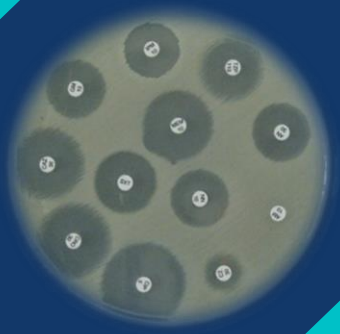
Guidance on Diagnosis & Management of Carbapenem Resistant Gram-negative Infections



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1. Background

Among gram negative pathogens, Enterobacterales, *Pseudomonas aeruginosa and Acinetobacter baumannii* that are resistant to carbapenems are a growing cause of nosocomial infections. Enterobacterales (ertapenem, meropenem or imipenem), *P. aeruginosa* (meropenem or imipenem) and *A. baumannii* (meropenem or imipenem) that shows resistance to at least one of the carbapenems are called carbapenem resistant Enterobacterales (CRE), carbapenem resistant *P. aerugin*osa (CRPA) and Carbapenem resistant *A. bauamannii* (CRAB) respectively (Fig 1). Owing to delay in administration of effective appropriate treatment, in view of the limited availability of treatment options, the infections with carbapenem resistant organisms are associated with higher mortality rates. According to the latest report from ICMR AMR surveillance network, resistance to imipenem was found in 28% of *E. coli,* 55% of *K. pneumoniae*, and 80% of *A. baumannii* isolates. Hypervirulent carbapenem-resistant *K. pneumoniae* strains present an additional threat in Indian hospitals with a potential for global dissemination.

In gram negative pathogens, carbapenem resistance occurs mainly due to plasmid-mediated carbapenemases or by chromosomal mechanisms (efflux pump and porin loss). Carbapenemase enzyme production is the most commonly seen mechanism of resistance among Enterobacterales. According to Ambler (molecular) classification scheme, carbapenemases are classified in three groups A, B and D. KPC and IMI carbapenemases are in Group A, metall beta-lactamases such as NDM, VIM, and IMP are in Group B, and OXA type carbapenemases are in Group D (Figure 1). Varied carbapenemase genes impart different phenotypic resistance patterns to various antibiotics, as well as vulnerability to beta lactamase inhibitors. In gram negative non-fermenters, carbapenem resistance occurs mainly due to plasmid-mediated carbapenemases such as OXA-23/24 like or class B metallo-beta lactamases (NDM), chromosomal-mediated mechanisms including outer membrane imperability and/or porin loss, or reduced affinity for penicillin-binding proteins (Figure 2). Enterobacterales, , *P. aeruginosa* and *A. baumannii* showing resistance to at least one of the carbapenems (meropenem or imipenem) are called CRE, CRPA and CRAB respectively (Fig 3).

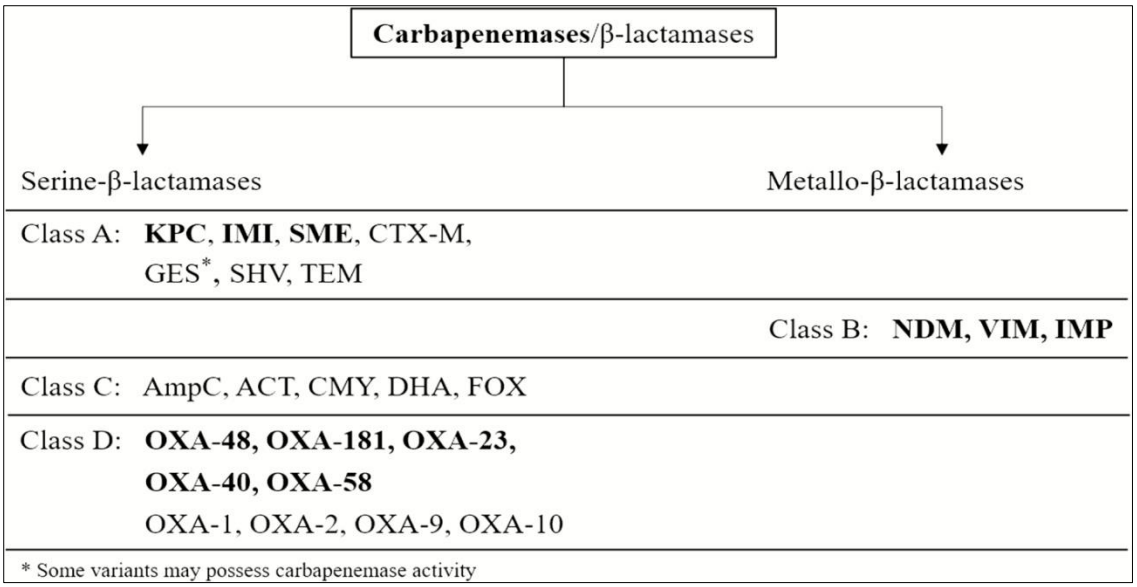

Figure 1. Classification of carbapenemases/β-lactamases (source https://doi.org/10.1093/cid/ciz824)

