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Oral treatment options for patients with urinary tract infections caused by extended spectrum *βeta-lactamase* (ESBL) producing *Enterobacteriaceae*

Nadeem Sajjad Raja*

Department of Clinical Micobiology, East Sussex Healthcare Trust, Hastings, England, UK

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ABSTRACT

Introduction: Frequent use of different antibiotics to treat urinary tract infections (UTIs) exerts a variety of selective pressure on pathogens which ultimately lead to the antimicrobial resistance. Extended Spectrum βeta-Lactamase (ESBL) producing *Enterobacteriacae* causing UTIs, which are usually multidrug resistant organisms, pose a great therapeutic treatment challenge. Rediscovery of forgotten antibiotics such as pivmecillinam, fosfomycin, and nitrofurantoin may be helpful in this situation until the discovery of new agents. The main aim of present study was to determine the prevalence of ESBL producing *Enterobacteriacae* causing UTIs and their sensitivity profile to determine alternate effective oral treatment options.

Methods: This retrospective study was conducted to determine the prevalence of ESBL producing *Enterobacteriacae* from urine samples and their sensitivity profile (pivmecillinam, fosfomycin, nitrofurantoin, trimethoprim and ciprofloxacin) from September 2015 to September 2017.

Results: A total of 986 organisms were isolated from the urine samples of 680 patients. Approximately 77% isolates were obtained from female patients (526). Of 986 organisms, *Escherichia coli* was the most common isolated organism (889, 90%); followed by *Klebsiella* species (71, 7%) and other *Enterobacteriacae* (26, 3%). Of 889 *E. coli*, approximately 98%, 96%, and 93% were found to be sensitive to fosfomycin, pivmecillinam and nitrofurantoin respectively. On the other hand pivmecillinam was most effective against *Klebsiella* species (83%, 59); followed by fosfomycin (62%, 44) and nitrofurantoin (42%, 30). Of 26 other *Enterobacteriacae*, 23 (88%), and 22 (85%) were sensitive to pivmecillinam and fosfomycin while lower sensitivity rate (15%, 4) was noted against nitrofurantoin. More than 95% of all ESBL producing *Enterobacteriacae* were sensitive to pivmecillinam, fosfomycin and nitrofurantoin. Trimethoprim and ciprofloxacin were least effective.

Conclusion: The emergence of multidrug resistant ESBL producing *Enterobacteriacae* restricts significantly the therapeutic options. This study shows higher sensitivity rates to pivmecillinam, fosfomycin and nitrofurantoin. We recommend their use to treat uncomplicated UTIs due to ESBL producing *Enterobacteriacae*.

Introduction

Urinary tract infections (UTIs) are the second most common infections which require antibiotics. Approximately 150 million cases of UTIs occur every year worldwide, costing more than 6 billion dollars [1–3]. Frequent use of different antibiotics to treat UTIs exert a variety of selective pressure on pathogens which ultimately lead to the antimicrobial resistance in the organisms. Antimicrobial resistance is widespread and it is a cause of major concern in the world. *Enterobacteriaceae* are the common causative agents of UTIs. The distribution of Extended Spectrum *βeta-Lactamase* (ESBL) producing *Enterobacteriacae* in the hospitals has been reported worldwide while the carriage of this group of organisms in the community is still low; however it is increasing now [4]. ESBL producing *Enterobacteriaceae* are resistant to frequently used oral antibiotics for example trimethoprim, quinolones, cephalosporins and penicillins that pose a therapeutic challenge. An infection caused by ESBL producing organism is linked to a worse clinical outcome, delayed microbiological and clinical response, prolonged hospital-

* Corresponding author at: Department of Clinical Micobiology, East Sussex Healthcare Trust, Hastings, TN37 7RD, East Sussex, England, UK.
E-mail address: nadeem.raja@nhs.net

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isation, higher treatment costs and higher mortality [5]. Resistance to carbapenems poses even a greater challenge to the clinicians and it has become a severe threat to the health worldwide. Multidrug resistance is a risk factor for inappropriate empirical treatment and it is associated with increased mortality [6]. There is an urgent need for discovery of new antimicrobials. Rediscovery of forgotten antibiotics such as pivmecillinam, fosfomycin, and nitrofurantoin may be helpful in this situation until the discovery of new antimicrobial agents [7,8]. Fosfomycin, a bactericidal antimicrobial agent, has been used to treat UTIs for more than 40 years and it has good activity against Gram positive and negative organisms. It has become increasingly important to treat multidrug resistant organisms causing UTIs. Nitrofurantoin has also been used to treat UTIs for the last 50 years [9]. Pivmecillinam, an oral antibiotic, has a good clinical and microbiological activity against multidrug resistant organisms and it is being used to treat uncomplicated UTIs [3].

