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SEPSIS IN THE ICU (J LIPMAN, SECTION EDITOR)

Difficult to Treat Gram-Negative Bacteria—The Indian Scenario

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Abstract

Purpose of Review Over 50% of the infections in most ICUs in tertiary care centres in India are caused by difficult to treat (DTR) gram-negative bacteria. The options available for the treatment of these infections are quite limited. This review discusses the epidemiology of these DTR infections in India and explores the various treatment strategies for these infections which are relevant in an Indian setting.

Recent Findings The most common organisms causing DTR infections in India are *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. The mechanisms of resistance in these organisms are not the same as those in DTR organisms prevalent in the western world. Treatment strategies recommended by western guidelines may not work in India. Management of these DTR organisms needs to be tailored to the situation in India.

Summary Overuse of antibiotics has led to an alarming rate of DTR infections in Indian ICUs. The polymyxins are often the only drugs which are effective against many of these infections. Physicians in India and the government need to take urgent measures to control the spread of these organisms.

Key points

- Antibiotic overuse has led to a situation where over 50% of infections in Indian ICUs are caused by DTR organisms.
- Carbapenemase production is the primary mechanism of resistance in carbapenem-resistant Enterobacterales (CRE). Efflux pumps, altered outer membrane porin and production of carbapenemases are all implicated in DTR *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.
- KPC production is very uncommon in the CRE prevalent in India. Western guidelines may therefore not be relevant in India.
- The polymyxins (in combination) and ceftazidime/avibactam with aztreonam are the drugs most often used to deal with DTR gram-negative bacteria in India.
- Local delivery of antibiotics may be indicated in the management of these DTR infections in special sites like meningitis and pneumonia.

Keywords Carbapenem-resistant organisms · CRO · CRE · Difficult to treat organisms · DTR · Infections in Indian ICUs

Introduction

Drug-resistant infections are the bane of intensive care units across the world but India has the dubious distinction of being at the fore front of antimicrobial resistance. Several factors are responsible for the unmitigated growth of antimicrobial resistance in India; sales of antibiotics are very poorly regulated. Antibiotics are relatively inexpensive and are easily available (even without a prescription) and are therefore over prescribed. It is no surprise then that India is the largest consumer of antibiotics in the world. There is an abundance of pharmaceutical companies which manufacture antibiotics in India and the drugs produced by some of these companies are of questionable quality. Poor public health infrastructure, poor sanitation and misuse of antibiotics in the poultry and veterinary industry also contribute [1].

Intensivists in India therefore often prescribe a combination of very broad spectrum antibiotics empirically to 'cover' resistant bugs. The Indicaps II study [2•] was a multicentre, observational, staggered point prevalence study performed on 4 separate days. This study included 5222 patients from

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141 Indian ICUs. The study noted that 70% of the patients were on at least 1 antibiotic and 17% of patients were receiving 3 or more antibiotics. This overuse of antibiotics in the ICU which is the epicentre of antibiotic resistance further compounds the problem.

Epidemiology of DTR Gram-Negative Bacteria in India (Table 1)

Kadri and colleagues recently proposed the definition of difficult to treat (DTR) resistance. Resistance to all first-line agents, that is, all β-lactams, including carbapenems and β-lactamase inhibitor combinations (this does not include the newer β-lactam/β-lactamase inhibitor combinations like ceftazidime/avibactam and meropenem vaborbactam) and fluoroquinolones, can be described as difficult-to-treat (DTR) resistance [3].

The Indian Council for Medical Research (ICMR) recently published the surveillance data for the year 2021 [4••]. The total number of culture positive isolates studied from centres across the length and breadth of the country was 95,728. Gram-positive infections were surprisingly uncommon in India. *Escherichia coli* was the most commonly isolated pathogen followed by the *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. These four organisms constitute the majority of the difficult to treat organisms in India and this article will focus on the treatment of these organisms.