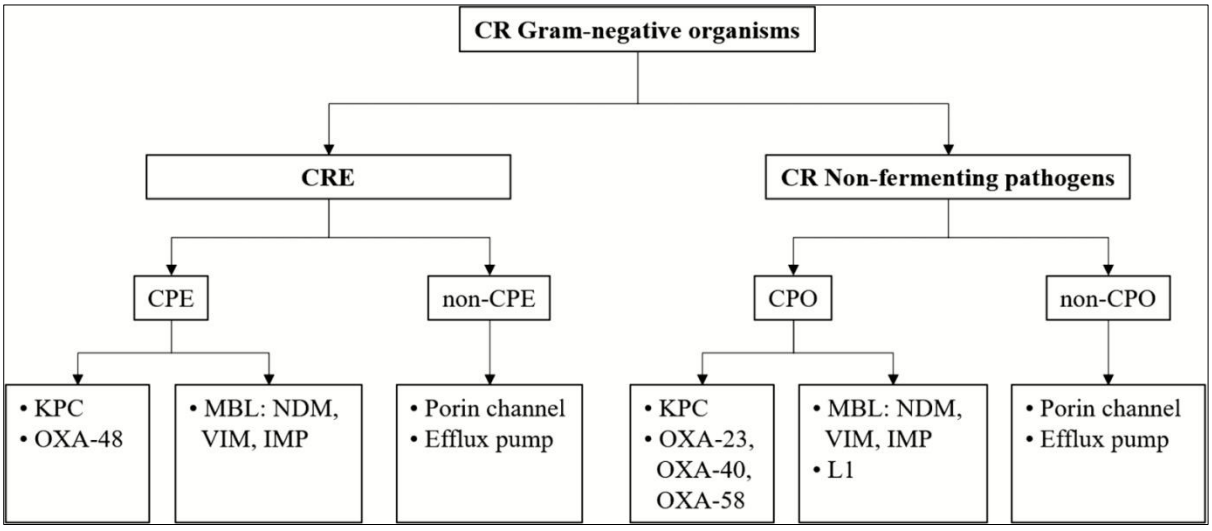

Figure 2: An algorithm to understand the mechanism of carbapenem resistance in Enterobacterales andnon-fermenting gram negative bacilli. CPE - carbapenemase-producing Enterobacterales; CPO -carbapenemase-producing organism; CR - carbapenem resistant; CRE - carbapenem-resistant Enterobacteriales; IMP - imipenemase; KPC -Klebsiella pneumoniae carbapenemase; L1 - class B metallo-β-lactamase; MBL -metallo beta-lactamase; NDM - New Delhi metallo beta-lactamase; OXA -oxacillinase; VIM - Verona integron-encoded metallo beta-lactamase.
(source https://doi.org/10.1093/cid/ciz824)

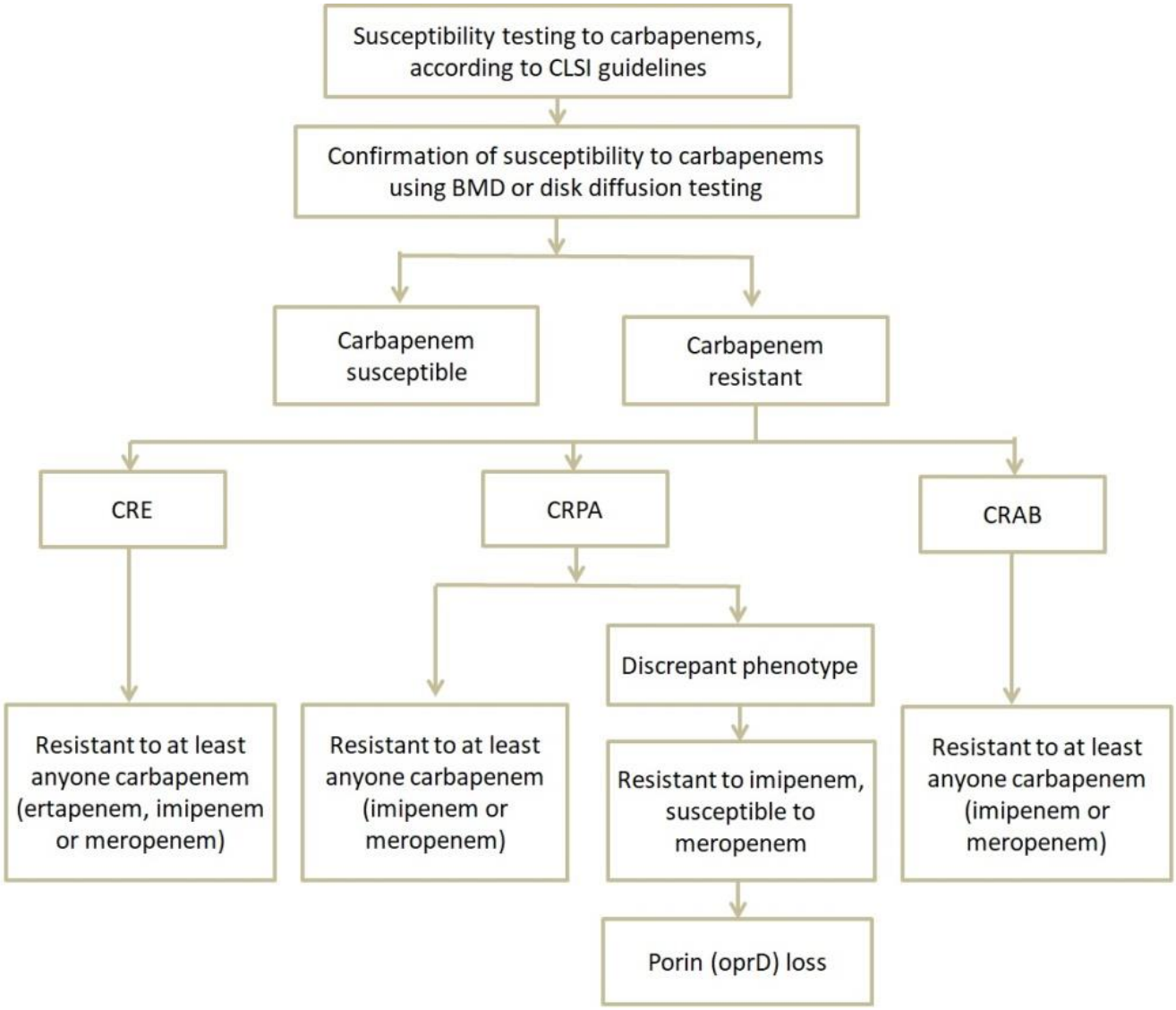

Fig 3: An overview of carbapenem resistance detection and characterisation in gram-negative organisms.

2. Diagnosis of carbapenem resistance

Early detection of carbapenem resistance is important for early diagnosis and appropriate management. Antimicrobial susceptibility testing performed by the clinical laboratory on isolates obtained in culture can reveal carbapenem resistance in individuals infected with carbapenem resistant gram negative pathogens. However, the conventional antimicrobial susceptibility testing takes a long turn-around time of 2 - 5 days from specimen collection to the time the results are avialable. There are several rapid molecular methods available for detection of carbapenemases that have a

turnaround time of less than 2 hours, which helps to minimise the length of hospitalisation and cost.

The identification of carbapenemase types is crucial for early targeted therapy and improving clinical outcomes. Isolates that are non-susceptible to carbapenems may also have unknown or novel mechanisms of resistance, and therefore, phenotypic susceptibility to carbapenem is considered the gold standard. To confirm the production of carbapenemases and/or the presence of additional resistance mechanism, a variety of biochemical assays and/or gene-based diagnostics are available.

Carbapenemase-producing organisms can be detected phenotypically using biochemical assays such as the Carba NP®, Blue Carba®, and Carba® tests , however these methods fails to detect other resistance mechanisms such as porin loss and efflux pump. The hydrolysis of the substrate imipenem or meropenem by these phenotypic methods determines the presence of carbapenemases in bacterial culture or isolates. Notably, some phenotypic test (carba NP) can detect the colorimetric positive signal in less than an hour and can be used immediately from clinical samples. The carbapenemase inactivation method, is an another inexpensive method for routine detection of carbapenemases. All of the methods discussed above, however, are unable to identify the type of carbapenemase enzyme and require bacterial isolates, in addition to having some specificity or sensitivity limitations.