Knowledge of local prevalence of ESBL producing *Enterobacteriaceae* causing UTIs and their antibiotic susceptibility pattern may help to select effective oral antimicrobial treatment as suggested by recent clinical guidelines [10]. The main aim of this study was to determine the prevalence of ESBL producing *Enterobacteriaceae* causing UTIs and their antibiotic sensitivity profile in order to discover alternative effective oral treatment options.

Material and methods

This retrospective study was conducted from September 2015 to September 2017 in East Sussex Healthcare NHS Trust (ESHT), England. ESHT consists of two acute hospitals with a total of 800 beds. Patients from the community and hospital with confirmed UTI due to ESBL producing *Enterobacteriaceae* were included in this study. Midstream or catheter stream urine samples obtained from patients were cultured onto 5% blood agar and Eosin-Methylene Blue (EMB) agar with 0.01 mL calibrated loops by a semi quantitative technique. Inoculated culture plates were incubated for 24 h at 37 °C. More than 10^5 organisms per mL of urine considered as a positive culture. The isolated bacteria were identified by the conventional and automated method systems such as API (BioMeurex) and Maldi-Tof. Antibiotic susceptibility testing on ESBL producing *Enterobacteriaceae* was done by the disc diffusion method in accordance with EUCAST (The European Committee on Antimicrobial Susceptibility Testing) [11]. ESBL screening was done using discs of cefpodoxime (10 μg) and Ceftazidime (10 μg) and ceftriaxone (30 μg) or cefotaxime (5 μg). Combination discs (discs containing the cephalosporins alone and with combination clavulanic acid) were also employed to detect ESBL as per EUCAST guidelines (EUCAST) [11]. Further confirmation of ESBL production was carried out using the VITEK II (bioMerieux, Marcy l'Etoile, France). Patients' demographics and laboratory data were collected from the Pathology information system. Data on pivmecillinam, fosfomycin, nitrofurantoin, trimethoprim and ciprofloxacin was also collected. No clinical information were collected.

Results

Patient demographics

During the study period, the urine samples on 680 (females 526) patients were sent to the microbiology laboratory for processing. In this study, 63% (334/526) females and 72% (111/174) male were more than 60 years old.

Table 1
Antibiotic sensitivity rates for pivmecillinam, fosfomycin and nitrofurantoin.

Organism/antibiotics	Pivmecillinam (%)	Fosfomycin (%)	Nitrofurantoin (%)
E. coli n = 889	855 (96)	869 (98)	826 (93)
Klebsiella species n = 71	59 (83)	44 (62)	41(58)
Other *Enterobacteriacae* n = 26	23 (88)	22 (92)	4(17)
Total n=986	937 (95)	935 (95)	871 (88)

Table 2
Antimicrobial resistance in trimethoprim and ciprofloxacin.

Organism/antibiotics	Trimethoprim (%)	Ciprofloxacin (%)
E. coli n = 889	697 (78)	554 (62)
Klebsiella species n = 71	52 (73)	35 (49)
Other *Enterobacteriacae* n = 26	20 (83)	5 (21)
Total (986)	769 (78)	594 (60)

Microbiology

A total of 986 ESBL producing *Enterobacteriaceae* were isolated (Fig. 1). Approximately 77% organisms were isolated from female urine samples. Of 986 organisms, *Escherichia coli* was the most common organism (889, 90%); followed by *Klebsiella* species (71, 7%) and other *Enterobacteriaceae* (26, 3%) (Fig. 1). A total of 609 (62%) organisms were isolated from the community urine samples while the hospital urine samples yielded 377 (38%) organisms (Fig. 2).