Of the ICU strains studied, 40% of the *Escherichia coli* were resistant to carbapenems. The resistance to the quinolones and third-generation cephalosporins was even more dismal at 85%. Of the *Klebsiella pneumoniae,* 70% were resistant to carbapenems and 8% were resistant to colistin. More than 90% of the *Acinetobacter baumannii* isolated from the ICUs across the country were resistant to every antibiotic except colistin (95% sensitive) and minocycline (52% sensitive). Of the *Pseudomonas aeruginosa*, 45% were carbapenem resistant and 5% were resistant to colistin as well. Such a high prevalence of carbapenem resistance therefore limits the choices available to the physician when having to prescribe empiric therapy to a critically ill patient with suspected infection.

Mechanisms of Resistance in the Difficult to Treat Gram-Negative Bacteria in India

There are 4 common mechanisms by which bacteria can become resistant [5].

(i) Alteration of the outer membrane porin such that the permeability of the antibiotic is reduced
(ii) Efflux pumps which extrude the antibiotic
(iii) Modification of the target site
(iv) Production of inactivating enzymes

Mechanisms of Resistance in the Carbapenem-Resistant Enterobacterales (CRE) in India [4••, 6•, 7] (Table 2)

The CDC defines CRE as members of the Enterobacterales order resistant to at least one carbapenem antibiotic or producing a carbapenemase enzyme.

Production of inactivating enzymes, viz., the carbapenemases, is by far the most common mechanism by which the Enterobacterales become resistant to the carbapenems. The carbapenemases most prevalent in India are the metallo

Table 1 Susceptibility profiles of common gram-negative organisms isolated from ICUs across India (2021) [4]

Antibiotic	Susceptibility% of *Escherichia coli*	Susceptibility% of *Klebsiella pneumoniae*	Susceptibility% of *Acinetobacter baumannii*	Susceptibility% of *Pseudomonas aeruginosa*
Amikacin	70	33	12	61
Cefotaxime	13	12		
Ceftazidime	13	09	5	55
Cefepime			5	56
Ciprofloxacin	17	20		55
Colistin*	100	92	95	95
Ertapenem	58	28		
Levofloxacin	15	22	09	50
Meropenem	60	31	07	55
Minocycline			52	
Pip-Taz	40	23	06	61

*Colistin represents percentage intermediate susceptibility

Table 2 Prevalence of resistance genes in *Escherichia coli* and *Klebsiella pneumoniae* isolates from various ICUs, in India [4]

	Gene	Positivity rate in *Klebsiella pneumoniae*	Positivity rate in *Escherichia coli*
1)	OXA 48	39%	18%
2)	NDM	40%	31%
3)	IMP	12%	37%
4)	VIM	4%	9%
5)	KPC	12%	5%
6)	CTX-M 15	53%	47%
7)	CTX-M	32%	18%
8)	TEM	46%	37%
9)	SHV	72%	2%
10)	CIT	6%	36%

beta lactamases (MBL) and OXA. Of the MBL, NDM (New Delhi metallo) is the most common in India. Carbapenem-resistant *Klebsiella pneumoniae* in India usually produce pure OXA or a combination of OXA and MBL. *E. coli* in India produce pure MBL (usually NDM) or a combination of MBL and OXA. Whereas KPC is the most prevalent carbapenemase in the western world, the incidence of KPC in India is quite low.

This difference has important implications—treatment approaches that have been recommended for infections caused by KPC-producing organisms may not work in India [8, 9]. The strategy of prescribing carbapenems in high doses as prolonged/continuous infusions will not work in India because the MICs of the carbapenems against the CRE are extremely high. Using two carbapenems, a ploy used against KPC has not been tried against CRE. The newer beta lactamase inhibitors like vaborbactam and relebactam which are effective against KPC do not work against OXA and MBL. Even ceftazidime/avibactam will not be effective against strains which produce MBL.

Along with the carbapenemases, the CREs usually co-produce other beta lactamases like ESBL and Amp C. The strategies used against the carbapenemases will be effective against these beta lactamases as well.