For the rapid diagnosis of carbapenem resistance, molecular techniques that use the principle of conventional polymerase chain reaction (PCR) or real-time qualitative PCR for the identification of carbapenemase expressing genes are commonly used. Most of the commercially available rapid molecular tests can detect the most common five carbapenemases (KPC, IMP, VIM, NDM and OXA-48 like variants) with the short turn-around time of less than 24hrs and with a sensitivity of 80-100%. Microarrays are more sensitive than PCR at identifying a large number of target genes, and they frequently include targets for bacterial identification and resistance indicators. Whole genome sequencing (WGS) improves understanding of both chromosomal mutations linked to resistance and acquired resistant determinants. In recent years, WGS had a substantial impact on surveillance and improvement in patient care. Rapid gene-based assays have the advantage of avoiding the need for culture and allowing for direct specimen

sampling (nasal swab, rectal swab, sputum, wound specimen, blood, urine), which cuts down on the time it takes to start targeted therapy and lowers the risk of treatment failure associated with empiric antimicrobial therapy.

Indeed, with the advancement of rapid molecular diagnostic tests, it is important to consider that most of these commercial panels target only the five most carbapenemase-encoding genes (KPC, IMP, VIM, NDM, and OXA-48 like). As a result, a negative test does not always suggest the organism is susceptible to carbapenem; it could be due to the existence of porin loss and/or an efflux pump. The presence of a gene does not always mean that an organism is carbapenem resistant due to the amount of expression of the resistance gene. With the calorimetric carbapenemase detection method, it is impossible to distinguish between different types of carbapenemases.

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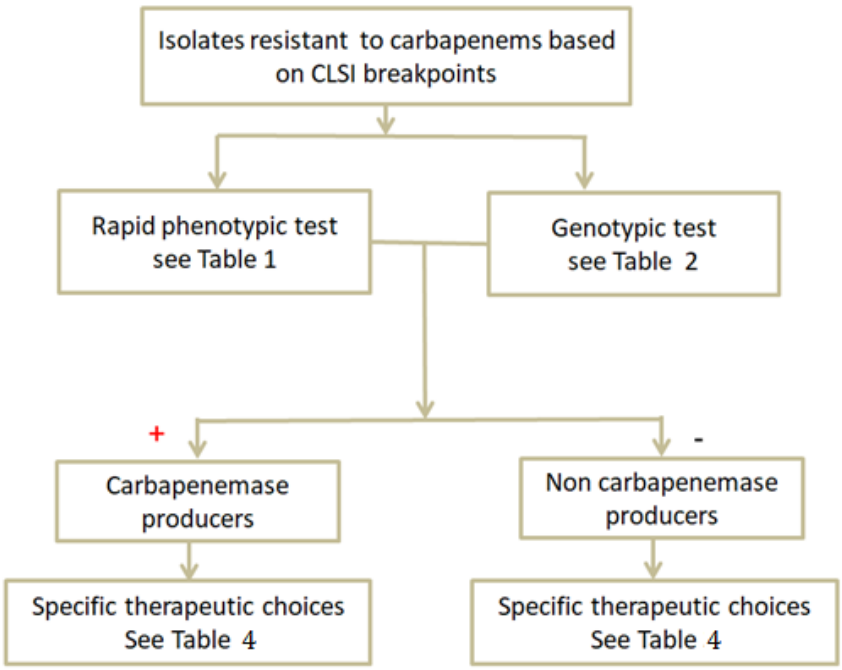

Fig 4: Infections caused by carbapenem-resistant gram-negative bacteria are being treated with precision medicine.

For routine diagnosis, most clinical laboratories rely on the phenotypic tests for carbapenemase production (mCIM,, mCIM plus eCIM or CarbaNP®) or molecular-based identification of carbapenemase-encoding genes such KPC, NDM, VIM, OXA-48-type, and IMP (3). On the other hand, the available phenotypic tests have a number of significant

flaws, which are outlined in Table 1. Carbapenem resistance can be detected more rapidly using a variety of commercial molecular diagnostic assay (Table 2). However, it is impossible to identify all carbapenemases and/or variations, or all resistance mechanisms that results in carbapenem resistance. As a result, antibiotic susceptibility testing should be considered for appropriate therapy.

Table 1: Phenotypic test that detect carbapenemases in Enterobacterales and *P. aeruginosa* isolates.

	Organisms	Strengths	Limitations	Regulatory Status
mCIM and/or eCIM (see Fig 5a)	Enterobacterales *P. aeruginosa*	• Detects KPC, IMP, VIM, NDM andOXA-48 like carbapenemases with high sensitivity and specificity of >90% • High sensitivity (>90%) and specificity (>90%) with class A (KPC), class B (IMP, VIM, NDM), and class D (OXA-48 like) carbapenemases • eCIM is capable of detecting class B enzymes.	• Long turn-around time (18–24 h) • When class B and class A/D carbapenemases are co-expressed, eCIM is unable to detect class B enzymes.	CLSI recommended
Carba NP® (see Fig 5b)	Enterobacterales *P. aeruginosa*	• Detects class A and class B carbapenemases with the sensitivity and specificity of >90% • Rapid turn-around time (5 min-2 h)	• Class D carbapenemases and mucoid isolates yielded false negatives Doesn't differentiate the class of carbapenemase	CLSI recommended
RAPIDEC carba NP® (see Fig 5b)	Enterobacterales *P. aeruginosa*	As mentioned in carba NP®	As mentioned in carba NP®	FDA
NG-Test CARBA 5® (Multiplex lateral flow immunoassay) (see Fig 5c)	Enterobacterales	• High sensitivity (100%) and specificity (100%) for carbapenemases of classes A, B, and DRapid turn-around time (<15 min) • Differentiate the classes of carbapenemase	• Fails to detect carbapenemases such as GES, SME, IMI, and NMC, which are rare carbapenemases.	FDA
Accelerate 8Pheno® system (In development)	Enterobacterales *P. aeruginosa* *A. baumannii*	-	-	-

*mCIM – Modified carbapenem inactivation; Ecim – EDTA modified carbapenem inactivation; TAT – turnaround time; CLSI – Clinical and Laboratory Standards Institute; FDA – Food and Drug Administration