Antibiotic susceptibility

More than 95% of all ESBL producing *Enterobacteriaceae* were sensitive to pivmecillinam, fosfomycin and nitrofurantoin (Table 1). Of 889 *E. coli*, 98%, 96%, and 93% were found to be sensitive to fosfomycin, pivmecillinam, and nitrofurantoin respectively. Pivmecillinam was the most effective antibiotic against *Klebsiella* species (83%, 59); followed by fosfomycin (62%, 44) and nitrofurantoin (42%, 30). Of other 26 *Enterobacteriaceae*, 23 (88%), and 22 (85%) were sensitive to pivmecillinam and fosfomycin respectively while nitrofurantoin sensitivity rate was low (15%, 4). Trimethoprim and ciprofloxacin were least effective against all ESBL producing *Enterobacteriaceae* (Table 2). No carbapenemase producing *Enterobacteriacae* was isolated during this study.

Discussion

The rising trend of EBSL producing organisms causing UTIs especially at the community level in recent years, and emergence and prevalence of CTX-M enzyme in these organisms have generated the need to re-evaluate current antimicrobial therapy for these infections. CTX-M enzyme in ESBL producing organisms confers the resistence to penicillins, cephalosporins and monobactams but not the carbapenems. The ESBL producing *Enterobacteriacae* are resistant to non-related antibiotics and pose a significant therapeutic and infection control challange. Choosing right empirical therapy is always challanging especially in elderly patient with comorbidities who present with vague clinical signs and symptoms of sepsis [1,7,12].

In this study, the majority of urinary ESBL producing isolates were related with community UTIs. Other studies reported higher isolation rates of ESBL producing *Enterobacteriacae* from the community urine samples [4,7]. Pivmecillinam, fosfomycin and nitrofurantoin are available in oral form. Their activity against ESBL producing *Enterobacteriacae* and oral availability make it appropriate for use in the treatment of uncomplicated UTIs. One study reported the good activity of fosfomycin (cell wall inhibitor) agan-

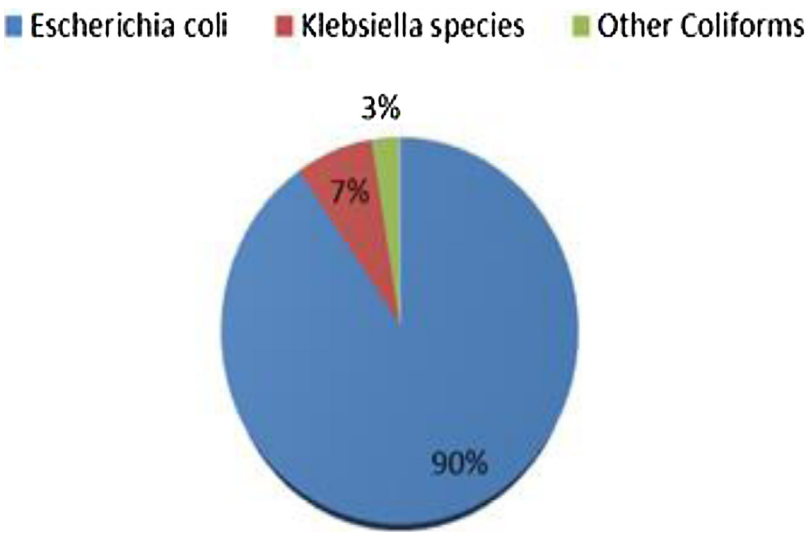

Fig. 1. Distribution of ESBL producing Enterobacteraceae.

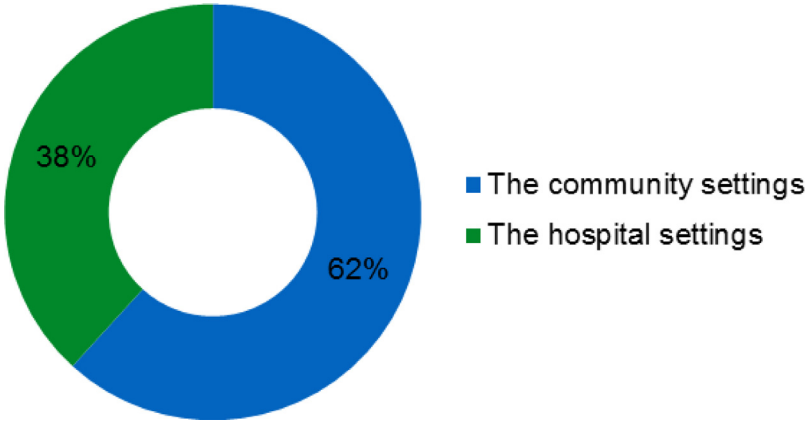

Fig. 2. Distribution of ESBL producing pathogens from the community and Hospital samples.

