

## SHORT COMMUNICATION

### ***In vitro* activity of cefepime against extended spectrum $\beta$ -lactamase- producing *Escherichia coli* and *Klebsiella pneumoniae* from clinical specimens at Bugando Medical Centre, Mwanza, Tanzania**

STEPHEN E. MSHANA<sup>1</sup>, BENSON R. KIDENYA<sup>2</sup> and JOHANNES B. KATARAIHYA<sup>3</sup>

<sup>1</sup>Department of Microbiology and Immunology, Weill Bugando University College of Health Sciences

<sup>2</sup>Department of Biochemistry and Molecular Biology, Weill Bugando University College of Health Sciences

<sup>3</sup>Department of Internal Medicine Weill Bugando University College of Health Sciences

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**Abstract:** There is an increase in isolation of extended spectrum beta-lactamase (ESBL) producing isolates from clinical samples worldwide. In developing countries the treatment option of ESBL producing isolates is limited. Recently fourth generation cephalosporins have been introduced for use in Tanzania. This study was done to determine *in vitro* activity of cefepime against ESBL producing clinical isolates. Disc diffusion testing was performed to 235 ESBL producing isolates; of which 73 (31%) were *Escherichia coli* and 162 (69%) *Klebsiella pneumoniae*. The sensitivity rate of *E. coli* and *K. pneumoniae* to cefepime were 15.1% and 4.3%, respectively ( $P=0.012$ ); intermediate sensitivity rate was observed in 13.7% for *E. coli* and 19.8% for *K. pneumoniae*. The mean zones of inhibition diameter among sensitive isolates were 24.9mm and 20.0mm for *E. coli* and *K. pneumoniae*, respectively ( $P=0.0085$ ). Cefepime is less active against ESBL producing organisms; hence the use of this drug should be guided using local resistance profile.

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**Key words:** *Escherichia coli*, *Klebsiella pneumoniae*, cefepime, susceptibility, Tanzania

Third generation cephalosporins are widely used worldwide in the treatment of severe infection due to enteric gram negative bacteria (Dafna *et al.*, 2007). The use of these drugs is limited in places with high prevalence of extended spectrum beta-lactamase (ESBL) producing isolates (Paterson *et al.*, 2001). The treatment option for ESBL producing isolates is expensive and most often not available in most hospitals in the developing countries. In Tanzania the prevalence of ESBL among *Escherichia coli* ranges from 25%-45% and the problem is worse with the *Klebsiella pneumoniae* isolates whereby more than 50% of the isolates are ESBL producers (Mshana *et al.*, 2009; Kayange *et al.*, 2010; Moyo *et al.*, 2010). ESBL producing isolates in Tanzania have been involved in wound infections, urinary tract infections, septicaemia and meningitis. High mortality has been observed with infections associated with ESBL producing isolates in Tanzania (Bloomberg *et al.*, 2008; Kayange *et al.*, 2010). Fourth generation cephalosporins are relatively cheap when compared to carbapenems and tigecycline, but their use for the ESBL producing isolates is limited (Paterson *et al.*, 2001; Zanetti *et al.*, 2003; Dafna *et al.*, 2007). About 75%-80% of the Enterobacteriaceae resistant to ceftazidime are susceptible to cefepime (Dafna *et al.*,

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<sup>1</sup> Corresponding Author: [mshana72@yahoo.com](mailto:mshana72@yahoo.com)

2007). Cefepime has a rapid penetration through the outer membrane (less time for  $\beta$ -lactamase effect) and have high affinity for penicillin binding proteins and stable to variety of *B*-lactamases (Zanetti *et al.*, 2003).

Clinical efficacy of cefepime is equal to ceftazidime in nosocomial pneumonia and neutropenic fever and equal to ceftriaxone in severe community acquired pneumonia; it is therefore reserved for empirical therapy for nosocomial infections in which highly resistant organisms are anticipated (Dafna *et al.*, 2007). Due to high prevalence of ESBL producing isolates in Tanzania, this study was done to determine *in vitro* susceptibility of these isolates to cefepime in order to provide an insight on the clinical use of this drug in our-setting.

