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Minimum inhibitory concentration of carbapenems and tigecycline against *Salmonella* spp.

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Antimicrobial resistance in *Salmonella* spp. is of grave concern, more so in quinolone-resistant and extended-spectrum β-lactamase (ESBL)-producing isolates that cause complicated infections. The MIC of azithromycin, ciprofloxacin, cefixime, cefepime, ceftriaxone, gatifloxacin, imipenem, levofloxacin, meropenem and ofloxacin (E-test strip) and tigecycline and faropenem (agar dilution) against 210 *Salmonella* spp. was determined. MIC_{90} (defined as the antimicrobial concentration that inhibited growth of 90 % of the strains) of the carbapenems (imipenem and meropenem) for *Salmonella* Typhi and *Salmonella* Paratyphi A was 0.064 μg ml^{-1}. MIC_{90} of faropenem was 0.25 μg ml^{-1} for *S.* Typhi, *S.* Paratyphi A and *Salmonella* Typhimurium. The MIC_{90} of azithromycin for all *Salmonella* spp. ranged from 8 to 16 μg ml^{-1}. Tigecycline showed an MIC_{90} of 2 μg ml^{-1} for *S.* Typhi, 1 μg ml^{-1} for *S.* Paratyphi A and 4 μg ml^{-1} for *S.* Typhimurium. We concluded that tigecycline and the carbapenems are likely to have roles in the final stage of treatment of quinolone-resistant and ESBL-producing multidrug-resistant salmonellae.

INTRODUCTION

Nalidixic acid-resistant (NAR) *Salmonella* causing enteric fever are now also found to be ciprofloxacin resistant; this has necessitated the search for novel antimicrobials. Options available for treatment of enteric fever include newer quinolones, extended-spectrum cephalosporins and azithromycin (Cooke *et al.*, 2006; Kownhar *et al.*, 2007; Parry *et al.*, 2007). A large number of current and previous studies question the efficacy of newer quinolones in treating enteric fever caused by ciprofloxacin-resistant *Salmonella* (Harish *et al.*, 2006; Joshi & Amarnath, 2007). A rise in the MIC of third and fourth generation cephalosporins for *Salmonella* spp. has been observed recently (Capoor *et al.*, 2006; Saha *et al.*, 1999).

A number of studies have observed a rise in the MIC of azithromycin. Despite its intracellular concentration and clinical efficacy, it cannot be used in routine treatment of enteric fever due to a lack of large-scale *in vivo* and *in vitro* studies (Capoor *et al.*, 2007; Frenck *et al.*, 2004; Girgis *et al.*, 1999; Parry *et al.*, 2007).

The roles of newer classes of antimicrobials, such as glycylcyclines and carbapenems, against salmonellae need to be elucidated. Tigecycline is a glycylcycline (tetracycline analogue), it inhibits protein synthesis and evades efflux and target-mediated resistance seen against classical tetracyclines (Livermore, 2005; Fritsche *et al.*, 2005). The carbapenems are a class of β-lactam antibiotics with broad-spectrum activity and are stable to hydrolysis by extended-spectrum β-lactamase (ESBL)-producing isolates (Sorbera *et al.*, 2002). Though the use of carbapenems is not recommended (CLSI, 2006), it may become crucial, especially when treating ESBL-producing salmonellae causing enteric fever (Pokharel *et al.*, 2006). Moreover, with an increase in the incidence of unusual and complicated paratyphoid fever (Harish *et al.*, 2006) and non-typhoidal salmonellae causing septicaemia (Egorova *et al.*, 2007; Sun *et al.*, 2005), the development of newer broad-spectrum antimicrobials needs to be explored.

The current study was carried out to assess the MIC of the currently available and novel antimicrobials for salmonellae isolates from a region that is endemic for NAR strains and is currently facing ciprofloxacin resistance in salmonellae that cause enteric fever.

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum β-lactamase; EUCAST, European committee on antimicrobial susceptibility testing; FDA, Food and Drug Administration; MDR, multidrug-resistant; MIC_{50} and MIC_{90}, antimicrobial concentration that inhibited growth of 50 and 90 %, respectively, of the strains; NAR, nalidixic acid-resistant.