Mechanisms of Resistance in Difficult to Treat *Pseudomonas aeruginosa* (DTR-PA) and Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) in India

These organisms develop resistance via a variety of mechanisms and hence are very difficult to treat. Efflux, altered outer membrane porin and production of carbapenemases are all involved in the resistance mechanisms.

Unlike the DTR-PA prevalent in the west, DTR-PA in India produce MBL and therefore the drugs recommended in western guidelines [8, 9] may not be effective in India.

Use of Genetic Testing in the Management of Difficult to Treat Gram-Negative Bacteria Prevalent in India [10]

In addition to phenotypic tests for resistance, molecular diagnostics may help the physician. These tests detect the presence of the most common resistance mechanisms. Results of molecular tests are available much earlier and may enable earlier streamlining of empiric antibiotic therapy. The results of genetic testing must however be corroborated by the results of phenotypic tests for resistance. These molecular tests are expensive and not freely available across the country however.

Molecular testing is not very useful in the management of carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* infections because their mechanisms of resistance (efflux, altered porin, OXA 21, etc.) are not detected by the molecular tests.

Drugs that Might Be Effective Against the Carbapenem-Resistant Organisms Prevalent in India

The Polymyxins [11, 12]

Polymyxin B and polymyxin E (colistin) have re-emerged as last resort antibiotics for many difficult to treat infections. These are cyclic polypeptide antibiotics which differ in structure by only one amino acid. The polymyxins bind to the lipopolysaccharides and phospholipids in the outer cell membrane of gram-negative bacteria and displace Ca and Mg from the phosphate group of membrane lipids. This leads to disruption of the outer cell membrane and bacterial death.

The polymyxins are effective against CRE, DTR-PA and CRAB but they are usually prescribed in combination when dealing with critically ill patients suffering from these difficult to treat infections.

Polymyxin has several pharmacokinetic advantages over colistin. It achieves higher levels in plasma faster than colistin which is administered as a prodrug (colistimethate) which needs to be then converted to colistin. Unlike colistimethate, polymyxin is not renally excreted and therefore does not require dose modification in patients with renal failure. Colistimethate is also unlikely to achieve adequate serum levels in patients with augmented renal clearance. Nephrotoxicity is also probably lower with polymyxin B. For all these reasons, polymyxin B is preferred over polymyxin E except in the management of urinary tract infections.

Phenotypic testing for colistin susceptibility has several limitations and currently only broth microdilution is recommended. The CLSI recommends that isolates with an MIC < 2 should be reported as I (intermediate). No isolate is reported as S (sensitive) [13]. Nevertheless, given the limited options available, the polymyxins are the most commonly used antibiotics for the management of difficult to treat gram-negative infections in India.

Ceftazidime/avibactam (Taz/Avi) [14, 15]

Ceftazidime/avibactam is a combination of the third-generation cephalosporin ceftazidime and a novel, non-β-lactam β-lactamase inhibitor avibactam. Avibactam is effective against most of the beta lactamases and carbapenemases produced by the CRE in India except for MBL. Since a significant proportion of the CRE in India produce MBL, ceftazidime/avibactam is usually combined with aztreonam in the initial empiric treatment of CRE.

Sulbactam [16]

Sulbactam is a beta lactamase inhibitor which has some intrinsic action against the penicillin binding proteins of *Acinetobacter*. High-dose sulbactam (available as ampicillin/sulbactam) is used in the treatment of CRAB in combination with other antibiotics. High-dose sulbactam may be used in combination even if the phenotypic tests reveal resistance.

Aztreonam

Aztreonam is a monobactam antibiotic. This antibiotic has made a comeback because it is resistant to destruction by the MBLs. The organisms producing MBL also produce other beta lactamases such as ESBL and Amp C which could destroy aztreonam. Aztreonam therefore needs to be combined with avibactam which protects aztreonam from the other beta lactamases [17]. Avibactam is not available in isolation. Aztreonam is therefore combined with ceftazidime/avibactam. Ceftazidime/avibactam and aztreonam need to be infused simultaneously over 3 h [18].