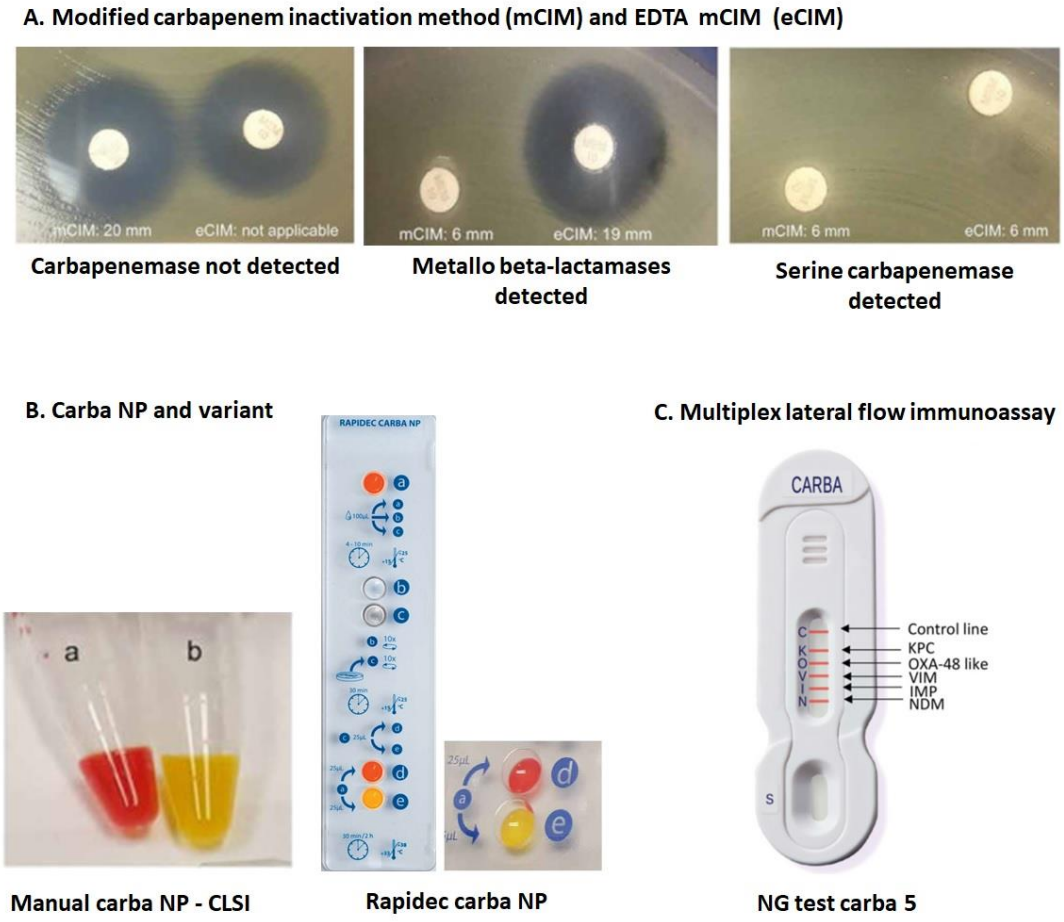

Fig 5: Various phenotypic methods used for detection of carbapenemase. A) Modified carbapenem inactivation method (mCIM) and EDTA-mCIM negative results (left); Positive mCIM and eCIM results indicate a metallo-beta-lactamase producer, as carbapenemase activity is inhibited in the presence of EDTA (middle); There is no inhibition of carbapenemase activity in the presence of EDTA in mCIM and EDTA-mCIM (eCIM) results that are positive for a serine carbapenemase (class A or D) producer. (right). B) CLSI Carba NP positive result; tube A (red), negative result; tube B (yellow), positive result. C) The findings of the lateral flow immunoassay NG-Test Carba 5 (NG Biotech) for the most common carbapenemase.

Table 2: Characteristics of commercial carbapenemase detection assays that have been approved for detection of carbapenemases in CRE isolates

Assay	Method	Time of results	Source	Detection of carbapenemases gene	Sensitivity (%)	Specificity (%)	Approval
Xpert Carba-R®	Real time multiplex PCR	2 hrs	Isolate	KPC, IMP, VIM, NDM, OXA-48 like	100	100	CE-IVD FDA IVD
BioFire film Array®	Real-time PCR	1-2 h	Positive blood culture	KPC	NA	NA	CE-IVD FDA IVD
Nanosphere Verigene BC-GN®	Microarray	2 h	Positive blood culture	KPC, NDM, VIM, IMP, OXA	NA	NA	CE-IVD FDA IVD
EntericBio CPE® assay	Real time multiplex PCR	2 h	Isolate, swabs	KPC, IMP, VIM, NDM, OXA-48 like, GES-5, IMI, OXA-23	100	100	RUO
Check- Direct CPE® assay	Real time multiplex PCR	3.5 h	Rectal swab/ Isolate	KPC, OXA-48 including OXA-181, VIM and NDM	100	94%	RUO
AID® line probe assay	Multiplex PCR and reverse hybridization with carbapenemases probes	5 h	Various clinical specimens	KPC, IMP, VIM, NDM, OXA-48, SIM, SPM, AIM, BIC, DIM, GIM, IMI, NMC-A	97.7	NA	RUO
Hyplex MBL ID® system	Multiplex PCR and reverse hybridization with carbapenemases probes	5 h	Various clinical specimens	VIM and IMP	98	98.6	RUO
BB MAX™ CRE Assay®	Real-time PCR	2 h	Rectal swab/ Isolate	KPC, NDM, oxa-48	93.1	97.3	RUO
Check-MDR 103 XL	PCR followed by microarray	6.5 h	Isolate	KPC, OXA-48, VIM, NDM, GES, GIM, SPM, OXA-23 like, Oxa-24 like	100	100	RUO
Eazyplex® SuperBug CRE®	Loop mediated	15 min	Positive blood	KPC, NDM, VIM	100	100	RUO

NA – not available; RUO – research use only; FDA - Food and Drug Administration; CE-IVD - Conformite Europeene *in-vitro* diagnostic

2.1 Susceptibility testing of aztreonam with ceftazidime-Avibactam against carbapenem resistant Enterobacterales

Azteronam, a monobactam, is extremely stable against all metallo beta-lactamases, including New Delhi metallo beta-lactamases (NDM), Imipenemases (IMP), and Verona integron-mediated metallo-lactamase (VIM). Therefore, aztreonam is a prudent choice for combating MBL-producing organisms, despite the fact that it can be hydrolyzed by extended-spectrum -lactamases (ESBLs) or Ambler class C -lactamases, both of which are co-produced in MBL-producing organisms. Avibactam is a novel non-lactam -lactamase inhibitor (BLI) that can neutralise Ambler class A (ESBLs and Klebsiella pneumoniae carbapenemase, KPC) and C enzymes, as well as certain class D enzymes (eg. OXA-48-like). Combining aztreonam with ceftazidime/avibactam provides a viable treatment option for "MBL-infections." Ceftazidime has no effect in this triple combination because it is easily hydrolyzed by MBL. Aztreonam MICs would suffice in the presence of avibactam. It should be noted, that the clinical utility of combining aztreonam with ceftazidime-avibactam is limited to MBL-expressing Enterobacterales. In MBL-expressing *P. aeruginosa* and *Acinetobacter* spp., where aztreonam's potency is compromised by efflux resistance mechanisms, avibactam is ineffective in reversing aztreonam activity. Aztreonam plus ceftazidime/avibactam combination therapy does not have to be empirical; it can be used as a salvage therapy if a susceptibility testing result is available.

