Loss of exclusivity of ceftazidime/avibactam in low- and middle-income countries: a test for antibiotic stewardship practice

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Summary

Ceftazidime/avibactam is a last-line antibiotic, to be used as a targeted therapy for certain carbapenem-resistant Gram-negative infections and not to be used as an empirical therapy or as a carbapenem-sparing therapy. After a span of 5 years, the antibiotic recently lost its exclusivity and become a generic drug in India. It is assumed that generic players will aggressively market the drug, making it freely available even in pharmacies catering to primary- and secondary-care hospitals. We thus foresee certain potential adverse implications of introducing generic versions of ceftazidime/avibactam into the Indian market; as they will be a challenge to the antibiotic stewardship. In the real world scenario, the stewardship system in India is fragile, therefore, we may see empirical use of ceftazidime/avibactam even in primary and secondary-care hospitals. The existing widespread prevalence of MBL-producing isolates in India, will be further enhanced by the indiscriminate use of ceftazidime/avibactam.

Keywords: Ceftazidime/avibactam; MBL; PBP3 insert; Generic drugs

Introduction

When the price of a life-saving drug drops, it is beneficial to the patients. However, in the case of antibiotics, it also leads to excessive prescriptions and the risk of developing resistance. Ceftazidime/avibactam is a last-line antibiotic, to be used as a targeted therapy for certain carbapenem-resistant Gram-negative infections and not to be used as an empirical therapy or as a carbapenem-sparing therapy. In India, the utility of ceftazidime/avibactam as standalone is restricted to infections caused by susceptible OXA-48-like-producing *Klebsiella pneumoniae* or *Escherichia coli* as KPC-producers are rare.[1] In other Low- and middle-income countries (LMICs), wherever KPCs are prevalent, ceftazidime/avibactam would find greater utility.

Ceftazidime/avibactam was initially registered with the U.S. FDA in 2015 and after 3 years it was approved in India. As of now, ceftazidime/avibactam is mostly available in the pharmacies of tertiary-care hospitals. After a span of 5 years, the antibiotic recently lost its exclusivity and become a generic drug in India.[2] The authors of this article have learnt that more than ten home grown pharmaceutical companies are set to introduce generic versions of ceftazidime/avibactam in India (personal communication, Prof Balaji V). When generic players aggressively market the drug, they will make it freely available even in pharmacies catering to primary- and secondary-care hospitals. Due to multiple sellers in the market, the cost of the drug is expected to fall. It is very likely that ceftazidime/avibactam will be available at a much cheaper cost in the near future compared to the innovator product. We foresee certain potential adverse implications of the introduction of generic versions of ceftazidime/avibactam into the Indian market, as they will be a challenge to antibiotic stewardship. In the real world scenario, the stewardship system in India is fragile, therefore, we may see the empirical use of ceftazidime/avibactam even in primary and secondary-care hospitals. The existing widespread prevalence of MBL-producing isolates in India, they will be further enhanced by the indiscriminate use of ceftazidime/avibactam. In the past there have been reports elsewhere of the detection of acquired resistance to ceftazidime/avibactam among isolates which were initially susceptible to this drug.

Therapeutic scope of ceftazidime/avibactam

The various resistance mechanisms found in the ceftazidime/avibactam-resistant isolates are described in Table 1. These are predominately variants of β-lactamases that escape inhibitory action of avibactam and

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porin defects leading to impermeability. In Indian context, excessive empirical use of ceftazidime/avibactam may lead to similar resistance selection among OXA-48-like-producing Enterobacterales. When the organism expresses an MBL, it should be combined with aztreonam.[3] Moreover, the clinical utility of aztreonam plus ceftazidime/avibactam for treating infections caused by MBL-producing *E. coli* is uncertain as these organisms also harbour 4 amino acid insert in their penicillin binding protein (PBP)3, which adversely impacts the activity of aztreonam.[4] Our current understanding is that >90% of NDM-producing *E. coli* also harbour four amino acid inserts in PBP3. Even in MBL-producing *Pseudomonas aeruginosa*, addition of ceftazidime/avibactam to aztreonam is of limited utility.[3] Since ceftazidime is hydrolyzed by MBL, aztreonam is the only antibacterially active component of this triple combination and is known to be a substrate of pseudomonal efflux pumps. This is evident from the reported aztreonam/avibactam MICs against *P. aeruginosa* which often remain above 8 mg/L.[5]

