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Original Article

Comparison of in vitro activities of levofloxacin, ciprofloxacin, ceftazidime, cefepime, imipenem, and piperacillin-tazobactam against aerobic bacterial pathogens from patients with nosocomial infections

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Background and Purpose: There is a rapid worldwide emergence of multidrug-resistant pathogens, especially in nosocomial isolates. This study compared the in vitro activities of levofloxacin, ciprofloxacin, ceftazidime, cefepime, imipenem, and piperacillin-tazobactam against 208 aerobic bacterial pathogens that caused 197 nosocomial infections in 184 patients.

Methods: Antimicrobial susceptibility was evaluated by E test in accordance with the guidelines of the National Committee for Clinical Laboratory Standards.

Results: Most (140/208, 67%) of the isolates were facultative Gram-negative bacilli. Levofloxacin and ciprofloxacin were the most effective (22/22, 100%) against oxacillin-sensitive *Staphylococcus aureus*. None of the antibiotics tested were found to be effective (0/25) against oxacillin-resistant *S. aureus*. Of the 11 isolates of *Acinetobacter baumannii* that were not pandrug-resistant (PDR), only 9 isolates (9/11, 81%) were sensitive to imipenem and 5 isolates (5/11, 45%) were sensitive to levofloxacin, ciprofloxacin, and ceftazidime. Another 22 isolates of *A. baumannii* that were PDR were completely resistant to all 6 antibiotics. The majority of isolates of *Pseudomonas aeruginosa* were sensitive to these 6 antimicrobial agents with 10/11 (91%) sensitive to levofloxacin and ciprofloxacin, 9/11 (83%) sensitive to ceftazidime, cefepime and piperacillin-tazobactam, and 8/11 (75%) sensitive to imipenem.

Conclusions: The majority of the bacterial isolates causing nosocomial infections were found to be sensitive to the 6 antibiotics tested. Bacterial isolates of nosocomial infections that were completely resistant to these 6 antibiotics were PDR *A. baumannii*, PDR *P. aeruginosa,* and oxacillin-resistant *S. aureus*. More potent antimicrobial agents are needed to treat infections caused by PDR *A. baumannii* and PDR *P. aeruginosa*.

Key words: Anti-bacterial agents; Bacterial infections; Cross infection; Drug resistance, bacterial; Taiwan

Introduction

The emergence of antimicrobial resistance among Gram-negative bacteria to cephalosporins or quinolone has complicated the treatment of many serious infections. In recent years, there has been a rapid worldwide emergence of multidrug-resistant pathogens; pathogens of concern to clinicians include extended spectrum beta-lactamase (ESBL) or quinolone-resistant *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, and *Citrobacter freundii*, oxacillin-resistant *Staphylococcus aureus* (ORSA), multidrug-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [1-8]. With continued antibiotic selective pressure in clinical settings, particularly in hospitals, pathogens resistant to these agents have emerged and pose challenges beyond the lack of available anti-microbial therapy [9,10].

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Antimicrobial resistance is a global problem [11,12]. In Taiwan, pandrug-resistant (PDR) *A. baumannii*, PDR *P. aeruginosa*, and multidrug-resistant *Enterobacteriaceae* with ESBL have emerged, especially in nosocomial infections [12]. A recent report by the National Nosocomial Infectious Surveillance system disclosed a remarkable increase in the prevalence of most of these resistant pathogens in intensive care unit patients in 1998 as compared with those from the previous 5 years. A similar epidemiological trend was also documented in several medical centers in Taiwan. However, the incidence of antimicrobial resistance among these important pathogens varies considerably among countries, among hospitals within a country, and even among different wards within a hospital. This study primarily focused on the isolates of nosocomial infections. The objectives of this study were to assess and compare the in vitro activity of levofloxacin, ciprofloxacin, ceftazidime, cefepime, imipenem, and piperacillin-tazobactam against aerobic bacterial pathogens isolated from patients with nosocomial infections. The antimicrobial agents reported here are commonly used to treat nosocomial infections.