ist carbapenemase producing *Enterobacteriacae* including NDM1 (New Delhi Metallo-beta-lactamase-1) [13]. One study from Brazil reported 98.8% sensitivity rate of fosfomycin in *E. coli* from community acquired UTIs despite the heavy usage of this antibiotic [14]. Fosfomycin resistance in the clinical isoaltes is rare because of higher concentration of fosfomycin in the urinary tract. Our findings of >95% fosfomycin susceptibility among ESBL producing *Enterobacteriacae* further support the use of this antibiotic in uncomplicated UTIs.

Pivmecillinam is a ß-lactam oral antibiotic which is effective specifically against *Enterobacteriacae*. It binds to penicillin-binding protein 2 and inhibits the bacterial cell wall synthesis. It has been recommended for the treatment of uncomplicated UTIs by the Infectious Diseases Society of America, the European Society for Clinical Microbiology and Infectious Diseases, the European Association of Urology, Scandinavian countries, UK, Germany and France [3,7]. Pivmecillinam resistance is still low. Previous studies confirmed the effectiveness of pivmecillinam against ESBL producing *Enterobacteriacae* [7,8]. Higher sensitivity rates of pivmecillinam were recorded in *E. coli* (96%), *Klebsiella* species (83%) and other *Enterobacteriacae* (88%) in this study which suggested this antibiotic is a suitable oral option to treat uncompliated UTIs.

Nitrofurantoin, a synthetic bactericidal antimicrobail agent, has been used in the clinical practice for the last 50 years. It's higher concerntration in the urinary tract after taking orally, makes it suitable oral option to treat lower UTIs [7,8]. Some studies around the world reported more than 90% nitrofurantoin sensitivity rates in ESBL producing *E. coli* [7,8]. One study reported decreased nitrifurantoin sensitivity rate (57%) in ESBL producing *Klebsiella pneumoniae* [9]. Our study confirmed the findings of previous studies [7,9]. Nitrofurantoin was effective in 93% *E. coli*, while reduced sensitivity was noted in *Klebsiella* species (58%) and other *Enterobacteriacae* (17%). Nevertheless 88% *Enterobacteriacae* were sensitive to nitrofurantoin. Nitrofurantoin sensitivity rate in ESBL producing urinary isolates in this study is much higher from other studies aroun the world such as Saudi Arabia (73%) and Baharian (61.8%) [15,16].

The evaluation of this data revealed a higher resistance rates to oral trimethoprim (78%) and ciproloxacin (60%). These agents should be avoided to treat UTIs due to ESBL producing organisms. One study detected higher resistance in 100 ESBL producing *E. coli* to aminoglycosides, quinolones and sulfonamides. More than 70% isolates were resistant to trimethoprim sulfamethaxazole and ciprfloxacin [7]. Another study showed similiar resistance rates in ESBL producing organisms to gentamicin (75%) trimethoprim sulfamethaxazole (70%) and ciprfloxacin (59%) [17]. Previous exposure to trimethoprim or quinolones increases the resistance rate in ESBL producing organisms [2].

Alternative antibiotics are required to combat with infections due to multidrug resistant organisms. Our study showed higher sensitivity rates to fosfomycin, pivmecillinam, and nitrofurantoin.

These antibiotics are suitable oral options to treat uncomplicated UTIs due to ESBL organisms.

Conclusion

The emergence of multidrug resistant organisms restricts the therapeutic options. Majority of ß-lactams are ineffective against ESBL producing *Enterobacteriacae*, the associated co-resistance further reduces the treatment options. Higher sensitivity rates to pivmecillinam, fosfomycin and nitrofurantoin in this study suggest the suitability of these agents to treat uncomplicated UTI due to ESBL producing *Enterobacteriaceae*.

Informed consent

No informed consent was needed as no clinical informations were obrtained.

Funding

There was no funding involved in this study.

Ethical approval

This study was approved by the clinical governace and audit of the East Sussex Healthcare NHS Trust (approval number 4218).

Conflict of interest

The authors declare that they have no conflict of interest.

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