# Other antimicrobials of interest in the era of extended-spectrum β-lactamases: fosfomycin, nitrofurantoin and tigecycline

*J. Garau*

Department of Medicine, Hospital Mutua de Terrassa, University of Barcelona, Barcelona, Spain

## ABSTRACT

The progressive increase of extended-spectrum β-lactamase (ESBL) -producing enteric bacteria in recent years has called for a re-evaluation of current antibiotic therapy for these infections. The activity and potential use of two old antimicrobials, nitrofurantoin and fosfomycin, and the new compound tigecycline for treatment of infections due to ESBL-producing Enterobacteriaceae, with special emphasis on E. coli, are reviewed. Fosfomycin continues to be active against the most common uropathogens; in a recent survey from Spain, among the 428 ESBL-producing isolates, the resistance rate of *E. coli* to fosfomycin was 0.3%, whereas the resistance rate of K. pneumoniae was 7.2%. Other recent surveys, from other parts of the world, confirm the activity of fosfomycin against ESBL-producing E. coli. The rate of resistance to nitrofurantoin in recent surveys in the USA and Canada was 1.1% among 1142 isolates of E. coli from outpatient urinary isolates. However, among 115 clinical isolates of *E. coli* ESBL producers, only 71.3% were sensitive to nitrofurantoin. Also, *E. coli* resistance to nitrofurantoin has been reported to be high in a recent survey in Latin American hospitals and in Italy. Tigecycline is a glycylcycline that circumvents efflux and ribosomal protection, the two most frequent genetic mechanisms of tetracycline resistance. The recent activity of tigecycline against 285 nonclonally related isolates expressing well-characterised ESBLs from hospital settings and the community reveal susceptibility rates for tigecycline of 97.5%. Because responses to nitrofurantoin may be less satisfactory and may require longer courses of therapy, nitrofurantoin is considered to be an alternative, rather than a first-line, therapeutic agent for this clinical syndrome. Fosfomycin trometamol is a safe and effective alternative for the treatment of cystitis and asymptomatic UTI during pregnancy, and has become, in many countries, the first choice for treatment of any type of cystitis. Finally, for treatment of systemic infections in the hospital setting, tigecycline could be an option that would reduce selection for ESBL-producing organisms.

**Keywords** ESBL, *Escherichia coli*, fosfomycin, nitrofurantoin, review, tigecycline, urinary tract infection

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## INTRODUCTION

The progressive increase of extended-spectrum β-lactamase (ESBL) -producing enteric bacteria in recent years has generated the need to re-evaluate current antibiotic therapy for these infections. The matter is increasingly important today in countries where the prevalence of ESBL-producing *Escherichia coli* has increased considerably at the community level, fuelled by the emergence and dissemination of CTX-M enzymes in this species in many parts of the world [1]. The burden of disease due to *E. coli* infections is enormous. In the elderly population, the incidence of community-onset *E. coli* bacteraemia was 150 cases/100 000 person-years, which is approximately three times higher than the rate of pneumococcal bacteraemia in this population. It is also substantially higher than the rates of community-onset bacteraemia due to *Staphylococcus aureus*, group A streptococci and group B streptococci in persons ≥65 years of age, as estimated from surveillance studies of other populations. These comparisons suggest that *E. coli* is the most common cause of community-onset bacteraemia in the elderly population [2].

Corresponding author and reprint requests: J. Garau, Department of Medicine, Hospital Mutua de Terrassa, University of Barcelona, Plaza Dr Robert 5, 08221 Terrassa, Barcelona, Spain
E-mail: jgarau@garmar.e.telefonica.net

The prevalence of CTX-M types has increased dramatically since 1995 in many parts of the world. All confer resistance to amino- and ureidopenicillins, oxyimino-cephalosporins and monobactams, but not to 7-α-substituted β-lactams. The ESBL strains are increasingly associated with resistance to other non-related antimicrobials and pose significant therapeutic challenges. This associated resistance to other classes of antimicrobials is especially problematic in urinary isolates and underscores the therapeutic challenge that they represent.