METHODS

The current study was conducted on *Salmonella* isolates recovered from enteric fever and septicaemia cases at Vardhman Mahaveer Medical College, Safdarjung Hospital (a tertiary care centre) and Majeedia Hospital (a private referral hospital) in New Delhi, India, over a period of 2 years (2006–2007). Blood for culture was collected prior to initiation of antimicrobial therapy using aseptic procedures, and was processed using standard microbiological protocols (Old, 1996). *Salmonella* spp. were identified using standard biochemical tests (Old, 1996) and confirmed by detection with specific antisera (Central Research Institute, Kasauli, India).

A total of 479 isolates of *Salmonella* spp. were recovered from 38 282 blood cultures. Of these, 210 isolates were randomly selected for the study. Antimicrobial susceptibility testing of the isolates was carried out by the standard Kirby Bauer disk-diffusion method using Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2006). The following antimicrobials were used: ampicillin (10 μg ml^{-1}), chloramphenicol (30 μg ml^{-1}), co-trimoxazole (1.25/23.75 μg ml^{-1}), ceftriaxone (30 μg ml^{-1}), cefixime (5 μg ml^{-1}), ciprofloxacin (5 μg ml^{-1}) and nalidixic acid (30 μg ml^{-1}). Isolates resistant to ampicillin, chloramphenicol and co-trimoxazole were defined as multidrug-resistant (MDR).

The MIC of azithromycin, ciprofloxacin, cefixime, cefepime, ceftriaxone, gatifloxacin, imipenem, levofloxacin, meropenem and ofloxacin for the 210 *Salmonella* isolates was determined by using E-test strips (AB Biodisk). The results were interpreted according to the CLSI guidelines (CLSI, 2006). The MIC of tigecycline and faropenem (Ranbaxy laboratories, Gurgaon, India) for *Salmonella* isolates was determined by agar dilution on cation-adjusted Mueller–Hinton agar. Isolates with intermediate levels of resistance were included in the percentage of resistant organisms for final analysis. *Escherichia coli* ATCC 25922 was used as a control strain.

The breakpoint MIC levels for azithromycin, tigecycline and faropenem for isolates of *Salmonella* spp. have not been determined. However, for the current study, breakpoints for faropenem and azithromycin that were determined in previous *in vitro* studies were used (Piddock *et al.*, 2003; Girgis *et al.*, 1999). For tigecycline, the Food and Drug Administration (FDA)-approved susceptibility test result interpretative criteria were used (Brown & Traczewski, 2007). These are defined as sensitive, $\leqslant$2 μg ml^{-1}; intermediate, 4 μg ml^{-1}; resistant, $\geqslant$8 μg ml^{-1}.

The *Salmonella* isolates were screened for the presence of ESBL production by using the double disk diffusion method using ceftazidime (30 μg ml^{-1}), cefoperazone (75 μg ml^{-1}), ceftriaxone (30 μg ml^{-1}) and cefotaxime (30 μg ml^{-1}). Presence of ESBL was confirmed by using combination E-test strips containing cefotaxime and cefotaxime–clavulanic acid or cefepime and cefepime–clavulanic acid. A threefold or more fall in MIC in the presence of clavulanic acid was considered to be indicative of ESBL production.

RESULTS AND DISCUSSION

Of the 210 isolates recovered from blood cultures from suspected cases of enteric fever and septicaemia, *Salmonella* Typhi was the predominant serotype (149, 70.95 %), followed by *Salmonella* Paratyphi A (43, 20.47 %) and *Salmonella* Typhimurium (17, 8.1 %); one *Salmonella* Enteritidis isolate was identified. Multidrug resistance was seen in *S.* Typhi (6, 4 %), *S.* Paratyphi A (2, 4.6 %) and *S.* Typhimurium (8, 47 %) but not in *S.* Enteritidis (0, 0 %). NAR isolates of *S.* Typhi (142, 95.3 %), *S.* Paratyphi A (40, 93 %) and *S.* Typhimurium (6, 35.3 %) were detected.

Tables 1, 2 and 3 depict the MICs of various antimicrobials for *S.* Typhi, *S.* Paratyphi A and *S.* Typhimurium, respectively.

For the quinolones that were tested (ciprofloxacin, gatifloxacin, levofloxacin and ofloxacin), the antimicrobial

Table 1. MIC of various antimicrobials for *S.* Typhi

The number of strains for each MIC is shown. –, No growth.

