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Short Communication

In vitro fosfomycin study on concordance of susceptibility testing methods against ESBL and carbapenem-resistant Enterobacteriaceae

Ausilia Aprile[a], Guido Scalia[a,b], Stefania Stefani[a], Maria Lina Mezzatesta[a,*]

[a] Department of Biomedical and Biotechnological Sciences, Section of Microbiology, University of Catania, Italy
[b] U.O.C. Laboratory Analysis Unit, A.O.U. 'Policlinico-Vittorio Emanuele', Via S. Sofia 78, Catania 95123, Italy

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ABSTRACT

Objectives: The increasing emergence and diffusion of multidrug-resistant (MDR) pathogenic bacteria, both in hospital and community settings, is inducing clinicians to reconsider old antibiotics, such as fosfomycin, to overcome the difficulties posed by these microorganisms. Recent studies have reported good *in vitro* activity of fosfomycin against extended spectrum ß-lactamases (ESBL) and carbapenem-resistant Enterobacteriaceae. The aim of this study was to assess the*in vitro* activity of fosfomycin by different methods against 120 clinical MDR isolates.
Methods: Fosfomycin minimum inhibitory concentrations were determined using the agar dilution reference method (AD), gradient test (GT), broth microdilution method (BMD), according to CLSI recommendations, and automated systems (VITEK 2 and BD Phoenix) against 85 carbapenem-resistant *Klebsiella pneumoniae* and 35 ESBL-producing *Escherichia coli*. Agreement and discrepancies between the evaluated methods and the reference method were calculated.
Results: Fosfomycin showed very good activity against ESBL-producing *E. coli* (88.6%). Excellent agreement (100%) between the three (AD, BMD and GT) susceptibility methods was found for *E. coli*. No major errors were observed. The fosfomycin resistance rate ranged from 24% (KPC-producing) to 100% (NDM-OXA-48 co-producing) *K. pneumoniae*. For all carbapenem-resistant *K. pneumoniae* strains, categorical agreement was >90% for all methods except for VITEK 2, which was 84%.
Conclusions: When ESBL *E. coli* isolates are found to be susceptible to fosfomycin with automated systems, it is not necessary to verify these results with the AD reference method; while for resistant strains, the GT can be used. In cases of KPC *K. pneumoniae* resistant to fosfomycin, the AD method is the only reference method.

1. Introduction

Antimicrobial resistance is globally recognized as one of the greatest threats to public health. Of particular concern are infections caused by resistant Gram-negative bacilli. Gram-negative antimicrobial resistance results largely from ß-lactamases, which are enzymes that bind and deactivate ß-lactam antibiotics, rendering them ineffective [1]. For years, carbapenems have been used successfully to treat infections caused by resistant Enterobacteriaceae, such as *Escherichia coli* and *Klebsiella pneumoniae*, including those producing extended spectrum ß-lactamases (ESBLs).

However, carbapenemase-producing Enterobacteriaceae commonly reported as carbapenem-resistant Enterobacteriaceae (CRE) have recently emerged, which confer broad resistance to most ß-lactam antibiotics including 'last-resort' carbapenems [2]. CRE can cause a number of serious infections and currently there is a limited selection of treatment options for these infections. Clinicians have been forced to re-evaluate the use of agents rarely used because of concerns regarding efficacy and/or toxicity, such as polymyxins, aminoglycosides and fosfomycin [3].

A number of *in vitro* studies have demonstrated that fosfomycin has excellent activity against many multidrug-resistant (MDR) Gram-negative bacteria, including ESBL and CRE, isolated from patients with urinary tract infections (UTIs) [4]. To be categorized correctly in clinical reports, the clinical use of fosfomycin requires