International Journal of Antimicrobial Agents 52 (2018) 100–103

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Which non-carbapenem antibiotics are active against extended-spectrum β-lactamase-producing Enterobacteriaceae?

Hélène Bouxom[a], Damien Fournier[b,c], Kevin Bouiller[c,d], Didier Hocquet[a,c,e], Xavier Bertrand[a,c,*]

[a] Hygiène Hospitalière, Centre Hospitalier Régional Universitaire, Besançon, France
[b] Bactériologie, Centre Hospitalier Régional Universitaire, Besançon, France
[c] UMR 6249 Chrono-environnement, Université de Bourgogne-Franche-Comté, Besançon, France
[d] Maladies infectieuses et tropicales, Centre Hospitalier Régional Universitaire, Besançon, France
[e] Centre de ressources biologiques–Filière microbiologique de Besançon, Centre Hospitalier Régional Universitaire, Besançon, France

ARTICLE INFO

Article history:
Received 5 February 2018
Accepted 17 March 2018

Keywords:
ESBL
Escherichia coli
Klebsiella pneumoniae
Antibiotics
Susceptibility
Alternatives

ABSTRACT

In this study, the activity of 18 non-carbapenem antibiotics was evaluated against 100 extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (ESBL-Ec) and 50 ESBL-producing *Klebsiella pneumoniae* (ESBL-Kp) isolated from urinary tract infections and bacteraemia in 2016. Minimum inhibitory concentrations (MICs) were determined using reference methods and the susceptibility profiles were defined according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2017 recommendations. All of the ESBL-Ec isolates were susceptible to ceftazidime/avibactam and a great majority of them were susceptible to fosfomycin (98%), piperacillin/tazobactam (97%), amikacin (97%) and nitrofurantoin (96%). Mecillinam, cefoxitin and ceftolozane/tazobactam remained active against 92%, 83% and 78% of the ESBL-Ec isolates, respectively. Moreover, 100%, 94% and 90% of the ESBL-Kp tested were susceptible to ceftazidime/avibactam, amikacin and mecillinam, respectively. This study showed that there are non-carbapenem options (including orally administrable drugs) for the treatment of all of the situations of ESBL-Ec or ESBL-Kp infections, with ceftazidime/avibactam being the most efficient alternative.

1. Introduction

Extended-spectrum β-lactamases (ESBLs) have become a major public-health concern in European in the last two decades [1]. For instance, the incidence of infections caused by ESBL-producing Enterobacteriaceae (ESBL-E) has increased dramatically in French hospitals, and *Escherichia coli* has become the most frequent species among ESBL-E (60%), followed by *Klebsiella pneumoniae* (25%) [2]. This has led to an increase of the use of carbapenems, which unsurprisingly has raised the resistance level to carbapenems and favours the spread of carbapenemase-producing bacteria [3]. The objective of this study was to evaluate the activity of a wide panel of antimicrobials, including recently launched combinations of β-lactam/β-lactamase inhibitors (ceftazidime/avibactam and ceftolozane/tazobactam) against ESBL-producing *E. coli* (ESBL-Ec) and ESBL-producing *K. pneumoniae* (ESBL-Kp) with the purpose of suggesting non-carbapenem options for the treatment of infections due to these organisms in order to preserve carbapenems.

2. Materials and methods

Besançon Hospital is a French university-affiliated hospital with 1200 acute-care beds. All Enterobacteriaceae isolates obtained from clinical specimens of inpatients were routinely tested for ESBL production by the double-disk synergy test [4]. A total of 100 consecutive non-duplicate isolates of ESBL-Ec and 50 isolates of ESBL-Kp were collected throughout 2016 from clinically certified urinary tract infections ($n = 119$) and bloodstream infections ($n = 31$) from 150 patients.

Minimum inhibitory concentrations (MICs) of 13 antibiotics, including amoxicillin/clavulanic acid, piperacillin/tazobactam (TZP), cefotaxime, ceftazidime, cefepime, cefoxitin, mecillinam, ertapenem, nitrofurantoin, fosfomycin, temocillin, trimethoprim and trimethoprim/sulfamethoxazole (SXT), were determined by the agar dilution method on Mueller–Hinton medium using a Steers multiple inoculator and an inoculum of ca. 10^4 CFU/spot [5]. MICs of ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, amikacin and gentamicin were determined by gradient strips

* Corresponding author. Present address: Hygiène Hospitalière, Centre Hospitalier Régional Universitaire, 3 boulevard Fleming, Besançon, Cedex 25030, France. Tel.: +33 3 70 63 21 36; fax: +33 3 70 63 23 64.
E-mail address: xbertrand@chu-besancon.fr (X. Bertrand).

https://doi.org/10.1016/j.ijantimicag.2018.03.014
0924-8579/

Table 1
Minimum inhibitory concentration (MIC) distribution for 18 antimicrobial agents against extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* ($n = 100$) isolated in CHU Besançon (Besançon, France), 2016