The CLSI (2006) interpretive criteria for sensitive, intermediate and resistant strains, respectively, are (μg ml^{-1}): ciprofloxacin (Cf), $\leqslant$1, 2, $\geqslant$4; levofloxacin (Le), ofloxacin (Of) and gatifloxacin (Ga), $\leqslant$2, 4, $\geqslant$8; imipenem (I) and meropenem (M), $\leqslant$4, 8, $\geqslant$16; faropenem (F) and azithromycin (Az), breakpoints analysed by prior *in vitro* studies indicated $\geqslant$32=resistant (Piddock *et al.*, 2003; Girgis *et al.*, 1999); ceftriaxone (Ci), $\leqslant$8, 16–32, $\geqslant$64; cefixime (Cfx), $\leqslant$1, 2, $\geqslant$4; cefepime (Cpm), $\leqslant$8, 16, $\geqslant$32; tigecycline (Ti), $\leqslant$2, 4, $\geqslant$8.

MIC (μg ml^{-1})	Cf	Le	Of	Ga	I	M	F	Az	Ci	Cfx	Cpm	Ti
$\leqslant$0.032	3	8	1	7	108	110	111	2	14	18	35	5
0.064	2	4	1	5	24	28	13	3	19	20	20	10
0.125	22	15	7	20	12*	9	9	4	75	53	56	1
0.25	44	45	41	30	5	2	15*	2	25	39	23*	49
0.5	23	24	31	20	–	–	1	8	7*	8*	5	45
1	14	10	27	24	–	–	–	19	3	8	–	21
2	2	6	4	13	–	–	–	31	4	1	–	14*
4	1	4	2	7	–	–	–	30	1	1	–	4
8	6	6	3	8	–	–	–	35*	–	–	–	–
16	2	2	–	15*	–	–	–	14	–	–	–	–
$\geqslant$32	30*	25*	32*	–	–	–	–	1	1	1	1	–
Total	149	149	149	149	149	149	149	149	149	149	149	149

*Indicates MIC_{90} values.

Table 2. MIC of various antimicrobials for *S.* Paratyphi A

The number of strains for each MIC is shown. –, No growth.

For CLSI interpretive criteria see Table 1.

MIC (μg ml^{-1})	Cf	Le	Of	Ga	I	M	F	Az	Ci	Cfx	Cpm	Ti
⩽0.032	4	4	0	1	32	34	25	0	3	1	2	1
0.064	1	0	3	2	8*	5*	10	0	8	5	6	1
0.125	3	1	2	2	2	3	3	1	15	13	15	2
0.25	10	12	4	4	1	1	5*	1	11	14	15*	15
0.5	9	13	6	9	–	–	–	–	5*	6*	1	13
1	10	8*	20	18	–	–	–	4	0	4	2	7*
2	–	1	4*	2*	–	–	–	9	1	–	1	4
4	1*	–	–	2	–	–	–	8	–	–	–	–
8	–	–	–	–	–	–	–	14	–	–	–	–
6	–	–	–	–	–	–	–	4*	–	–	–	–
⩾32	5	4	4	3	–	–	–	1	–	–	–	–
Total	43	43	43	43	43	43	43	43	43	43	43	43

*Indicates MIC_{90} values.

concentration that inhibited growth of 90 % of the strains (MIC_{90}) ranged from 16 μg gatifloxacin ml^{-1} to 32 μg ml^{-1} for the other quinolones for *S.* Typhi. For *S.* Paratyphi A, the MIC_{90} of ciprofloxacin and levofloxacin was 1 μg ml^{-1} and was 2 μg ml^{-1} for ofloxacin and gatifloxacin. The MIC_{90} of all the quinolones for *S.* Typhimurium was in the susceptible range. For the cephalosporins tested (cefixime, cefepime and ceftriaxome), the lowest MIC_{90} was 0.25 μg ml^{-1} of cefepime for *S.* Typhi and *S.* Paratyphi A. A single *S.* Typhi isolate (0.67 %) and 16 *S.* Typhimurium isolates (94.1 %) were ESBL producers. The MIC_{90} of all cephalosporins for *S.* Typhimurium was ⩾32 μg ml^{-1}.

