LETTER TO THE EDITOR

The Rise of Irrational Antimicrobial Combinations: Need for Clinical Jurisprudence?

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Dear Editor,

Recent years have seen an increase in nosocomial infections with multidrug-resistant (MDR) gram-negative infections in our ICUs. The search for antimicrobials to combat the threat of MDR bugs has led to the introduction of novel β-lactam agents which offer hope in their management.[1,2] However, this has unfortunately also led to the introduction and prescription of dubious antibiotic combinations which often lack scientific rationale.

Traditionally β-lactam inhibitors like tazobactam and sulbactam have been used to prevent the degradation of the antibiotics by organisms producing β-lactamases.

Sulbactam, a penicillanic acid sulfone has antibacterial activity against class A β-lactamases while having no action against class B, C, and D β-lactamases. The β-lactamases known to produce resistance to carbapenems are KPCs, Amp C, NDM, and OXA-48 enzymes, and these are not inhibited by sulbactam.[3] Of them, NDM, and OXA-48 appear to be the predominant subtype in the Indian ICUs.[4] Hence, there seems not much of a case to combine sulbactam with carbapenems, as it is unlikely to provide any additional benefit over carbapenem alone in such infections. Indeed, after a PUBMED search, we could not come across any RCTs showing the benefit of Carbapenem-sulbactam combinations in the treatment of MDR bugs.

Recently there has been a renewed interest in sulbactam as an antibacterial agent of its own given the efficacy of high-dose sulbactam in treating multidrug-resistant Acinetobacter infections.

The recent IDSA guidelines suggest the use of high-dose ampicillin-sulbactam as a viable option to treat MDR acinetobacter.[5] Nonetheless, there seems no benefit of using meropenem-sulbactam combinations to treat the same, as it will unnecessarily increase the cost of therapy. It will also lead to a possible risk of selecting resistant strains to meropenem.

The more curious case is that of combining Tazobactam with carbapenems. Tazobactam, an irreversible inhibitor of bacterial β-lactamases, has little antibacterial action of its own. Hence there seems weak biological plausibility, if at all any benefit of combining it with carbapenems.

Again, there is a complete lack of supporting literature for prescribing such antibiotic combinations in resistant gram-negative infections. The other veritable concern with the use of such combinations is underdosing either of the component drugs as they are usually marketed as fixed-dose combinations. Finally, testing for resistance and determination of MICs for such combinations is not routinely done in the laboratory.

The evidence in favor of the use of ethylenediaminetetraacetic acid (EDTA) as an adjunct in combination with antimicrobials stems from *in vitro* data. It is believed that EDTA by chelating Zinc (Zn2+) ions would neutralize metallo-beta-lactamase enzymes that depend on Zinc ions for their activity.[6] The data in support of this combination is mostly retrospective, with prospective RCTs showing conflicting evidence.[7,8] Nonetheless, this has led to widespread enthusiasm about the potential application of EDTA in Indian markets where it continues to be combined with meropenem and even polymyxin B by various manufacturers. The most common mechanism of resistance to polymyxins is through alteration in lipopolysaccharide structure, as polymyxins interact primarily with negatively charged Lipid A component of LPS.[9] Hence, we are unsure how the addition of EDTA is going to help overcome polymyxin resistance or confer any additional benefit.

In summary, we feel the use of such antibiotic combinations should be discouraged, outside the ambit of well-designed RCTs, or unless we have more reliable data supporting its use. Given the introduction of a plethora of newer antimicrobials in recent years, perhaps a clinical guideline addressing the judicious use of newer antimicrobial combinations would help physicians in making better therapeutic decisions for their patients.

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References

1. Hetzler L, Kollef MH, Yuenger V, Micek ST, Betthauser KD. New antimicrobial treatment options for severe Gram-negative infections. Curr Opin Crit Care 2022;28(5):522–533. DOI: 10.1097/MCC.0000000000000968.
2. Kundu R, Chowdhury SR. Takeaways from the recarbrio conundrum: Has the FDA jumped the gun? Indian J Microbiol 2023;63(4):702–703. DOI: 10.1007/s12088-023-01105-5.
3. Bush K, Bradford PA. β-Lactams and β-Lactamase inhibitors: An overview. Cold Spring Harb Perspect Med 2016;6(8):a025247. DOI: 10.1101/cshperspect.a025247.
4. Prayag PS, Patwardhan SA, Panchakshari S, Sambasivam R, Dhupad S, Soman RN, et al. Ceftazidime-avibactam with or without aztreonam vs polymyxin-based combination therapy for carbapenem-resistant Enterobacteriaceae: A retrospective analysis. Indian J Crit Care Med 2023;27(6):444–450. DOI: 10.5005/jp-journals-10071-24481.
5. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. Clin Infect Dis 2023:ciad428. DOI: 10.1093/cid/ciad428.
6. Singh S, Sahu C, Patel SS, Singh A, Yaduvanshi N. A comparative *in vitro* sensitivity study of "ceftriaxone-sulbactam-EDTA" and various antibiotics against gram-negative bacterial isolates from intensive care unit. Indian J Crit Care Med 2020;24(12):1213–1217. DOI: 10.5005/jp-journals-10071-23573.
7. Samantaray S, Kumar D, Bohra GK, Meena DS, Agarwal A, Chaudhary GR, et al. Effect of Ceftriaxone+sulbactam+disodium EDTA combination in treatment of complicated urinary tract infections caused by metallo beta-lactamase producing Enterobacterales: An open label randomized controlled trial. Open Forum Infectious Diseases 2023;10 (Supplement_2). DOI: https://doi.org/10.1093/ofid/ofad500.451.
8. Mir MDA, Chaudhary S, Payasi A, Sood R, Mavuduru RS, Shameem M. CSE (Ceftriaxone+ Sulbactam+ Disodium EDTA) versus meropenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: PLEA, a double-blind, randomized noninferiority trial. Open Forum Infect Dis 2019;6(10):ofz373. DOI: 10.1093/ofid/ofz373.
9. Moffatt JH, Harper M, Boyce JD. Mechanisms of polymyxin resistance. Adv Exp Med Biol 2019;1145:55–71. DOI: 10.1007/978-3-030-16373-0_5.