Methods

Aerobic and facultative bacteria isolated from blood, sputum, urine, pus, pleural fluid, and cerebrospinal fluid of patients with nosocomial infections between January 2, 2004 and June 30, 2005 in Chang Gung Memorial Hospital, Keelung were identified using standard procedures. Clinically significant aerobic bacterial isolates were collected and stored in tryptic soy broth and frozen at –70°C. Nosocomial infections were defined according to the criteria of nosocomial infection set by the Centers for Disease Control in 1988 [13].

Antimicrobial susceptibility was evaluated by the E test (AB Biodisk, Solna, Sweden) in accordance with the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS). Minimal inhibitory concentrations (MICs) of 6 antimicrobial agents, (levofloxacin, ciprofloxacin, ceftazidime, cefepime, imipenem, and piperacillin-tazobactam) for the bacterial isolates were determined by the E test. Concentrations tested ranged from 0.002-32 μg/mL for levofloxacin, 0.002-32 μg/mL for ciprofloxacin, 0.016-256 μg/mL for ceftazidime, 0.016-256 μg/mL for cefepime, 0.002-32 μg/mL for imipenem, and 0.016/4-256/4 μg/mL for piperacillin-tazobactam. E tests were performed on Mueller-Hinton agar (pneumococci and streptococci: blood agar; Haemophilus: Haemophilus test medium). The MICs were read where the inhibition ellipse intersected the scale on the strip after incubation at 35°C for 24 h. Macrocolonies within the ellipse are regarded as significant growth, whereas microcolonies can be neglected. For quality control, standard control strains were included with each test run. The following organisms with acceptable MIC limits were included as control strains in accordance with NCCLS M7-A5: *S. aureus* American Type Culture Collection (ATCC) 29213 (0.12-0.5 μg/mL for ciprofloxacin, 4-16 μg/mL for ceftazidime, 1-4 μg/mL for cefepime, 0.25/4-2/4 μg/mL for piperacillin-tazobactam), *E. coli* ATCC 25922 (0.004-0.016 μg/mL for ciprofloxacin, 0.06-0.5 μg/mL for ceftazidime, 0.016-0.12 μg/mL for cefepime, 1/4-4/4 μg/mL for piperacillin-tazobactam), *P. aeruginosa* ATCC 27853 (0.25-1 μg/mL for ciprofloxacin, 1-4 μg/mL for ceftazidime, 1-8 μg/mL for cefepime, 1/4-8/4 μg/mL for piperacillin-tazobactam), *Streptococcus pneumoniae* ATCC 49619 (0.06-0.25 μg/mL for cefepime), *Enterococcus faecalis* ATCC 29212 (0.25-2 μg/mL for ciprofloxacin, 1/4-4/4 μg/mL for piperacillin-tazobactam).

According to NCCLS M7-A5, MIC (μg/mL) breakpoints for *Enterobacteriaceae*, non-fermenters, and staphylococci are: levofloxacin: ≤2 sensitive, 4 intermediate, ≥8 resistant; ciprofloxacin: ≤1 sensitive, 2 intermediate, ≥4 resistant; ceftazidime: ≤8 sensitive, 16 intermediate, ≥32 resistant; cefepime: ≤8 sensitive, 16 intermediate, ≥32 resistant; imipenem: ≤4 sensitive, 8 intermediate, ≥16 resistant; piperacillin-tazobactam: ≤16/4 sensitive, 32/4-64/4 intermediate, ≥128/4 resistant (*P. aeruginosa*: ≤64/4 sensitive, ≥128/4 resistant; staphylococci: ≤8/4 sensitive, ≥16/4 resistant). MIC breakpoints for streptococci are: levofloxacin: ≤2 sensitive, 4 intermediate, ≥8 resistant; ciprofloxacin: ≤1 sensitive, 2 intermediate, ≥4 resistant; ceftazidime: ≤8 sensitive, 16 intermediate, ≥32 resistant; cefepime: ≤1 sensitive, 2 intermediate, ≥4 resistant; imipenem: ≤0.12 sensitive, 0.25-0.5 intermediate, ≥1 resistant; piperacillin-tazobactam: ≤8/4 sensitive, ≥16/4 resistant. MIC breakpoints for enterococci are: levofloxacin: ≤2 sensitive, 4 intermediate, ≥8 resistant; ciprofloxacin: ≤1 sensitive, 2 intermediate, ≥4 resistant; piperacillin-tazobactam: ≤8/4 sensitive, ≥16/4 resistant. NCCLS does not list interpretive MIC breakpoints of ceftazidime, cefepime, and imipenem for enterococci.

