

## EDITORIAL

# Fosfomycin: A Revived Antibiotic for Urinary Tract Infections

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Urinary tract infections (UTIs) are the most commonly encountered bacterial infections. Approximately 100,000 hospitalizations occur due to UTIs mostly in susceptible population like women, elderly, diabetics, patients on indwelling catheters, patients with bladder involvement due to spinal cord diseases or multiple sclerosis etc.

Enterobacteriaceae are commonly implicated organisms. Various studies from India have shown presence of *Escherichia coli* (E coli) as the commonest bacteria causing UTI followed by *Klebsiella*.<sup>1</sup> Multi-resistant enterobacteriaceae due to the production of extended spectrum  $\beta$ -lactamases (ESBL) have become very common in India.<sup>2,3</sup>

Just as in other infections there is an increasing incidence of multi drug resistant and extensively drug resistant bacteria causing UTI especially in patients with co morbidities and repeated antibiotic exposures.<sup>4,5</sup> Easy availability of over the counter antibiotics and inappropriate antibiotic use compound the problem. Symptomatic UTIs are often treated on empiric basis for short duration without sending urine cultures causing incomplete clearance of the bacteria and development of resistance. Rapidly increasing resistance in uropathogens compels physicians to use still higher antibiotics like beta lactam betalactamase inhibitors, carbapenems and now even colistin. The resistance spectrum

of pathogens varies in different regions.

Extended spectrum beta lactamase (ESBL) are plasmid or chromosomally mediated beta lactamases with broad activity against penicillins, cephalosporins and monobactams. They inactivate the beta lactam antibiotic function by breaking amide bond of beta lactam ring. 28-84% ESBL production is reported from various Indian studies.<sup>3,6,7</sup> Carbapenemase enzyme renders carbapenems like imipenem and meropenem useless. These are of serious concern as there are very few new antibiotics in the pipeline.

There is a worldwide concern about the MDR and XDR organisms causing UTI and Infectious Diseases Society of America recommends that the physicians obtain information on local resistance spectrum of organism causing UTIs and that ongoing surveillance be conducted to monitor changes in susceptibility of uropathogens.<sup>8</sup>

Fosfomycin, originally named phosphonomycin, was discovered in Spain in 1969.<sup>9</sup> Fosfomycin inhibits phosphoenolpyruvate transferase, the first enzyme involved in the synthesis of peptidoglycan, inhibiting cell-wall synthesis.<sup>10</sup>

There are three forms of Fosfomycin: Fosfomycin tromethamine (a soluble salt) and Fosfomycin calcium for oral use, and Fosfomycin disodium for intravenous use. Fosfomycin, is a safe antibiotic with limited adverse events.

Oral Fosfomycin is mainly

used in the treatment of urinary tract infections, particularly those caused by *Escherichia coli* and *Enterococcus faecalis*.

It remains a reliable therapeutic option for uncomplicated UTI due to its main advantages, including single dose usage and very high and sustained urinary concentrations that rapidly kill bacteria, reducing the opportunity for mutant selection.

Intravenous fosfomycin has been administered in combination with other antibiotics for the treatment of nosocomial infections due to multidrug-resistant (MDR) bacteria.<sup>11-13</sup> Intravenous fosfomycin is available in India since 2016. The recommended dose for complicated UTI is 12-16 g in 2-3 divided doses.

The laboratory methods that have been used for the determination of *in vitro* susceptibility of Gram-positive and Gram-negative pathogens to Fosfomycin include agar (Mueller-Hinton agar) dilution, broth dilution, disk diffusion, and E test techniques.

In this issue of the Journal, Patel et al present their findings about Fosfomycin susceptibility using E test in urinary tract infections caused by enterobacteriaceae. Of the 72 isolates 57(79%) were susceptible, 5 were intermediate and 10 were resistant to fosfomycin. There was 92% susceptibility in ESBL producing enterobacteriaceae and 72.34% sensitivity in

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carbapenemase resistant bacteria. Number of resistant isolates was more by EUCAST as compared to CLSI breakpoint criteria.

Using more stringent criteria may help for selecting appropriate antibiotic doses with the goal of increasing treatment efficacy and reducing the risk of selecting multidrug-resistant pathogens.

Microbiological evidence of high in vitro susceptibility of the enterobacteriaceae to Fosfomycin makes it a potentially effective antimicrobial option for UTIs.

It necessitates further exploration in order to determine the appropriate therapeutic regimen, whereas the possibility of monotherapy to induce resistance in vivo requires careful clinical studies.

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