In this article, the activity and potential use of two old antimicrobials, nitrofurantoin and fosfomycin, and the new compound tigecycline in infections due to ESBL-producing Enterobacteriaceae, with special emphasis on *E. coli*, are reviewed.

## FOSFOMYCIN

Fosfomycin is a bactericidal antibiotic that acts as a cell-wall inhibitor by interfering with the first step in peptidoglycan biosynthesis. It has a broad spectrum of activity, with a wide therapeutic range and characteristic pharmacological properties. It penetrates excellently into various tissues [3] and cerebrospinal fluid [4], and, in Europe, is frequently administered in combination with other antimicrobial agents to combat severe bacterial infections. It exerts bactericidal activity under anaerobic conditions [5], as is the case within encapsulated purulent lesions, and has negligible protein-binding activity.

Resistance to fosfomycin develops rapidly in *E. coli* under experimental conditions, but in spite of the relatively high mutation rate *in vitro*, resistance in clinical isolates is rare. In-vitro-selected mutants show a decreased growth rate in both the absence and presence of fosfomycin; this provides an explanation for why most of the resistant bacteria have difficulty in becoming established in the bladder, due to their lowered fitness [6]. Also, many strains of *E. coli* can adhere to the bladder epithelium, and, as a result, they can be maintained in the bladder even though their growth rate is below the threshold required to prevent wash-out. Thus, if the antibiotic also decreases adhesion, this might further prevent bacterial establishment. Indeed, it has been shown that fosfomycin decreases bacterial adhesion [7], and this effect, conceivably, could also reduce resistance development. Although the mutator phenotypes found among *E. coli* expressing CTX-M β-lactamases have an increased propensity to fosfomycin resistance [8], this resistance remains rare among *E. coli* expressing CTX-M enzymes in countries with a high use of fosfomycin in the treatment of urinary tract infections (UTIs) [9].

Fosfomycin tromethamine is a stable salt of fosfomycin that is licensed for the single-dose treatment of acute uncomplicated UTIs caused by susceptible organisms. In-vitro time-kill kinetics of fosfomycin against *E. coli* and *Proteus mirabilis* show primarily concentration-dependent activity, with a prolonged post-antibiotic effect [10]. After oral administration of 3 g of the trometamine salt of fosfomycin, high urinary concentrations (1000–4000 mg/L) are achieved, and concentrations remain at 100 mg/L for at least 30–40 h, guaranteeing good efficacy in the treatment of uncomplicated UTI even after a single administration [11].

After many years of fosfomycin use, fosfomycin continues to be active against the most common uropathogens, and there is a very low incidence of resistant strains in *E. coli* (*c.* 2%). It is becoming increasingly common to isolate ESBL-producing *E. coli* from outpatients with uncomplicated UTIs. It is common to find that the same plasmid coding for ESBL also contains genes conferring resistance to several groups of antimicrobial agents, such as aminoglycosides and co-trimoxazole. The concurrence of quinolone resistance, particularly in ESBL-producing *Klebsiella pneumoniae*, is frequent, there being few alternatives for the appropriate oral treatment of uncomplicated UTIs caused by ESBL-producing microorganisms.

In a recent survey done in Spain, among the 428 ESBL-producing isolates studied, 417 (97.4%) were susceptible to fosfomycin (MIC ≤64 mg/L). The resistance rate of *E. coli* to fosfomycin was 0.3%, whereas the resistance rate of *K. pneumoniae* was 7.2%. Co-trimoxazole and ciprofloxacin were the least active antibiotic agents against ESBL-producing isolates (sensitivity <50%). Only one strain of *E. coli*, among all 290 tested, showed intermediate susceptibility to fosfomycin (MIC 128 mg/L). *K. pneumoniae* isolates had the highest MICs for fosfomycin ($MIC_{50}$ and $MIC_{90}$ of 16–64 mg/L) but are still within the susceptible range, whereas more than 90% of *E. coli* isolates showed very low MICs (≤4 mg/L) [9]. These results are similar to those described in previous