Tigecycline [19, 20]

Tigecycline is a glycylcycline antimicrobial structurally related to minocycline. Tigecycline binds to the bacterial 30S ribosome and ultimately prevents protein synthesis and limits bacterial growth. When compared with minocycline or tetracycline, tigecycline has a much greater affinity for the ribosomal target. Tigecycline therefore has a broader spectrum of activity and a decreased susceptibility to the development of resistance.

Tigecycline has a wide volume of distribution and therefore does not achieve high serum levels. It is therefore not usually recommended for the treatment of blood stream infections. With the limited options available for treatment of carbapenem-resistant organisms in India, tigecycline is often combined with the polymyxins in the treatment of CRE or CRAB infections. Tigecycline is prescribed in double the usual dose, i.e. 200 mg loading dose and 100 mg twice daily in an attempt to achieve higher serum levels.

Minocycline [21]

It is a tetracycline derivative and like the tetracyclines and tigecycline inhibits the 30S ribosome. Minocycline achieves better levels in serum and in the lung. It also has good penetration into the CSF. In high doses, it is used in combination with sulbactam and/or polymyxins in the treatment of infections caused by CRAB. Minocycline is generally ineffective against CRE and DTR-PA.

Fosfomycin [22]

Fosfomycin is a phosphonic acid derivative discovered from the strains of *Streptomyces* spp. in Spain, in 1969. It has a unique mode of action in interfering with bacterial cell wall synthesis and there is therefore little cross resistance between fosfomycin and other antibiotics. It is a small relatively hydrophilic molecule with negligible protein binding and therefore has excellent penetration into various tissues including the brain. It is almost 100% effective against *E. coli* (including CRE) and has up to 60% efficacy against CR *Klebsiella*. It has limited activity against *Acinetobacter baumannii* and variable activity against *Pseudomonas aeruginosa*.

Fosfomycin is usually prescribed in combination because resistance to this drug can develop quickly if prescribed alone. Fosfomycin is often combined with the polymyxins in the treatment of CRE especially CR *E. coli*.

The use of fosfomycin is associated with a high sodium load. Caution is therefore advised when fosfomycin is used in patients with cardiac insufficiency, hypertension or pulmonary oedema. Fosfomycin also causes a significant decrease in potassium levels.

Cefiderocol and Eravacycline

These antibiotics are not yet available in India but might be used as salvage therapy if and when they become accessible.

Strategies to Manage DTR Gram-Negative Infections in India [23••, 24, 25••] (Figs. 1 and 2)

Ceftazidime/avibactam plus aztreonam infused simultaneously over 3 h is preferred for the empiric treatment of carbapenem-resistant Enterobacterales in ICUs where *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are unlikely causes of nosocomial infections.

If the organism is subsequently identified as *Klebsiella pneumoniae* and if molecular testing reveals the presence of both OXA and MBL, the combination of Taz/Avi is continued. If MBL is absent, aztreonam is discontinued.

If the organism is identified as an *Escherichia coli* producing carbapenemases, Taz/Avi and aztreonam are continued.

It is important to test for synergy between Taz/Avi and aztreonam when treating carbapenem-resistant *E. coli* because a small percentage of these *Escherichia coli* may harbour a PBP3 insert which may increase their MICs against Taz/Avi + aztreonam [26].

If molecular testing is not easily available, the pragmatic solution would be to continue the combination of Taz/Avi and aztreonam until the results of phenotypic sensitivity are available.

Polymyxin-based combination therapy (usually combined with high-dose tigecycline or fosfomycin) is preferred as empiric therapy in ICUs where in addition to the CRE, carbapenem-resistant *Acinetobacter baumannii* and/or *Pseudomonas aeruginosa* are also likely causes of nosocomial infection.

In a patient on empiric polymyxin-based therapy:

If the organism is subsequently identified as a *Klebsiella pneumoniae*, it is advisable to switch to Taz/Avi ± aztreonam depending on the results of molecular testing as outlined above. This is because a few studies have demonstrated better outcomes with this combination as compared to polymyxin-based therapies [27, 28].