A total of 235 ESBL producing isolates from clinical specimens were used in this study. These isolates were from urine, wound swabs, pus and blood. They were identified using in house biochemical testing as described previously (Mshana *et al.*, 2009) and ESBL producers were confirmed using disc approximation method (CLSI, 2006).

Disc diffusion testing was used to determine *in vitro* susceptibility of ESBL producing isolates to cefepime (Cadilla Pharmaceuticals, India and Oxoid UK). Colonies from overnight pure culture were suspended to 0.5 McFarland using normal saline and inoculated on Mueller Hiton agar (Oxoid, UK) on 15mm Petri dish. Using sterile forceps cefepime discs were placed on the centre and plates incubated at 37°C for 18 hr. Interpretation was done according to the Clinical Laboratory Standard Institute (CLSI); the diameter of  $\leq 14$ mm was recorded as resistant, 15-17mm as intermediate sensitivity and  $\geq 18$ mm as sensitive.

The majority of the ESBL producing *E. coli* and *K. pneumoniae* were found to be resistant to cefepime, with resistance rates of 84.9% and 95.7%, respectively (Table 1). While carbapenems continue to be preferred as drug of choice for the treatment of extended spectrum  $\beta$ -lactamase (ESBL)-producing bacteria (Paterson *et al.*, 2001), this option is expensive for most developing countries like Tanzania. Cefepime might be an alternative choice in such settings. However its use requires availability of local data on the susceptibility of ESBL producing isolates to this agent. *In vitro* susceptibility results are useful before cefepime is clinically used to achieve good outcome on patients suffering serious infection due to ESBL producing bacteria (Zanetti *et al.*, 2003). In our setting, with high resistance rate observed in this study cefepime should not be used in patients with treatment failure of the third generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime, cefpodoxime) or in patients suspected to have infections due ESBL producing organisms unless susceptibility results are available.

**Table 1: Susceptibility of 235 ESBL producing Isolates to cefepime (Fourth Generation Cephalosporins)**

Isolate	Resistance	Intermediate	Sensitive	Total
<i>Escherichia coli</i>	52(71.2%)	10(13.7%)	11(15.1%)	73

<i>K. pneumoniae</i>	123(75.9%)	32 (19.8%)	7(4.3%)	162
<b>Total</b>	<b>175(74.5%)</b>	<b>42(17.9%)</b>	<b>18(7.7%)</b>	<b>235</b>

$P=0.012$

The sensitivity rate of these isolates to cefepime in this study were 15.1% and 4.3% among *E. coli* and *K. pneumoniae* respectively ( $P=0.012$ ). The mean zone of inhibition of sensitive *E. coli* of  $24.9\pm 4.3$ mm was higher when compared with mean diameter of sensitive *K. pneumoniae* isolates (Table 2) ( $P=0.00085$ ). No significant difference was observed between mean diameters of resistance isolates.

When the activity of third generation cephalosporins are compared to fourth generation cephalosporin (cefepime); cefepime has an extended spectrum of activity, enhanced stability to  $\beta$ -lactamase hydrolysis, and superior penetration through the outer membrane of Gram-negative bacteria (Dafna *et al.*, 2007). This supports the use of cefepime for treatment of infections due to ESBL producing bacteria.

**Table 2: Mean zone diameter and Standard deviation of *Escherichia coli* and *Klebsiella pneumoniae* ESBL producing isolates against Cefepime**

Isolate	Sensitive		Resistant	
	Mean diameter	SD	Mean diameter	SD
<i>E. coli</i>	24.9	4.3	10.9	2.5
<i>K. pneumoniae</i>	20.0	2.8	11.3	2.6

Clinicians treating serious infections due multi-resistant Gram negative bacteria are required to prescribe the most useful locally-available broad-spectrum parental antibiotics. The empirical treatment needs retrospective data on the susceptibility profile of circulating organisms, without these data the prescription might be far from ideal and treatment failure is likely. These data on cefepime in ESBL-producing *K. pneumoniae* and *E. coli* are crucial information to clinicians in our setting so that appropriate treatment is administered timely to achieve good outcome.

In conclusion, the use of cefepime in treating infections due to ESBL producing bacteria should depend on availability of local susceptibility data.

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