Antimicrobial agent	Proportion of isolates with indicated MIC (μg/mL):														Breakpoints	Susceptibility		MIC (μg/mL)	
																%S	%R	MIC_{50}	MIC_{90}
	≤0.03	0.06	0.13	0.25	0.5	1	2	4	8	16	32	64	128	>128					
Amoxicillin/clavulanic acid							**1**	**4**	**21**	37	24	4	5	4	8/8 [a]	26	74	16	64
Piperacillin/tazobactam			**1**		**1**	**16**	**44**	**28**	**7**		1			2	8/16 [a]	97	3	2	4
Mecillinam		**1**		**5**	**37**	**16**	**26**	**4**	**3**	2	2		1	3	8/8 [a]	92	8	1	8
Temocillin						**1**	**3**	**29**	**37**	27	2	1			8/8 [b]	70	30	8	16
Cefoxitin						**1**	**2**	**38**	**42**	14	3				8/16 [b]	83	3	8	16
Cefotaxime				**1**			3	1	1	8	11	7	36	32	1/2 [a]	1	96	128	>128
Ceftazidime				**2**	**8**	**16**	15	14	9	21	10	4	1		1/4 [a]	26	45	4	32
Cefepime			**2**	**1**	**2**	**3**	10	21	35	13	8	3	2		1/4 [a]	8	61	8	32
Ceftazidime/avibactam			**6**	**42**	**44**	**8**									8/8 [a]	100	0	0.5	0.5
Ceftolozane/tazobactam				**1**	**28**	**49**	20	2							1/1 [a]	78	22	1	2
Ertapenem	**83**	**12**	**3**	**2**											0.5/1 [a]	100	0	≤0.03	0.06
Fosfomycin				**1**	**19**	**62**	**11**	**1**	**1**	**2**	**1**	1		1	32/32 [a]	98	2	1	2
Nitrofurantoin									**12**	**40**	**30**	**14**	3	1	64/64[1]	96	4	16	64
Ciprofloxacin	**26**	**1**	**4**	**8**	1	4			1		55 [c]				0.25/0.5 [a]	39	60	–	–
Amikacin						**4**	**57**	**24**	**12**	2				1	8/16 [a]	97	1	2	8
Gentamicin			**1**	**7**	**32**	**20**	**5**	1	3	8	13	5	3	2	2/4 [a]	65	34	1	32
Trimethoprim	**1**		**3**	**7**	**19**	**4**					66 [c]				2/4 [a]	34	66	–	–
Trimethoprim/sulfamethoxazole	**3**	**5**	**17**	**3**	**5**	**1**	**2**		1		63 [c]				2/4 [a]	36	64	–	–

Shaded areas correspond to resistant isolates; susceptible isolates are shown in bold.

%S, percent susceptible; %R, percent resistant; $MIC_{50/90}$, MICs required to inhibit 50% and 90% of the isolates, respectively.

[a] European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2017 breakpoints.

[b] Antibiogram Committee of the French Society of Microbiology (CA-SFM) 2017 breakpoints.

[c] MIC ≥ than the value indicated.

[Etest (bioMérieux, Marcy-l'Étoile, France) and Liofilchem® MIC Test Strips (Liofilchem, Roseto degli Abruzzi, Italy)] as recommended by the manufacturers. Wild-type *E. coli* ATCC 25922 was used as a reference strain. The results were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2017 recommendations [4], except for temocillin and cefoxitin for which the Antibiogram Committee of the French Society of Microbiology (CA-SFM) 2017 recommendations were used [6].

3. Results and discussion

The results of antimicrobial susceptibility testing are detailed in Tables 1 and 2 for ESBL-Ec and ESBL-Kp, respectively. Briefly, all of the ESBL-Ec isolates were susceptible to ertapenem and ceftazidime/avibactam and a great majority were susceptible to fosfomycin (98%), TZP (97%), amikacin (97%) and nitrofurantoin (96%). Mecillinam, cefoxitin and ceftolozane/tazobactam remained active in 92%, 83% and 78% of isolates, respectively. Among the 18 tested drugs, 7 reached ≥90% activity for ESBL-Ec compared with only 4 for ESBL-Kp. Ceftazidime/avibactam was fully active against ESBL-Kp, whereas ertapenem, amikacin and mecillinam were active against 98%, 94% and 90% of isolates, respectively. The single ertapenem-non-susceptible ESBL-Kp isolate produced the OXA-48 carbapenemase.

Here we show that several drugs remain active against ESBL-Ec and that many alternatives to carbapenems are available. For ESBL-Kp, such alternatives were less frequent considering that ESBL production in this species is often accompanied by mutational loss of its porins, especially OmpK35 [7].

Orally administered drugs such as fosfomycin, nitrofurantoin and mecillinam, recommended as first options in the treatment of cystitis in France [8], are active against 98%, 96% and 92% of ESBL-Ec, respectively. These rates are similar to those described in European reports and broadly do not differ from those of non-ESBL-producers [9–11]. Therefore, these three drugs remain very good options for treatment of cystitis in women even in the case of ESBL production. The current results also suggests that trimethoprim was almost as active against ESBL-Ec as SXT, but the low proportion of susceptible isolates (ca. 35%) limits its use for urinary tract infections [11].

The association TZP remained active against nearly all ESBL-Ec (97%) and we observed that this susceptibility rate was higher than that assessed by disk diffusion in our routine methodology (ca. 80%) during the study period. It thus seems that the disk diffusion method overestimates resistance of *E. coli* isolates to TZP, as suggested by the comparative data of MIC and inhibition diameter values available in the EUCAST database [12]. Use of TZP to treat infections due to ESBL-E remains controversial [13]. Nevertheless, we propose that TZP could be used in documented infections when the MIC does not exceed 8 mg/L or in combination with amikacin (the most active aminoglycoside) for empirical treatment of infections occurring in patients presenting risk factors of ESBL-E.

Temocillin was active against 70% of ESBL-Ec and 54% of ESBL-Kp in this collection. These rates may be significantly improved