If the organism is identified as *Escherichia coli*, the options are either colistin + fosfomycin or Taz/Avi + aztreonam.

If the organism is identified as CRAB, polymyxin + high-dose minocycline + high-dose sulbactam (as ampicillin/sulbactam) is recommended for patients who are critically ill.

DTR-PA pose a challenge in treatment [29]. Ceftolozane/tazobactam or Taz/Avi may be effective if the organism is not a producer of MBL. Unfortunately unlike the strains prevalent in the west, the *Pseudomonas aeruginosa* in India quite often produce MBL. For these organisms, polymyxin in combination with high-dose fosfomycin is probably an option.

If the final phenotypic sensitivity reports reveal that the organism is sensitive to a carbapenem or a narrower spectrum antibiotic, de-escalation should be practised in most cases. In cases where the organism has demonstrated the production of a carbapenemase however, a carbapenem cannot be prescribed even if susceptibility to the carbapenems is reported.

There is no evidence that patients with DTR infections need longer courses of treatment. In patients who respond quickly to treatment, around 7 days of antibiotic treatment is therefore adequate. Serial CRP or PCT monitoring might help in determining when to stop antibiotics in patients who recover slowly.

Inadequate source control, inappropriate dose reduction (in patients with renal dysfunction) and treatment of colonisers may be some of the reasons for apparent failure of treatment. If the organism is truly PAN drug resistant, various combinations of antibiotics including polymyxins, cotrimoxazole, quinolones, fosfomycin and rifampicin (with polymyxin as the backbone) have been tried with varying degrees of success.

Urinary Tract Infections

Polymyxin B should not be used for the treatment of urinary tract infections because it is not excreted through the kidneys. Colistin (polymyxin E) is preferred [10].

VAP

Polymyxin-based combination therapy is preferred for VAP caused by CR *Acinetobacter baumannii* or *Pseudomonas*. The polymyxins however do not achieve adequate levels in the lung. A combination of nebulised colistin (in high doses) preferably delivered through a vibrating mesh along with intravenous polymyxin and high-dose minocycline/fosfomycin is suggested [30].

Nosocomial Meningitis/Ventriculitis

Carbapenem-resistant *Acinetobacter baumannii* are commonly responsible for nosocomial ventriculitis in patients with an external ventricular drain. These patients are usually treated with a combination of intravenous polymyxin and high-dose minocycline along with intra-ventricular colistin [31].

The challenge of difficult-to-treat gram-negative infections in India warrants urgent and multifaceted action.