Thus, the following interpretive MIC breakpoints of ceftazidime, cefepime and imipenem for enterococci

were used in this study for reference: ceftazidime: ≤8 sensitive, 16 intermediate, ≥32 resistant; cefepime: ≤8 sensitive, 16 intermediate, ≥32 resistant; imipenem: ≤4 sensitive, 8 intermediate, ≥16 resistant. MIC breakpoints for *Haemophilus* spp. are: levofloxacin: ≤2 sensitive; ciprofloxacin: ≤1 sensitive; ceftazidime: ≤2 sensitive; cefepime: ≤2 sensitive; imipenem: ≤4 sensitive; piperacillin-tazobactam: ≤1/4 sensitive, ≥2/4 resistant.

Results

A total of 208 aerobic bacterial isolates causing 197 nosocomial infections were identified in 184 patients at Chang Gung Memorial Hospital, Keelung, Taiwan, between January 2, 2004 and June 30, 2005. Of the 208 isolates, 148 were isolated from blood; 40, from urine; 8, from sputum; 5, from wound discharge; 4, from cerebrospinal fluid; 1, from pleural effusion; 1, from central venous pressure catheter (CVP) tip; and 1, from subcutaneous tissue. The isolates caused 197 cases of nosocomial infections — 142 cases of bacteremia; 36, urinary tract infections; 9 (1 isolate from pleural effusion and 8 from sputum), pneumonia; 5, wound infections; 3, meningitis; 1, CVP wound infection; and 1, subcutaneous tissue wound infection. Most (140/208, 67.3%) of the isolates were facultative Gram-negative bacilli. The most common single organism was *S. aureus*, which accounted for 49/208 (23.5%) of the total. Antimicrobial activities of these 6 antimicrobial agents against all bacteria tested are summarized in Table 1.

Table 1. Comparative in vitro activity of levofloxacin, ciprofloxacin, ceftazidime, cefepime, imipenem, and piperacillin-tazobactam against 208 isolates of nosocomial infections