There is currently no practical and widely accepted susceptibility testing method available to assess the efficacy of the azteronam-ceftazidime-avibactam (ATM-CZA) combination in routine diagnosis. For testing the susceptibility of this combination, various in-vitro susceptibility methods have been proposed, including broth disc elution, disc stacking, gradient strip stacking, and strip crossing. Despite the fact that the Clinical Laboratories Standards Institute (CLSI) has not yet recommended a method for testing this combination, there are reliable methods for determining MBL-isolate susceptibility to this combination. Susceptibility to this triple combination can be tested in laboratories that are familiar with routinely performing broth microdilution (BMD) by determining aztreonam MIC in the presence of a fixed 4 mg/L of avibactam. The MICs should be compared to the CLSI aztreonam criteria (Table 4). When the MICs of standalone aztreonam and ceftazidime/avibactam are >128 mg/L and the combination MIC drops to 32 mg/L, it suggests synergy but does not imply'susceptibility' because

aztreonam activity remains above the treatable threshold of 4 mg/L for Enterobacterales.

Table 3: The Clinical Laboratories Standards Institute (CLSI) recommended aztreonam interpretative breakpoints for Enterobacterales and *P. aeruginosa*

	Azteronam interpretative breakpoints					
Organism	**Disc diffusion (mm)**			**MIC breakpoints (mg/L)**		
Enterobacterales	≥ 21	18-20	≤ 17	≤ 4	8	≥ 16

*Breakpoints are based on dosage regimen of 1g q8h

2.1.1 Susceptibility testing using gradient strips

The susceptibility of an MBL-Enterobacterales can be determined in two ways in a routine gradient strip based MIC determination: gradient strip stacking and gradient strip crossing methods. The gradient strip stacking method (Fig 6a) involves placing an aztreonam gradient strip on the surface of culture-inoculated agar and allowing it to diffuse for 10 minutes. Following that, the aztreonam strip is removed and a ceftazidime/avibactam strip is placed in the same location. Finally, an aztreonam strip should be placed over a ceftazidime/avibactam strip to aid in reading the MIC values of aztreonam after 16 to 18 hours of incubation. After placing an aztreonam strip over the agar surface, a ceftazidime/avibactam strip is placed across (perpendicularly) to the aztreonam strip at an intermediate aztreonam susceptibility breakpoint (8 mg/L for Enterobacterales, Table 4). Another option is to place the azteronam E-test strip closer to the ceftazidime-avibactam E-test strip. The Aztreonam MIC is read and interpreted after incubation. The MIC of aztreonam is interpreted using CLSI criteria in all three approaches (Table 4).

2.1.2 Modified E-test / disc diffusion method for ceftazidime-avibactam and azteronam susceptibility testing

In this method, a ceftazidime-avibactam E-test containing the fixed concentration of avibactam 4 µg/ml is positioned on the surface of the inoculated culture agar. . Subsequently, an azteronam disc (30 µg) is placed at 15 mm from the centre of the ceftazidime-avibactam E-test strip (**Fig 7**). The azteronam disc is placed at the susceptibility breakpoint of ceftazidime-avibactam, 8 µg/ml for Enterobacterales. After incubation, the zone of inhibition on both sides of the azteronam disc is measured for

azteronam alone as well as for ceftazidime-avibactam with azteronam. The zone diameter is measured and compared to the aztreonam interpretive criteria (a zone diameter of 21 mm is considered susceptible). In laboratories where the azteronam E-test is unavailable, an alternative approach involving modified E-test / disc diffusion method can be used. Indeed, this method requires validation using the reference broth microdilution method to assess its reliability for routine diagnosis.