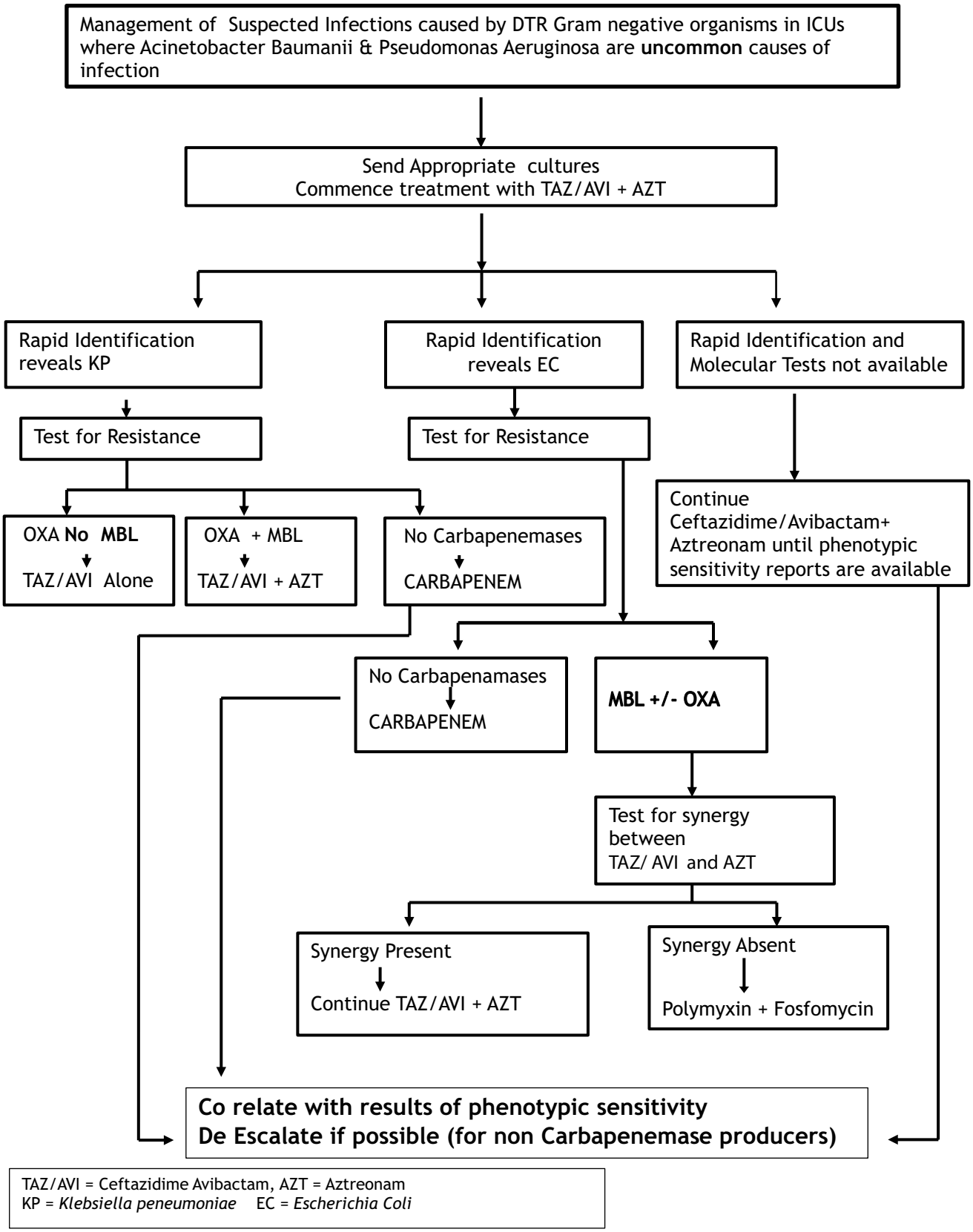

Fig. 1 Management of suspected infections caused by DTR gram-negative organisms in ICUs where *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are uncommon causes of infection