Organism[a]	Antibiotic	MIC (μg/mL)			Susceptible (%)
		Range	MIC_{50}	MIC_{90}	
OSSA (n = 22)	Levofloxacin	0.064-0.75	0.25	0.25	100
	Ciprofloxacin	0.064-0.5	0.38	0.5	100
	Ceftazidime	2-256	16	128	4
	Cefepime	0.25-32	4	16	43
	Imipenem	0.047-32	0.047	1.5	95
	Piperacillin-tazobactam	0.75-24/4	2/4	8/4	51
ORSA (n = 25)	Levofloxacin	8-32	32	32	0
	Ciprofloxacin	32	32	32	0
	Ceftazidime	256	256	256	0
	Cefepime	256	256	256	0
	Imipenem	32	32	32	0
	Piperacillin-tazobactam	256/4	256/4	256/4	0
Coagulase-negative staphylococci (n = 4)	Levofloxacin	0.094-0.125	0.094	0.125	100
	Ciprofloxacin	0.125-0.19	0.125	0.19	100
	Ceftazidime	24-32	24	32	0
	Cefepime	3-24	3	24	50
	Imipenem	0.25	0.25	0.25	100
	Piperacillin-tazobactam	0.5-1.5/4	0.5/4	1.5/4	100
Enterococcus spp. (n = 10)	Levofloxacin	0.125-32	1.5	32	60
	Ciprofloxacin	0.125-32	1.5	32	20
	Ceftazidime	0.75-256	256	256	20
	Cefepime	0.25-256	256	256	20
	Imipenem	0.38-32	1.5	32	80
	Piperacillin-tazobactam	0.38-256/4	3/4	256/4	80
Streptococcus spp. (n = 6)	Levofloxacin	0.064-32	0.19	2	83
	Ciprofloxacin	0.032-32	0.125	32	67
	Ceftazidime	0.05-256	2	256	67
	Cefepime	0.038-256	1	256	33
	Imipenem	0.025-32	0.19	0.25	16
	Piperacillin-tazobactam	0.016-256/4	0.064/4	12/4	33
Acinetobacter baumannii (PDR; n = 22)	Levofloxacin	8-32	32	32	0

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	Ciprofloxacin	32	32	32	0
	Ceftazidime	96-256	256	256	0
	Cefepime	48-256	256	256	0
	Imipenem	32	32	32	0
	Piperacillin-tazobactam	256/4	256/4	256/4	0
Acinetobacter baumannii (non-PDR; n = 11)	Levofloxacin	0.19-32	12	32	45
	Ciprofloxacin	0.19-32	32	32	45
	Ceftazidime	2-256	256	256	45
	Cefepime	1.5-256	32	256	36
	Imipenem	0.25-32	2	32	81
	Piperacillin-tazobactam	0.016-16/4	256/4	256/4	36
Escherichia coli (ESBL; n = 23)	Levofloxacin	0.064-32	32	32	30
	Ciprofloxacin	0.023-32	32	32	30
	Ceftazidime	0.5-256	48	256	30
	Cefepime	1-256	32	256	39
	Imipenem	0.19-0.75	0.38	0.5	100
	Piperacillin-tazobactam	0.125-256/4	4/4	32/4	69
Escherichia coli (non-ESBL; n = 15)	Levofloxacin	0.023-32	0.047	32	73
	Ciprofloxacin	0.008-256	0.023	32	66
	Ceftazidime	0.047-256	0.25	256	66
	Cefepime	0.032-256	0.094	256	80
	Imipenem	0.19-32	0.5	32	86
	Piperacillin-tazobactam	0.5-256/4	1.5/4	256/4	80
Klebsiella pneumoniae (ESBL; n = 16)	Levofloxacin	0.094-32	32	32	43
	Ciprofloxacin	0.047-32	32	32	18
	Ceftazidime	1-256	64	256	25
	Cefepime	8-256	256	256	12
	Imipenem	0.19-32	0.25	32	93
	Piperacillin-tazobactam	3-256/4	32/4	256/4	37
Klebsiella pneumoniae (non-ESBL; n = 15)	Levofloxacin	0.094-32	0.094	0.125	93
	Ciprofloxacin	0.008-32	0.047	0.047	93
	Ceftazidime	0.025-256	0.25	1.5	93
	Cefepime	0.032-256	0.094	256	93
	Imipenem	0.19-32	0.25	32	86
	Piperacillin-tazobactam	2-256/4	2/4	4/4	93
Enterobacter cloacae (ESBL; n = 3)	Levofloxacin	0.125-2	0.125	2	100
	Ciprofloxacin	0.032-1	0.032	1	100
	Ceftazidime	48-256	48	256	0
	Cefepime	2-4	2	4	100
	Imipenem	0.5	0.5	0.5	100
	Piperacillin-tazobactam	24-256/4	24/4	256/4	0
Enterobacter cloacae (non-ESBL; n = 3)	Levofloxacin	0.94-1	1	32	66
	Ciprofloxacin	0.012-0.5	0.47	0.5	66
	Ceftazidime	0.125-256	0.25	256	66
	Cefepime	0.064-6	0.064	6	100
	Imipenem	0.38-4	0.5	4	100
	Piperacillin-tazobactam	1.5-12/4	2/4	12	100
Serratia marcescens (n = 5)	Levofloxacin	0.125-32	1	32	60
	Ciprofloxacin	0.064-32	1	32	60
	Ceftazidime	0.064-3	2	3	100
	Cefepime	0.064-12	8	12	60
	Imipenem	0.25-0.75	0.5	0.75	100
	Piperacillin-tazobactam	1-16/4	1.5/4	16/4	100
Pseudomonas aeruginosa (n = 11)	Levofloxacin	0.5-32	0.75	1.5	91