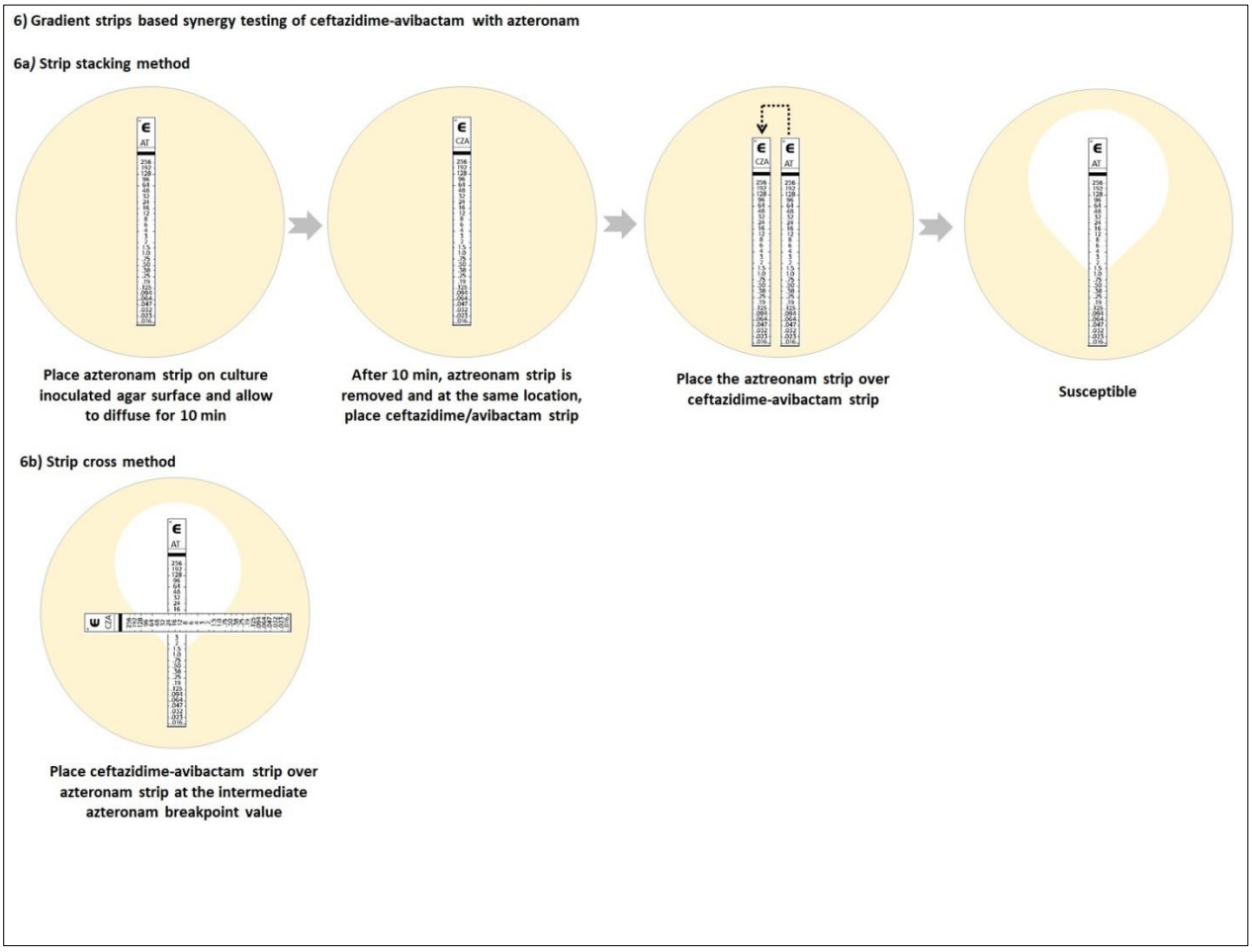

Fig 6: Susceptibility testing of triple combination ceftazidime-avibactam with azteronam using gradient strips. 1a) strip based stacking method. 1b) strip cross method.

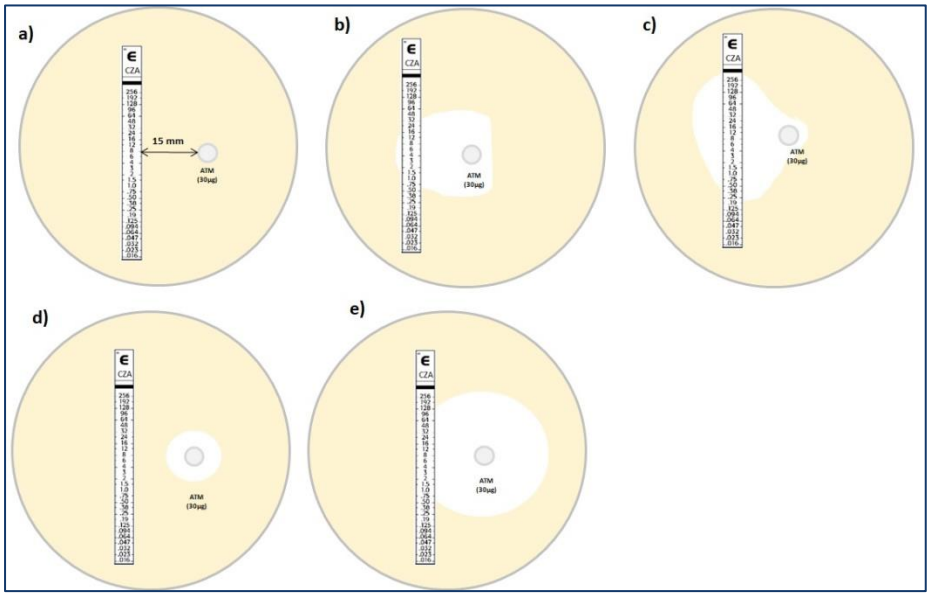

Fig: 7 E-test/disc set up with ceftazidime-avibactam E-test and azteronam disc (30µg) placed 15mm apart. a) synergy demonstrated by inverse-D; b) ceftazidime-avibactam sensitive with azteronam synergy; c) azteronam resistant, no synergy; d) azteronam susceptible, no synergy.

3. Recommendations for the management of carbapenem resistant gram negative infections

It is almost always difficult to choose an antimicrobial regimen for carbapenem-resistant gram-negative infections. Understanding of the mechanism of resistance, either by carbapenemase production (KPC, IMP, VIM, NDM, OXA-48, OXA-23/24 like) or by other mechanisms (carbapenem resistance due to efflux pump and porin loss) has important clinical implications (4). New beta-lactamase combinations have become available in recent years, and preliminary results indicate that they are safer and more effective for the treatment of CRE infections than some of the older agents, particularly polymyxin regimens. Table 4 summarises the preferred a and alternative treatment options for carbapenem-resistant gram-negative infections (based on the specific mechanism of carbapenem resistance mechanism).

Clinical Management

3.1 Empiric therapy

Empiric regimens should be based on

1. The organisms identified earlier in the patient in the previous 6 months and their anti- microbial susceptibility
2. The antimicrobial exposure in the previous 30 days, and
3. Local antibiogram

For hospital acquired organisms like carbapenem resistant *Acinetobacter* and *S. maltophila* distinction should be made between bacterial colonization and true infection and because in general, empiric regimens do not target these organisms, any decision to treat must be made after careful evaluation of the risk versus benefit of therapy.

3.2 Directed Therapy

3.2.1 Carbapenem Resistant Enterobacterales (*K. pneumoniae*, *E. coli*)

a) Treatment options when carbapenemase testing result is available are given in Table 4.

b) Treatment options when Carbapenemase testing result is not available

1. For complicated infections or hemodynamically unstable patients, polymyxins (do not use polymyxin B for UTI) plus another agent to which organism has demonstrated susceptible MIC (like tigecycline, aminoglycosides, IV fosfomycin) or high dose carbapenems if MIC < 16
2. Ceftazidime-avibactam alone if *in-vitro* susceptibility has been demonstrated or in combination with aztreonam if synergy test is demonstrating zone of inhibition.

3. Tigecycline (approved for intra-abdominal infection and skin –soft tissue infection)- DO NOT use for blood stream infection or pneumonia as a standalone agent
4. Polymyxins (colistin is preferred over polymyxin B for UTI) as a single agent (for uncomplicated infections like UTI, any other infection for which source reduction has been done and patient is hemodynamically stable)
5. Aminoglycosides (for uncomplicated infections like UTI, any other infection for which source reduction has been done)

Table 4: Available treatment options for carbapenem resistant Enterobacterales in India

Carbapenemase	
Metallo-β-lactamase (*eg*. NDM)	1st Choice: Prolonged infusion of ceftazidime-avibactam and aztreonam (over 3 hours)* Other options: a. Polymyxins (Do-not use polymyxin B for UTI) plus other agent to which organism has demonstrated susceptible MIC (like tigecycline, aminoglycosides, IV fosfomycin) or high dose carbapenems if MIC < 16 b. Tigecycline (approved for intra-abdominal infection and skin –soft tissue infection)- DO-NOT use for blood stream infection or pneumonia as a standalone agent c. Aminoglycosides (for uncomplicated infections like UTI, any other infection for which source reduction has been done)
Metallo-β-lactamase (eg. NDM) + OXA-48	1st Choice: Prolonged infusion of ceftazidime-avibactam and aztreonam (over 3 hours)* Other options: a. Polymyxins (do-not use polymyxin B for UTI) plus other agent to which organism has demonstrated susceptible MIC (like tigecycline, aminoglycosides, IV fosfomycin) or high dose carbapenems if MIC < 16 b. Tigecycline (approved for intra-abdominal infection and skin –soft tissue infection)- DO-NOT use for blood stream infection or pneumonia as a standalone agent c. Aminoglycosides (for uncomplicated infections like UTI, any other infection for which source reduction has been done)
OXA-48 like	1st Choice: Prolonged Infusion of ceftazidime-avibactam** Other options: a. Polymyxins (do-not use polymyxin B for