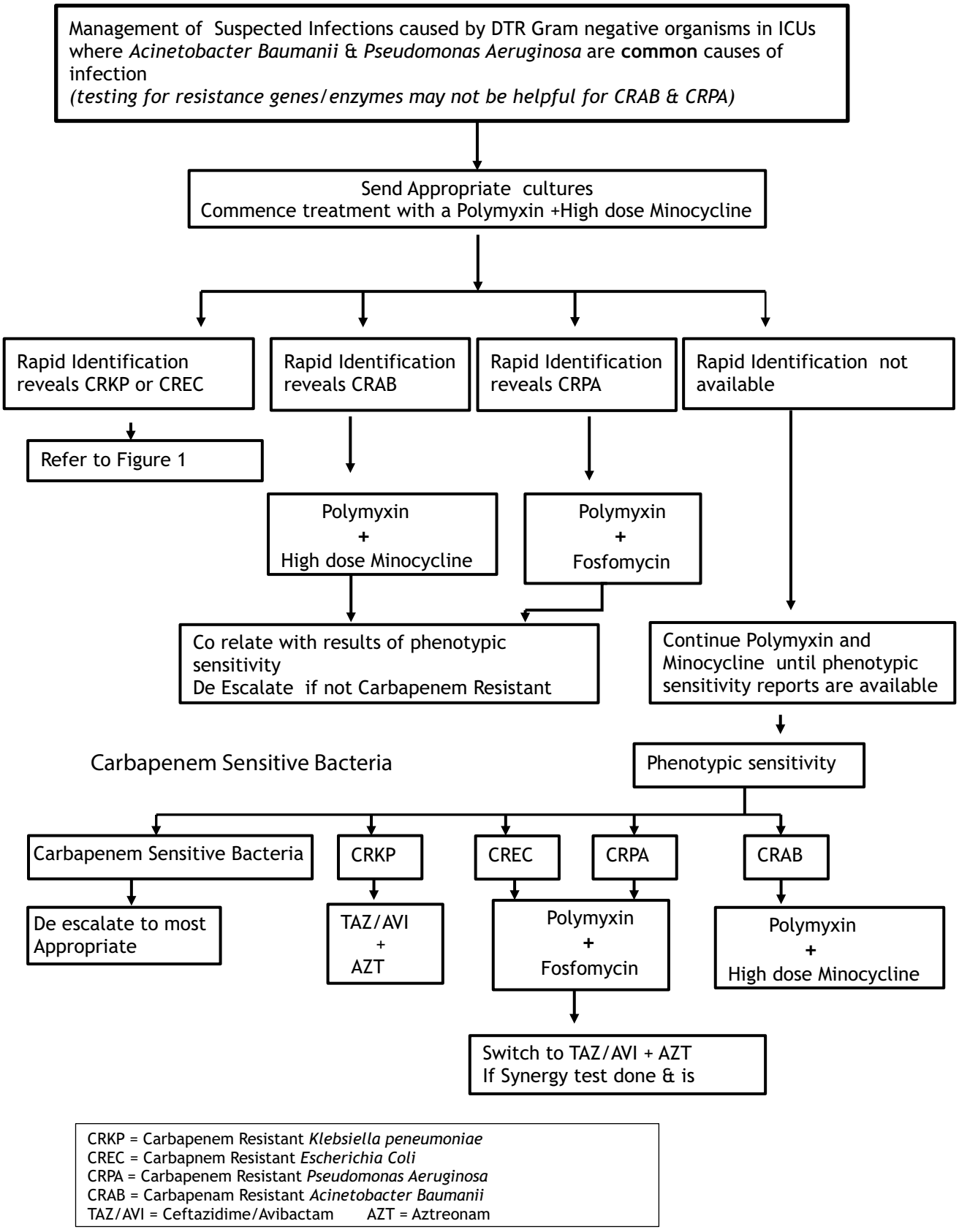

Fig. 2 Management of suspected infections caused by DTR gram negative organisms in ICUs where *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are common causes of infection (testing for resistance genes/enzymes may not be helpful for CRAB and CRPA)

The adoption of antimicrobial stewardship programmes in healthcare facilities may help curb the overuse and misuse of antibiotics.

Improved sanitation, hygiene practices and infection control protocols may reduce the spread of infections and subsequently decrease the selective pressure on bacteria.

The Indian government needs to enact and enforce legislation to regulate the use of antibiotics, strengthen surveillance systems to monitor the prevalence of resistance and incentivise the development of new antimicrobial drugs.

Lastly, international collaboration and knowledge-sharing are crucial to tackle this health crisis which is not just Indian but is global.

Author Contribution NB did a literature search and summarised important sections of each article. AH prepared a rough draft of the final article. FNK wrote the final draft and added the section on individual antibiotics. All 3 authors reviewed the final manuscript. FNK and NB prepared the figures and tables. AH made the modifications suggested by the reviewer.

Compliance with Ethical Standards

Conflict of Interest Dr. HEGDE reports personal fees from Glenmark Pharmaceutical, personal fees from Pfizer Pharmaceutical, personal fees from Alkem Pharmaceutical , personal fees from Sanofi Pharmaceutical, outside the submitted work; . Dr Kapadia & Dr Bannore have no conflict of interest

Human and Animal Rights and Informed Concent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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