Early and appropriate antibiotic therapy has been known to improve clinical outcomes in patients with septic shock and this has been shown to be true even in patients with infections due to carbapenem resistant gram-negative pathogens.[6,7] Because of the proven mortality benefit early and empiric antibiotic therapy is given to patients with sepsis. As per the latest antimicrobial resistance surveillance conducted by ICMR (Surveillance network of over 20 centres across India), *Acinetobacter baumannii, Klebsiella pneumoniae, and P. aeruginosa* were the most common gram-negative pathogens among patients with healthcare associated infections. Carbapenem resistance rates are over 50% in *A. baumannii* and *K. pneumoniae*.[8] Ceftazidime/avibactam in combination with aztreonam is recommended by most international guidelines for the treatment of infections caused by metallo beta-lactamase producing Enterobacterales (other BL-BLIs like meropenem-vaborbactam and imipenem-relebactam are not yet available in India, and are also not likely to be active against most Indian isolates).[9–11] This has led to the wide-spread use of ceftazidime/avibactam alone or in combination with aztreonam empirically particularly in Indian ICUs.[12] But this comes with many caveats, Firstly, as per the surveillance network, *A. baumannii* is the most common organism responsible for HAI in Indian ICUs,[8] but ceftazidime-avibactam alone or in combination with aztreonam has no activity against carbapenem resistant *A. baumannii*. Secondly, for its use for other pathogens (like *K. pneumoniae, and P. aeruginosa)* synergy testing is needed to confirm the activity of the combination of ceftazidime-avibactam with aztreonam, this requires excellent microbiology laboratory support in terms of skilled technicians and a rapid turn-over time. Unfortunately, many Indian secondary care centres are not equipped with microbiology laboratories. The use of

Organism	Beta-lactamases/other resistance mechanism	Mutations	Ceftazidime-avibactam MIC (mg/L)	Mechanism of resistance
E. coli	SHV-1	S130G	8	Inhibitor-resistant variant, resistant to the inhibition of avibactam
	CTX-M-15	L169Q, S130G	16	Partially inhibited by avibactam, but retained ceftazidime hydrolysis activity
	CMY-6	Y150C	128	Weakly inhibited by avibactam
	DHA-1	N346Y	16	Increases ceftazidime hydrolysis
	KPC-2	N179D	16	Increases ceftazidime hydrolysis
		D179Y	32	Increases ceftazidime hydrolysis
	OXA-48	P68A, Y211S	16	Decreases the inhibitory activity of avibactam
K. pnuemoniae	CTX-M-14	P170S, T264I	32	Increases ceftazidime hydrolysis
	VEB-1	K234R	16–64	Impaired inhibition of avibactam
	CMY-172	–	128	Increases ceftazidime hydrolysis
	KPC-2	L169P	16	Reduced susceptibility to ceftazidime/avibactam, but increases the susceptibility to carbapenems
	KPC-3	D179Y, T243M, A177E Insertion of glutamic acid, E and leucine, L between 165 and 166	16	Confer extended spectrum beta-lactamase activity that increases ceftazidime hydrolysis, but increases the susceptibility to carbapenems
		V240G	16	Impaired inhibition of avibactam
		Increased copy number KPC-3 carrying plasmids	32	Impaired inhibition of avibactam
	Porin loss (ompK35/36 ± mutations in KPC-2 and KPC-3)	OmpK36: T333N OmpK35: Truncation at the amino acid position 42	32	Porin loss prevent the entry of cephalosporins Mutations in KPC-2/3 variants, increases ceftazidime hydrolysis

Table 1: **Most common resistance mechanism reported in carbapenem resistant Enterobacterales for ceftazidime-avibactam.**

ceftazidime/avibactam alone or in combination with aztreonam empirically and without proper synergy testing, could thus prove to be detrimental to patients who require early and appropriate therapy. We believe that with ceftazidime/avibactam losing its exclusivity and becoming a generic drug, more rampant and empirical use of this drug is to be expected, which may detrimental patient care. Hence, it is important that the use of ceftazidime/avibactam alone or in combination with aztreonam should be restricted to targeted therapy after susceptibility results and MIC values are available to the treating clinicians and/or clinical microbiologists.

Generic ceftazidime/avibactam – challenges and solutions

In 2015, the Drug Controller General of India categorised higher generation anti-infectives as a Schedule H1 drug.[13] The drugs included under this schedule are sold only on the prescription of a registered medical practitioner. Supply of the drug is recorded in a separate register at the time of the supply; giving the name and address of the prescriber, the name of the patient, the name of the drug and the quantity supplied, such records should be maintained for three years and be available for inspection.[13] Examples of other schedule H1 drugs includes cefixime, cefoperazone, cefotaxime, and ceftriaxone. The implementation of such a system is fraught with many challenges and it is difficult to track violations.

One option to limit the rampant use of valuable generic drugs is that the government to control the supply chain. There have been previous examples of this approach in India. For example, when the antivirals oseltamivir phosphate and zanamivir which are used to treat infections with influenza viruses were launched in India, manufacturing and distribution could not occur without approval from the drugs controller.[14] Initially, these drugs were supplied directly to hospitals without any retail sales.