	UTI) plus other agent to which organism has demonstrated susceptible MIC (like tigecycline, aminoglycosides, IV fosfomycin) or high dose carbapenems if MIC < 16 b. Tigecycline (approved for intra-abdominal infection and skin –soft tissue infection)- DO-NOT use for blood stream infection or pneumonia as a standalone agent c. Aminoglycosides (for uncomplicated infections like UTI, any other infection for which source reduction has been done)
KPC	1st Choice: Prolonged Infusion of ceftazidime-avibactam ** Other options: a. Polymyxins (do-not use polymyxin B for UTI) plus other agent to which organism has demonstrated susceptible MIC (like tigecycline, aminoglycosides, IV fosfomycin) or high dose carbapenems if MIC < 16 b. Tigecycline (approved for intra-abdominal infection and skin –soft tissue infection)- DO-NOT use for blood stream infection or pneumonia as a standalone agent c. Aminoglycosides (for uncomplicated infections like UTI, any other infection for which source reduction has been done)

*Ceftazidime-avibactam + aztreonam: Perform a synergy test and demonstrate zone of inhibition. Prolonged infusion over 3 hours yields best result. This combination is not well studied in pediatric situations, de-ranged creatinine clearance and CNS infections. (Consultation with an Infectious Disease Physician or a physician having experience in treating such infection is advised)

** Ceftazidime-avibactam alone: Apart from carbapenemase test; *in-vitro* susceptibility testing is recommended prior to use.

3.2.2 Carbapenem Resistant Non- Enterobacterales (*Acinetobacter baumanii*, *Pseudomonas aeruginosa*)

a. Carbapenem Resistant *Acinetobacter baumannii (CRAB)*

Treatment Options

1. High dose sulbactam (6-9g/day) on its own or as ampicillin-sulbactam (if susceptible) or cefoperazone-sulbactam (1g/1g).
2. Polymyxins (use colistin instead of polymyxin B for UTI)
3. Minocycline
4. Tigecycline (do not use for UTI)
5. Other agents like trimethoprim-sulfamethoxazole, aminoglycosides, if susceptible

Use of these agents as standalone therapy or in combination is a matter of debate.

- Combination therapy with at least two active agents (include high dose sulbactam even if non-susceptible), whenever possible, is suggested for the treatment of moderate to severe CRAB infections
- A single active agent may be considered for the treatment of patients with mild CRAB infections. Mild infections although maybe difficult to define, but may include urinary tract infection or, skin and soft tissue infections without hemodynamic instability. The agent of choice is sulbactam due to sulbactam's activity against CRAB demonstrated in-vitro. It is useful to note that even if non-susceptibility to sulbactam is demonstrated, high dose sulbactam may still be an effective option.
- Nebulised antibiotics for the treatment of respiratory CRAB is not recommended due to the unequal distribution of the drugs in the infected lung and the potential for adverse reactions like bronchoconstriction.

b. Carbapenem Resistant *Pseudomonas aeruginosa*
Treatment Options

1. Use a β-Lactam (ceftazidime or cefepime) or β-lactam-β-lactamase inhibitor combination (piperacillin-tazobactam or cefoperazone-sulbactam) if *in-vitro* susceptibility is demonstrated
2. Aminoglycosides (if *in-vitro* susceptibility is demonstrated)
3. Polymyxins (for infections in which no other treatment option is available)

- For patients with severe infections caused by CRPA susceptible in vitro only to polymyxins, aminoglycosides, or fosfomycin, a combination therapy is suggested. Polymyxins plus other agent to which organism has demonstrated susceptible MIC or in intermediate range or SDD (susceptible dose dependent) can be used in such scenario. (Consultation with an Infectious Disease Physician or a physician having experience in treating such infections is advised)

- In patients with non-severe infections or among patients with low risk CRPA infections monotherapy to be considered on an individual basis according to the source of infection

Table 5: Treatment of choice as per clinical syndrome

Clinical Syndrome	**Treatment options**
Uncomplicated cystitis	Trimethoprim-sulfamethoxazole Nitrofurantoin Oral Fosfomycin (single dose) Single-dose aminoglycoside
Pyelonephritis and complicated Urinary Tract Infections	Choose therapy as per discussion above ➢ Do-not use Tigecycline or Polymyxin B

Infections outside urinary tract	Choose therapy as per discussion above ➢ Tigecycline is an acceptable alternative in patients with intra-abdominal infections ➢ Avoid using aminoglycosides for lung and intra-abdominal infection (use if other options are not available)

Table 6: Duration of therapy for common clinical syndromes

Clinical Syndromes	Duration of therapy
Ventilator associated pneumonia or hospital acquired pneumonia	7-10 days
Complicated urinary tract infections	10 days
Catheter associated UTI	5-7 days
Intra-abdominal infections	4-7 days
Central line associated blood stream Infections	10 ays

*Removal of catheter or central line is strongly recommended if infection with an MDR organism is confirmed

Table 7: Dosage of common antibiotics used in treatment of MDR Organisms

Antibiotics	Dosage in adults
Ceftazidime-avibactam and aztreonam	Ceftazidime-avibactam: 2.5 g IV q8h, infused over 3 hours PLUS aztreonam: 2 g IV q8h, infused over 3 hours
Colistin	9 million units as loading dose and then 4.5 million units q12h
Polymyxin B	15 lacs IU as loading dose and then 7.5 lacs IU q12h.
High dose meropenem	2 g IV q8h, infused over 3 hours
High dose imipenem	1g IV q8h, infused over 2 hours
Tigecycline	200 mg IV x 1 dose, then 100 mg IV q12h
Minocycline	200mg IV q12h
Sulbactam	2g IV q6 - 8h
IV Fosfomycin	4-6g IV q6h
High dose ampicillin-sulbactam (2g of ampicillin and 1 gm of sulbactam)	9g IV q8h over 4 hours
Cefoperazone-sulbactam (1g/1g)	4g IV q6-8h

4. Prevention

Infection Control

Horizontal interventions (for all patients)

1. Standard precautions including hand-hygiene
2. Adherence to device insertion and maintenance bundles for prevention of device related infections (VAP/CLABI/CAUTI)

Vertical Interventions (for patients infected or colonized with CRE, CRAP, CRPA)

1. Isolating these patients or cohorting (if many patients with same organism) into a single room or separate area
2. Following contact precautions as per WHO guidelines
3. Active surveillance (rectal samples) to look for CRE and subsequently isolating these patients can be done as a part of hospital policy to mitigate the spread of such organisms

Anti-microbial stewardship (AMS)

It is strongly recommended for all hospitals to have an active AMS programme running to stop irrational use of antibiotics and to optimize antibiotic usage.