The MIC_{90} of the carbapenems (imipenem and meropenem) for *S.* Typhi and *S.* Paratyphi A was 0.064 μg ml^{-1}. The MIC_{90} of faropenem for *S.* Typhi, *S.* Paratyphi A and *S.* Typhimurium was 0.25 μg ml^{-1}. The MIC_{90} of azithromycin for *S.* Typhi, *S.* Paratyphi A and *S.* Typhimurium was 8, 16 and 8 μg ml^{-1}, respectively. Tigecycline displayed an MIC_{90} at 2 μg ml^{-1} for *S.* Typhi, 1 μg ml^{-1} for *S.* Paratyphi A and 4 μg ml^{-1} for *S.* Typhimurium.

Table 3. MIC of various antimicrobials for *S.* Typhimurium

The number of strains for each MIC is shown. –, No growth.

For CLSI interpretive criteria see Table 1.

MIC (μg ml^{-1})	Cf	Le	Of	Ga	I	M	F	Az	Ci	Cfx	Cpm	Ti
⩽0.032	13	7	2	12	1	1	1	2	0	0	0	0
0.064	0	7	3	0	8	8	6	0	0	0	0	0
0.125	1	1	7	2	8*	8*	6	0	0	0	0	0
0.25	2*	0	2	13*	–	–	4*	0	0	0	0	0
0.5	1	2*	0	–	–	–	–	0	0	0	0	0
1	–	–	3*	–	–	–	–	3	0	0	0	2
2	–	–	–	–	–	–	–	3	0	0	2	6
4	–	–	–	–	–	–	–	5	0	0	5	8*
8	–	–	–	–	–	–	–	2*	8	8	1	1
16	–	–	–	–	–	–	–	1	2	2	1	–
⩾32	–	–	–	–	–	–	–	1	7*	7*	–	–
Total	17	17	17	17	17	17	17	17	17	17	17	17

*Indicates MIC_{90} values.

The MICs of quinolones, cephalosporins, carbapenems, azithromycin and tigecycline for *S.* Enteritidis were in the sensitive range.

Amongst the fluoroquinolones tested, the MIC_{90} of gatifloxacin (MIC_{90} 16 μg ml^{-1}) was marginally lower compared with the MIC_{90} of other quinolones (MIC_{90} $\geqslant$32 μg ml^{-1}) for *S.* Typhi. The MIC_{90} of gatifloxacin for *S.* Paratyphi A was 2 μg ml^{-1} and was 1 μg ml^{-1} for other quinolones. Nonetheless, the antimicrobial concentration that inhibited growth of 50 % of the strains (MIC_{50}) of all quinolones for *S.* Typhi and *S.* Paratyphi A was 0.5 μg ml^{-1} and 0.5–1 μg ml^{-1}, respectively. In contrast, the MIC_{50} and MIC_{90} of all quinolones for *S.* Typhimurium were in the susceptible range. The resistant MICs seen for the majority of isolates in this study have also been observed in prior studies (Capoor *et al.*, 2007; Cooke *et al.*, 2006; Joshi & Amarnath, 2007; Kownhar *et al.*, 2007). Thus, the higher (resistant) MICs suggest that quinolones should be withdrawn from use in treatment of enteric fever and that their use should be restricted to septicaemia cases caused by other salmonellae. Quinolones should not be used in the therapy of patients infected with NAR isolates as these are associated with therapeutic failures, despite their decreased susceptibility (0.125–1 μg ml^{-1}) to ciprofloxacin and other quinolones (Capoor *et al.*, 2006; Cooke *et al.*, 2006; Kownhar *et al.*, 2007).

Cefepime had the lowest MIC_{90}, at 0.25 μg ml^{-1}, for *S.* Typhi and *S.* Paratyphi A. This may be attributed to its parenteral route of administration, making it less effective than cefixime. Only a single isolate of *S.* Typhi was an ESBL producer and had a high MIC for cephalosporins (resistant phenotype). Until now, there have been few reports of ESBL producers in *S.* Typhi and *S.* Paratyphi A strains (Pokharel *et al.*, 2006). Overuse of cephalosporins in ciprofloxacin-resistant salmonellae causing enteric fever has selected for the production of ESBL-producing isolates. In stark contrast to ESBL production in *S.* Typhi, there are many reports of ESBL-producing *S.* Typhimurium in the literature (Egorova *et al.*, 2007; Weill *et al.*, 2006; AitMhand *et al.*, 2002; Otkun *et al.*, 2001). This was also observed in our study, as 94.1 % of the *S.* Typhimurium isolates were ESBL producers. Frequent production of ESBL in *S.* Typhimurium is attributable to plasmid-mediated class A ESBLs belonging to the TEM, SHV and CTX-M or PER CMY family (Weill *et al.*, 2006). As this type of resistance is commonly transferred by these isolates to other bacteria, the transfer to *S.* Typhi and *S.* Paratyphi A is a major risk.