Recently, delamanid and bedaquiline have been approved under the revised national tuberculosis control programme (RNTCP) for conditional access.[15] In order to prevent the overuse of these drugs which are indicated for treating multi-drug resistant tuberculosis (MDR-TB), the RNTCP manages the use of delamanid and bedaquiline through the programmatic management of drug resistant tuberculosis (PMDT) framework in alignment with the world health organisation (WHO) consolidated guideline on drug-resistant tuberculosis treatment.[16,17] It is recommended that delamanid and bedaquiline can only be given to patients with MDR-TB under the following conditions, i) when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide according to WHO recommendations cannot be designed, ii) when there is documented evidence of resistance to any fluroquinolones or second-line injectable drug in addition to MDR and iii) when there is higher risk for poor outcomes due to drug intolerance or contraindication, or advanced disease. This is a example of stewardship effort directed towards the controlled use of TB drugs to check the emergence of resistance to it.[16,18]

It is now time for all stakeholders concerned about the upcoming availability of generic version of ceftazidime/avibactam to actively educate the medical community on the need to only prescribe ceftazidime/avibactam for the infections caused by confirmed OXA-48-like-producing-Enterobacterales. Currently, recommendations to safe guard the use of new high-end antibiotics, when they are introduced into the Indian market, have not been implemented. However, there is an urgent need to rationalise their usage. The national policy for the containment of antimicrobial resistance which was published in 2011, recommended restricting the usage of high-end antibiotics only to tertiary care centres (National Policy for Containment of Antimicrobial Resistance, India, 2011). Responsible access is vital for all, and introducing new antibiotics with measures to foster rational use, including stewardship efforts is essential for patient care.

Contributors

All authors contributed significantly to this manuscript. VB, YDB & KW: prepared the initial draft. RDS, SM, NB: revised and edited the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

All authors declared no conflict of interest related to this work.

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References

1 Soman R, Bakthavatchalam YD, Nadarajan A, et al. Is it time to move away from polymyxins?: evidence and alternatives. *Eur J Clin Microbiol Infect Dis.* 2021;40:461–475.
2 *AVYCAZ, ceftazidime pentahydrate & avibactam sodium. Applications for patent term extension and patent terms extended under 35 U.S.C. § 156.* USPTO; 2023. https://www.uspto.gov/patents/laws/patent-term-extension/patent-terms-extended-under-35-usc-156. Accessed April 3, 2023.
3 Veeraraghavan B, Bakthavatchalam YD, Soman R, 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.
4 Periasamy H, Joshi P, Palwe S, et al. High prevalence of Escherichia coli clinical isolates in India harbouring four amino acid inserts in PBP3 adversely impacting activity of aztreonam/avibactam. *J Antimicrob Chemother.* 2020;75(6):1650–1651.
5 Lee M, Abbey T, Biagi M, et al. Activity of aztreonam in combination with ceftazidime–avibactam against serine-and metallo-β-lactamase–producing Pseudomonas aeruginosa. *Diagn Microbiol Infect Dis.* 2021;99(1):115227.
6 Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med.* 2010;38(9):1773–1785.
7 Falcone M, Tiseo G, Carbonara S, et al. Mortality attributable to bloodstream infections caused by different carbapenem-resistant Gram negative bacilli: results from a nationwide study in Italy (ALARICO Network). *Clin Infect Dis.* 2023:ciad100.

8 ICMR Annual Report Antimicrobial resistance research and surveillance network. Available from: https://main.icmr.nic.in/sites/default/files/upload_documents/AMR_Annual_Report_2021.pdf; 2021. Accessed February 26, 2023.

9 Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect*. 2022;28(4):521–547.

10 Tamma PD, Aitken SL, Bonomo RA, et al. 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*. 2022;75(2):187–212.

11 ICMR. Guidance on diagnosis and management of carbapenem resistant gram-negative infections. Available from: https://main.icmr.nic.in/sites/default/files/upload_documents/Diagnosis_and_management_of_CROs.pdf. Accessed February 26, 2023.

12 Rathish B, Wilson A, Warrier A, Prakash S, Babu R, Joy S. Clinical outcomes in carbapenem-resistant enterobacteriaceae infections treated with ceftazidime-avibactam: a single-center observational study. *Cureus*. 2021;13(2):e13081.

13 Hazra A. Schedule H1: hope or hype? *Indian J Pharmacol*. 2014;46(4):361–362.

14 Mathew P, Thomas SA, Chandy SJ. The role of Schedule H1 and Red Line campaign in improving antibiotic use in India. *J Family Med Prim Care*. 2022;11(6):2656–2661.

15 TB India report, 2016. *Revised National TB control programme*. New Delhi, India: RNTCP; 2016.

16 Central TB Division. *Guidelines on programmatic management of drug resistant TB (PMDT) in India. Revised national tuberculosis control programme*. New Delhi: Directorate-General of Health Services, Ministry of Health & Family Welfare, Government of India; 2017. Available from: https://tbcindia.gov.in/showfile.php?lid=3590. Accessed April 2, 2023.

17 World Health Organization. *WHO consolidated guidelines on drug-resistant tuberculosis treatment*. Geneva: WHO; 2019. Available from: https://apps.who.int/iris/handle/10665/311389. Accessed April 2, 2023.

18 Central TB Division. *Guidelines for use of delamanid in the treatment of drug resistant TB in India, 2018 reference*. Directorate-General of Health Services, Ministry of Health & Family Welfare, Government of India; 2018. Available from: https://tbcindia.gov.in/WriteReadData/l892s/8131480597Guidelines%20for%20use%20of%20Delamanid%20for%20treatment%20of%20DR-TB%20in%20India.pdf. Accessed April 2, 2023.