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	Ciprofloxacin	0.19-1	0.25	1	91
	Ceftazidime	1.5-256	4	256	83
	Cefepime	1-16	4	16	83
	Imipenem	1.5-32	1.5	32	75
	Piperacillin-tazobactam	2-256/4	8/4	12/4	83
Miscellaneous *Enterobacteriaceae* (n = 10)	Levofloxacin	0.023-32	0.5	32	80
	Ciprofloxacin	0.016-32	0.75	32	50
	Ceftazidime	0.064-4	0.38	1	100
	Cefepime	0.047-256	0.125	3	100
	Imipenem	0.032-32	1	2	100
	Piperacillin-tazobactam	0.125-16/4	0.75/4	16/4	100
Miscellaneous non-fermenters (n = 3)	Levofloxacin	0.38-8	0.5	8	67
	Ciprofloxacin	0.094-1.5	0.5	1.5	67
	Ceftazidime	2-256	4	256	67
	Cefepime	3-256	3	256	33
	Imipenem	0.75-32	32	32	33
	Piperacillin-tazobactam	4-12/4	8/4	12/4	100
Stenotrophomonas maltophilia (n = 2)	Levofloxacin	0.75-12	0.75	12	50
	Ciprofloxacin	1-32	1	32	50
	Ceftazidime	2-32	2	32	50
	Cefepime	48-256	48	256	0
	Imipenem	32	32	32	0
	Piperacillin-tazobactam	256/4	256/4	256/4	0
Haemophilus influenzae (n = 1)	Levofloxacin	0.128	0.128	0.128	100
	Ciprofloxacin	0.094	0.094	0.094	100
	Ceftazidime	4	4	4	100
	Cefepime	1.5	1.5	1.5	100
	Imipenem	0.125	0.125	0.125	100
	Piperacillin-tazobactam	0.016/4	0.016/4	0.016/4	100
Corynebacterium jeikeium (n = 1)	Levofloxacin	0.5	0.5	0.5	100
	Ciprofloxacin	0.5	0.5	0.5	100
	Ceftazidime	256	256	256	0
	Cefepime	256	256	256	0
	Imipenem	32	32	32	0
	Piperacillin-tazobactam	12/4	12/4	12/4	100

Abbreviations: MIC = minimal inhibitory concentration; MIC_{50} = MIC at which 50% of isolates are inhibited; MIC_{90} = MIC at which 90% of isolates are inhibited; OSSA = oxacillin-susceptible *Staphylococcus aureus*; ORSA = oxacillin-resistant *S. aureus*; PDR = pandrug-resistant; ESBL = extended-spectrum beta-lactamase

[a]*Enterococcus* spp. include 8 *Enterococcus faecalis*; *Streptococcus* spp. include 1 beta-hemolytic *Streptococcus* Group B, 1 *Streptococcus bovis*, 1 *Streptococcus mitis*, 1 *Streptococcus salivarius*, 1 *Streptococcus sanguis*, 1 *Streptococcus viridans*; miscellaneous *Enterobacteriaceae* include 1 *Aeromonas hydrophilia*, 1 *Citrobacter amalonaticus*, 1 *Enterobacter aerogenes*, 1 *Enterobacter agglomerans*, 1 *Morganella morganii*, 1 *Proteus mirabilis*, 1 *Providencia alcalifaciens*, 2 *Salmonella enteritidis*, 1 *Serratia liquefaciens*; miscellaneous non-fermenters include 1 *Acinetobacter haemolyticus*, 1 *Chryseobacterium meningosepticum*, 1 *Alcaligenes faecalis*.