The MIC_{90} values of azithromycin for *S.* Typhi, *S.* Paratyphi A and *S.* Typhimurium were 8, 16 and 8 μg ml^{-1}, respectively. In a prior study on ciprofloxacin-resistant *S.* Typhi and *S.* Paratyphi A (Capoor *et al.*, 2007), the MIC_{90} was 24 μg ml^{-1}. The high MIC_{90} may have been due to the fact that this study was performed using ciprofloxacin-resistant isolates only. In contrast, isolates were randomly selected in the current study and there was no selection bias for quinolone-resistant isolates. A rise in the MIC of azithromycin was predicted (Girgis *et al.*, 1999; Butler *et al.*, 1999; Frenck *et al.*, 2004; Capoor *et al.*, 2007) because of its injudicious out-patient use. Nonetheless, keeping in mind its intracellular concentration, large-scale randomized clinical trials are warranted to determine the correlation between *in vivo* and *in vitro* studies.

In this study, the MIC_{90} of the penems (imipenem and meropenem) for *S.* Typhi and *S.* Paratyphi A (0.064 μg ml^{-1}) was lower compared with that for *S.* Typhimurium (0.125 μg ml^{-1}). Overall, faropenem had a high MIC_{90} (0.25 μg ml^{-1}) for *S.* Typhi, *S.* Paratyphi A and *S.* Typhimurium compared with the other penems. Previous reports (Piddock *et al.*, 2003; Sun *et al.*, 2005) also observed that faropenem was less active than imipenem, where the MIC_{90} for salmonellae was reported as 0.5–1 μg ml^{-1}. Penems are a class of β-lactam antibiotic which possess potent broad-spectrum activity and are extremely stable against ESBLs (Sorbera *et al.*, 2002).

Against our collection of isolates, tigecycline was very potent, inhibiting 97.3 % of *S.* Typhi, as well as 100 % of *S.* Paratyphi A and *S.* Enteritidis. This is in agreement with the European committee on antimicrobial susceptibility testing (EUCAST) data and a prior study conducted on a large group of *Salmonella* isolates [European Committee on Antimicrobial Susceptibility Testing (EUCAST) Steering Committee, 2006; Morosini *et al.*, 2006; Brown & Traczewski, 2007]. Only 55.5 % of *S.* Typhimurium isolates were in the sensitive range for tigecycline. It should be noted, however, that the MIC_{90} for *S.* Typhimurium isolates (4 μg ml^{-1}) was higher than that for the other species tested, and it was at the breakpoint of susceptibility, as approved by the FDA. The findings of our study are consistent with those of EUCAST.

In vivo and *in vitro* studies have demonstrated that acquired resistance to tigecycline is associated with upregulation of a chromosomally mediated efflux pump (Livermore, 2005; Brown & Traczewski, 2007). Tigecycline lacks cross-resistance with other compounds and it could aid in the therapy of MDR salmonelloses. Resistance to or a high MIC of tigecycline was rare in our collection of *Salmonella* isolates showing resistance to or high MIC of quinolones. Furthermore, tigecycline was also active against ceftriaxone-resistant *Salmonella* isolates. Nevertheless, systematic large-scale *in vivo* studies are needed to assess the relative merits of tigecycline versus other antimicrobials in the treatment of these infections. Unfortunately, owing to presence of the β-lactam ring, strains resistant to the penems show cross-resistance to other antimicrobials.

Enteric fever caused by ciprofloxacin-resistant salmonellae is found uniquely in countries of the Indian subcontinent. In India, this may be attributed to misuse of ciprofloxacin due to administration via the oral route, affordability, over-the-counter availability and its spurious quality

(Capoor *et al.*, 2006). The observations of this study imply that tigecycline and the penems represent a reserve of antimicrobials that have therapeutic potential for the treatment of ESBL-producing MDR salmonellae in the future. Clinical efficacy trials are warranted to reach a conclusion in this regard.

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