell wall synthesis**
- **Active carbapenem resistant enterobacteriaceae. All classes (A,B,C,D)of beta lactamases**
- **IV Fosfomycin an adjunctive agent in successful treatment of blood and disseminated infections due to extremely drug resistant klebsiella pneumonia**
- **Oral single 3g dose is approved by FDA to treat uncomplicated UTI**
- **High urinary concentration.**

- **PLAZOMYCIN-is an novel aminoglycoside antibiotic approved by FDA**
- **Used in complicated UTI**

Eravacycline-

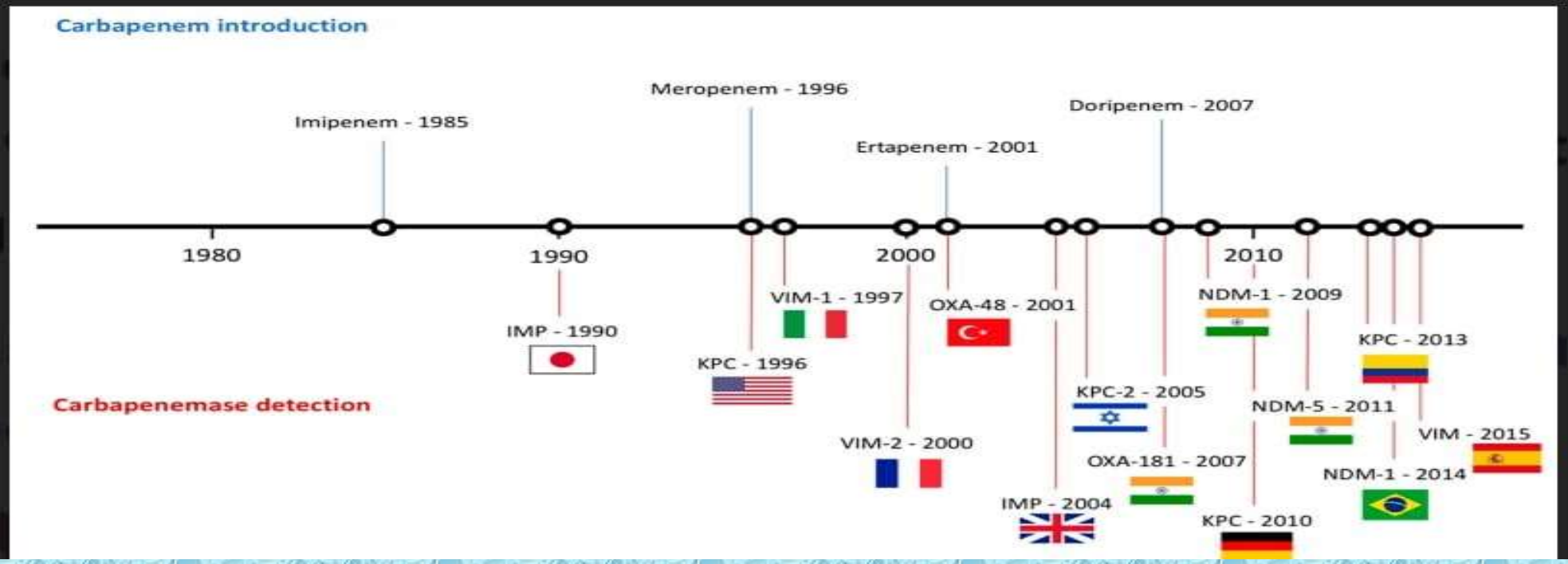
- **Novel tetracycline antibiotic structurally similar to tigecycline**
- **FDA recently approved for complicated intra abdominal infections**
- **Side effects-hypersensitivity,tooth discolaration,clostridium difficile. diarrhea**

- **Carbapenem/BLI combination**
- **Meropenem and vaborbactam** –vaborbactam boronic acid prevent destroying meropenem- beta lactamase inhibitor (amber class A and C enzymes)most notable the KPC enzyme
- Indicated in cUTI
- **Imipenem and relebactim-** similar to avibactam
- Indicated cUTI and cIAI
- **Avibactam Aztreonam-** avibactam inhibit the serein carbapenamases
- Aztreonam hydrolise mettalo-Beta lactamases
- Indicated in cIAI, cUTI, and hospital acquired bacterial pneumonia(HABP)

SPREAD AWARE NESS AND STOP RESISTANCE (SPREAD OF RESISTANCE)

Timeline representing the introduction of carbapenems and the appearance of carbapenemases worldwide.

biotics 2019, 8(3), 122;
s://doi.org/10.3390/antibiotics8030122



Carbapenem resistant in enterobactericeae –NMC&Hospital

	SAMPLE NAME	TOTAL SAMPLE	TOTAL NEG -	TOTAL POS +	SENCITIVE	RESTANCE			KLEB		E.COLI		OTHER	
						%		%		%		%		%
Aug-21	SPUTAM	33	8	25	19.00	76.00	6	24.00	4	16.00	1	4.00	1	4.00
	URINE	102	76	26	16.00	61.54	10	38.46	2	7.69	4	15.38	4	15.38
	BLOOD	55	49	6	4.00	66.67	2	33.33	0	0.00	0	0.00	2	33.33
	PUS	53	28	25	25.00	100.00	0	0.00	0	0.00	0	0.00	0	0.00
Sep-21	SPUTAM	38	16	22	16.00	72.73	6	27.27	2	9.09	1	4.55	3	13.64
	PUS	57	34	23	20.00	86.96	3	13.04	0	0.00	3	13.04	0	0.00
	BLOOD	60	52	8	8.00	100.00	0	0.00	0	0.00	0	0.00	0	0.00
	URINE	149	118	31	23.00	74.19	8	25.81	0	0.00	8	25.81	0	0.00
Oct-21	SPUTAM	55	23	32	24.00	75.00	8	25.00	4	12.50	2	6.25	2	6.25
	PUS	38	18	20	16.00	80.00	4	20.00	0	0.00	4	20.00	0	0.00
	BLOOD	74	60	14	14.00	100.00	0	0.00	0	0.00	0	0.00	0	0.00
	URINE	209	145	64	48.00	75.00	16	25.00	3	4.69	13	20.31	0	0.00