AMS team is a multi-disciplinary team comprising of Infectious Disease physician, Clinical Microbiologist, Clinical Pharmacist, Hospital Administrator and an Infection Control Nurse, inputs of this team are extremely important in managing such difficult to treat infections.

Limitations

Management of infections caused by resistant organisms is both challenging and rapidly evolving. Some of the treatment options mentioned in this review may not be based on high quality evidence as these options are not supported by well conducted RCTs. Newer agents like plazomicin, cefiderocol, meropenem-vaborbactam and imipenem-relebactam have not been discussed because they are not available in India, at the time of writing this guideline.

References:

1. ICMR Antimicrobial Resistance Research and Surveillance Network Annual report 2020 https://main.icmr.nic.in/sites/default/files/guidelines/AMRSN_annual_report_2020.pdf
2. Patrice Nordmann, Laurent Poirel, Epidemiology and Diagnostics of Carbapenem Resistance in Gram-negative Bacteria, Clinical Infectious Diseases, Volume 69, Issue Supplement_7, 1 December 2019, Pages S521–528, https://doi.org/10.1093/cid/ciz824
3. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18:318 –327.
4. Livermore DM, Nicolau DP, Hopkins KL, Meunier D. Carbapenem-Resistant Enterobacterales, Carbapenem Resistant Organisms, Carbapenemase-Producing Enterobacterales, and Carbapenemase-Producing Organisms: Terminology Past its "Sell-By Date" in an Era of New Antibiotics and Regional Carbapenemase Epidemiology. Clin Infect Dis. 2020;71(7):1776-1782.
5. Clinical and Laboratory Standards Institute (2020) Performance standards for antimicrobial susceptibility testing; 24th informational supplement. CLSI document M100-S30. Clinical and Laboratory Standards Institute, Wayne, PA
6. Reyes S, Nicolau DP. Precision medicine for the diagnosis and treatment of carbapenem-resistant Enterobacterales: time to think from a different perspective. Expert Rev Anti Infect Ther. 2020;18(8):721-740.
7. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis. 2021 Apr 8;72(7):e169-e183. doi: 10.1093/cid/ciaa1478. PMID: 33106864.
8. Falcone M, Daikos GL, Tiseo G, Bassoulis D, Giordano C, Galfo V, Leonildi A, Tagliaferri E, Barnini S, Sani S, Farcomeni A, Ghiadoni L, Menichetti F. Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase-Producing Enterobacterales. Clin Infect Dis. 2021 Jun 1;72(11):1871-1878. doi: 10.1093/cid/ciaa586. PMID: 32427286.
9. Bakthavatchalam YD, Walia K, Veeraraghavan B. Susceptibility testing for aztreonam plus ceftazidime/avibactam combination: A general guidance for clinical microbiology laboratories in India. Indian J Med Microbiol. 2022 Jan-Mar;40(1):3-6. doi: 10.1016/j.ijmmb.2021.12.006. Epub 2021 Dec 20. PMID: 34949482.
10. Veeraraghavan B, Bakthavatchalam YD, Soman R, Swaminathan S, Manesh A, Nagvekar V, et al. Management of serious infections caused by metallo β-lactamases with or without OXA-48-like expressing Enterobacterales with aztreonam and ceftazidime/avibactam combination: Dosing strategy for better clinical outcome. Indian J Med Microbiol. 2021;39(3):286-288.
11. Khan A, Erickson SG, Pettaway C, Arias CA, Miller WR, Bhatti MM. 2021. Evaluation of susceptibility testing methods for aztreonam and ceftazidime-avibactam combination therapy on extensively drug-resistant Gram-negative organisms. Antimicrob Agents Chemother.2021;65:e00846-21.
12. Lashinsky JN, Henig O, Pogue JM, Kaye KS. Minocycline for the Treatment of Multidrug and Extensively Drug-Resistant A. baumannii: A Review. *Infect Dis Ther*. 2017;6(2):199-211. doi:10.1007/s40121-017-0153-2
13. International consensus guidelines for the optimal use of the polymyxins (Pharmacotherapy 2019;39(1):10–39) doi: 10.1002/phar.2209 accessed on 28th October, 2021
14. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, Venditti M, Tumbarello M, Daikos G, Cantón R, Doi Y, Tuon FF, Karaiskos I, Pérez-

Nadales E, Schwaber MJ, Azap ÖK, Souli M, Roilides E, Pournaras S, Akova M, Pérez F, Bermejo J, Oliver A, Almela M, Lowman W, Almirante B, Bonomo RA, Carmeli Y, Paterson DL, Pascual A, Rodríguez-Baño J; REIPI/ESGBIS/INCREMENT Investigators. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis. 2017 Jul;17(7):726-734. doi: 10.1016/S1473-3099(17)30228-1. Epub 2017 Apr 22. PMID: 28442293.

15. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, Skiada A, Andini R, Eliakim-Raz N, Nutman A, Zusman O, Antoniadou A, Pafundi PC, Adler A, Dickstein Y, Pavleas I, Zampino R, Daitch V, Bitterman R, Zayyad H, Koppel F, Levi I, Babich T, Friberg LE, Mouton JW, Theuretzbacher U, Leibovici L. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis. 2018 Apr;18(4):391-400. doi: 10.1016/S1473-3099(18)30099-9. Epub 2018 Feb 16. PMID: 29456043.
16. https://apps.who.int/iris/bitstream/handle/10665/312226/WHO-UHC-SDS-2019.6-eng.pdf accessed on 28th October 2021
17. Yamada K, Imoto W, Yamairi K, Shibata W, Namikawa H, Yoshii N, Fujimoto H, Nakaie K, Okada Y, Fujita A, Kawaguchi H, Shinoda Y, Nakamura Y, Kaneko Y, Yoshida H, Kakeya H. The intervention by an antimicrobial stewardship team can improve clinical and microbiological outcomes of resistant gram-negative bacteria. J Infect Chemother. 2019 Dec;25(12):1001-1006. doi: 10.1016/j.jiac.2019.05.026. Epub 2019 Jun 26. PMID: 31255524.

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