Discussion

Among these 6 antimicrobial agents, levofloxacin and ciprofloxacin were the most effective (22/22, 100%) against oxacillin-sensitive *S. aureus* [7,10]. However, none of the 6 antimicrobial agents were found to be effective (0/25) against ORSA. Levofloxacin and ciprofloxacin were also found to be the most effective (4/4, 100%) against coagulase-negative staphylococci. Of these 6 antimicrobial agents, piperacillin-tazobactam and imipenem were the most effective (8/10, 80%) for *Enterococcus* spp., while levofloxacin and imipenem were the most effective (5/6, 83.3%) for *Streptococcus* spp. that infrequently cause nosocomial infections [14].

A. baumannii, which is a frequent pathogen found in nosocomial infections, was the most antibiotic-resistant bacteria isolated. Of the 11 isolates of *A. baumannii* that were non-PDR, only 9 isolates (9/11,

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81%) were sensitive to imipenem and 5 isolates (5/11, 45%) were sensitive to levofloxacin, ciprofloxacin, and ceftazidime [7,15,16]. Another 22 isolates of *A. baumannii* that were PDR were completely resistant to all 6 antimicrobial agents [5,6,17-19]. Of the 23 isolates of *E. coli* with ESBL, the most effective antimicrobial agent was imipenem (23/23, 100%) [20,21]. However, of the 15 isolates of *E. coli* without ESBL, the efficacy of imipenem was 13/15 (86%), and cefepime 12/15 (80%). Of the 3 isolates of *E. cloacae* with ESBL, levofloxacin, ciprofloxacin, cefepime, and imipenem were the most effective (3/3, 100%). However, of the 3 isolates of *E. cloacae* without ESBL, the efficacy of imipenem was 3/3, cefepime 3/3, levofloxacin 2/3, and ciprofloxacin 2/3. For *K. pneumoniae* with ESBL, imipenem was the most effective (15/16, 93%). For *K. pneumoniae* without ESBL, the efficacy of levofloxacin, ciprofloxacin, ceftazidime, cefepime, and piperacillin-tazobactam was 14/15 (93%) and that of imipenem was 13/15 (86%). Of the 5 isolates of *S. marcescens*, ceftazidime, piperacillin-tazobactam, and imipenem were the most effective antimicrobial agents (5/5, 100%). The majority of the isolates of *P. aeruginosa* were sensitive to these 6 antimicrobial agents — levofloxacin and ciprofloxacin 10/11 (91%); ceftazidime, cefepime and piperacillin-tazobactam 9/11 (83%); imipenem 8/11 (75%) [9,17,20]. One of the 2 isolates of *Stenotrophomonas maltophilia* was sensitive to levofloxacin, ciprofloxacin, and ceftazidime.

In summary, the majority of the bacterial isolates causing nosocomial infections were sensitive to levofloxacin, ciprofloxacin, ceftazidime, cefepime, imipenem, and tazobactam-piperacillin. Bacterial isolates of nosocomial infections that were completely resistant to these 6 antimicrobial agents were PDR *A. baumannii*, PDR *P. aeruginosa*, and ORSA. New or more potent antimicrobial agents or combination antimicrobial agents therapies are needed to treat nosocomial infections caused by PDR *A. baumannii* and PDR *P. aeruginosa*. For nosocomial infections caused by ORSA, vancomycin, teicoplanin, or linezolid are usually effective.

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