



Letter to Editor

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Role of Aminoglycosides and Fosfomycin in Enteric Fever: A Call for Clinical Trials

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To Cite This Article: Rizwanullah*, Fardin Akbar Hyderi, Bubli Ahmed, Waqar Khan, Shivani Shah, et al. Role of Aminoglycosides and Fosfomycin in Enteric Fever: A Call for Clinical Trials. *Am J Biomed Sci & Res.* 2025 27(3) *AJBSR.MS.ID.003558*, DOI: [10.34297/AJBSR.2025.27.003558](https://doi.org/10.34297/AJBSR.2025.27.003558)

Received: 📅 June 06, 2025; **Published:** 📅 June 16, 2025

Abstract

The escalating Antimicrobial Resistance (AMR) in enteric fever, particularly in South Asia, has compromised the efficacy of standard treatments. Recent data from Pakistan reveal high resistance rates to first-line agents, including third-generation cephalosporins and azithromycin, prompting the need for alternative therapies. This letter highlights the overlooked potential of aminoglycosides (amikacin and gentamicin) and fosfomycin, which have shown high in vitro sensitivity against *Salmonella* Typhi. Supported by regional studies and case reports, we advocate for the urgent initiation of clinical trials to evaluate the clinical efficacy and safety of these agents. Their inclusion in treatment protocols may offer a cost-effective solution to the growing burden of drug-resistant typhoid fever.

Letter to Editor

The management of enteric fever, predominantly caused by *Salmonella enterica* serovar Typhi and Paratyphi, is increasingly challenged by the rising tide of Antimicrobial Resistance (AMR). In endemic regions such as Pakistan and neighboring South Asian countries, the surge in Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) strains has eroded the efficacy of conventional treatment regimens, leading to increased treatment failures, prolonged hospital stays, and higher healthcare costs.

The recent publication offers vital insights into the resistance

patterns observed in tertiary care settings in Peshawar. The study, based on 3,137 blood culture-positive cases of *Salmonella* species, demonstrates striking resistance rates: amoxicillin-clavulanate (80.1%), co-trimoxazole (66.6%), chloramphenicol (86.9%), ceftriaxone (79.7%), and ciprofloxacin (51.6%). Even azithromycin, considered one of the few remaining oral options for XDR typhoid, displayed reduced sensitivity (66.5%). These findings are consistent with broader surveillance reports highlighting the erosion of empirical therapies for typhoid fever in Pakistan [1-3]. Amid this resistance crisis, the study highlights a potentially underutilized

therapeutic avenue: aminoglycosides and fosfomycin. Amikacin showed a sensitivity of 90.7%, gentamicin 81.5%, and fosfomycin 93.4%-impressive figures, particularly in contrast to the waning sensitivity of first-line and oral agents. These results echo earlier findings that reported significant in vitro activity of gentamicin and amikacin against *S. Typhi* and advocated for their potential use in treatment regimens in regions facing MDR strains [4].

Moreover, an Indian study reaffirmed the potency of aminoglycosides. Their antibiogram analysis revealed sustained in vitro sensitivity of *S. Typhi* isolates to amikacin and gentamicin, underscoring the therapeutic viability of these agents where resistance to cephalosporins and fluoroquinolones is rampant. Given the comparable regional epidemiology and resistance trends, these findings are especially relevant to the Pakistani clinical landscape [5]. Adding further weight to this proposition, a documented case showed successful treatment of a patient with MDR and Extended-Spectrum Beta-Lactamase (ESBL)-producing *S. Typhi* using a combination of meropenem and fosfomycin. Fosfomycin, despite its limited clinical use in typhoid treatment, holds promise due to its distinct mechanism of action, low toxicity, and potential for oral administration in uncomplicated cases [6].

Despite these promising data, neither aminoglycosides nor fosfomycin are included in current typhoid treatment guidelines-an omission that points to a critical evidence gap. Their use remains empirical and largely unsupported by clinical trial data. It is imperative that Randomized Controlled Trials (RCTs) be urgently initiated to evaluate the safety, efficacy, pharmacokinetics, and cost-effectiveness of these agents-both alone and in combination. Such trials would be particularly valuable in low-resource settings, where alternatives to costly carbapenems are desperately needed. Furthermore, integrating these findings into broader public health interventions-such as Salmonella vaccination, robust antibiotic stewardship programs, and sustained microbiological surveillance-will be essential to reducing the burden of resistant enteric fever and preserving the efficacy of existing drugs.

In conclusion, we strongly advocate for the clinical evaluation of

aminoglycosides and fosfomycin in the treatment of drug-resistant enteric fever. In light of the current evidence and increasing resistance to mainstream agents, these drugs may represent a valuable addition to our treatment arsenal. Addressing this knowledge gap through well-structured clinical trials is not only timely but necessary to confront the growing AMR crisis in enteric fever management.

Acknowledgments

None.

Conflict of Interest

None.

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