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Comparative in vitro activity of tigecycline and other antimicrobial agents against *Shigella* species from Kuwait and the United Arab of Emirates

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Summary *Shigella* species isolated from stool samples of symptomatic patients of all age groups at the Mubarak Al Kabir Hospital and Infectious Diseases Hospital, Kuwait and Tawam Hospital, UAE during a 2-year period were investigated for their susceptibility to tigecycline and several other antibiotics by determining the minimum inhibitory concentrations (MICs) using the E test method. A total of 100 and 42 strains were collected from UAE and Kuwait, respectively. The extent of drug resistance in the *Shigella* spp. isolates from these two countries was analyzed by criteria recommended by the Clinical and Laboratory Standards Institute (CLSI). Amikacin, cefotaxime, cefuroxime, ciprofloxacin, imipenem, meropenem, piperacillin-tazobactam and tigecycline had excellent activities against all isolates from UAE and Kuwait with MIC_{90s} of 12, 0.094, 4, 0.012, 0.25, 0.032, 3 and 0.25 μg/ml and 4, 1, 4, 0.125, 0.38, 0.19, 3 and 0.25 μg/ml, respectively. Half of all isolates from both countries were resistant to ampicillin. None of the isolates in Kuwait was resistant to amoxicillin—clavulanic acid compared with 22% in UAE. Resistance to chloramphenicol was recorded in 50 and 36% of the isolates in Kuwait and UAE, respectively. The percentages of non-susceptibility to trimethoprim-sulfamethoxazole and tetracycline were very high in Kuwait and UAE (76% vs. 92% and 76% vs. 98%, respectively). Notably, one isolate, *S. flexneri*, from UAE had reduced susceptibility to ciprofloxacin (MIC, 0.25 μg/ml). Four (2.8%) of the isolates were ESBL producers by the E test ESBL method but could not be confirmed by PCR using primers for bla_{CTX-M}, bla_{SHV} and bla_{TEM}. In conclusion, *Shigella* spp. isolated from symptomatic patients in Kuwait and the UAE demonstrated high

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rates of resistance to the first-line antibiotics but very susceptible to the carbapenems, cephalosporins, fluoroquinolones and tigecycline. Tigecycline holds promise as a potential drug of choice for the therapy of severe shigellosis.

Introduction

Shigella species is an important public health problem throughout the world both in developing and developed countries. Shigellosis, the infection caused by *Shigella* spp., is regarded as a major cause of diarrhoea with high morbidity and mortality especially in children. *Shigella* infections can lead to mild self-limiting diarrhoea to severe dysentery. Complications are often seen in children, elderly, malnourished and immunosuppressed patients. Although conservative oral rehydration therapy may be adequate treatment for milder cases of infections caused by *Shigella* spp. other than *S. dysenteriae* type 1, antimicrobial chemotherapy is often required for treating shigellosis in general, and cases of *S. dysenteriae* type 1 in particular. However, since *S. dysenteriae* type 1 produces Shiga toxin, the use of antibiotics may become a dilemma. Effective and appropriate antimicrobial chemotherapy may reduce the duration of fecal excretion of the micro-organisms, reduce the duration of the illness and reduce the spread of the infection [1]. Ampicillin was the drug of choice until the mid-1980s when it was replaced by trimethoprim-sulfamethoxazole and nalidixic acid [2]. Antimicrobial resistance of *Shigella* spp. is increasing because of antimicrobial agents that are used widely in clinical medicine especially in developing countries [3,4]. Multi-drug resistant *Shigella* spp. have been reported including resistance to fluoroquinolones and the third-generation cephalosporins such as cefotaxime and ceftriaxone, in which antimicrobial therapy has become very limited [4,5]. Third-generation cephalosporins or ciprofloxacin are the main drugs used for treating invasive *Shigella* infection in Kuwait and UAE.

The aim of the present study is to evaluate the antimicrobial susceptibility of clinical isolates of *Shigella* spp. in Kuwait and UAE and determine the extent of resistance problem in the two countries.

Materials and methods

Bacterial strains

In Kuwait, *Shigella* spp. isolated from the stool samples of patients with acute diarrhoea were collected between April 2003 and March 2005 from Mubarak Al Kabir Hospital, Jabriya and Infectious Disease Hospital while in the UAE, *Shigella* spp. isolated from patients with similar symptoms attending Tawam Hospital, Al Ain were collected between January 2003 and December 2004. Only the *Shigella* spp. isolated from stool cultures were evaluated. There were no replicate strains in this study. The isolates were then stored at $-80\,^{\circ}C$ until used. Isolates from Kuwait were identified at the Clinical Microbiology Laboratory of Mubarak Al Kabir Hospital, Kuwait by standard methods using automated Vitek II system (BioMerieux, Marcy-l'Eoile, France) and those from UAE by API 20E (BioMerieux, France) in the Microbiology Laboratory of Tawam Hospital, Al Ain, UAE. The strains were identified to species levels using serological latex agglutination (Denka Seiken UK Ltd., Derbyshire, UK).

Antimicrobial susceptibility testing

The susceptibility testing was performed at the Anaerobe/Hospital Infection Laboratory, Department of Microbiology, Faculty of Medicine, Kuwait. All isolates were tested for their susceptibility to the following antibiotics: amikacin, ampicillin, amoxicillin—clavulanic acid, cefotaxime, ceftriaxone, cefuroxime, chloramphenicol, ciprofloxacin, gentamicin, imipenem, meropenem, piperacillin-tazobactam, tetracycline, tigecycline, and trimethoprim-sulfamethoxazole by determining the minimum inhibitory concentrations (MICs) using E test (AB Biodisk, Solna, Sweden). Breakpoints for antibiotics used to interpret the results of the *Shigella* spp. were according to the Clinical and Laboratory Standard Institute [6] except for tigecycline where the US Food and Drug Administration (FDA) breakpoint was applied (Tigacil package insert; Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA). The antibiotic breakpoints used were as follows: amikacin $\leq 16\,\mu g/ml$, ampicillin $\leq 8\,\mu g/ml$, amoxicillin—clavulanic acid $\leq 8/4\,\mu g/ml$, cefotaxime $\leq 8\,\mu g/ml$, ceftriaxone $\leq 8\,\mu g/ml$, cefuroxime $\leq 8\,\mu g/ml$, chloramphenicol $\leq 8\,\mu g/ml$, ciprofloxacin $\leq 1\,\mu g/ml$, gentamicin $\leq 4\,\mu g/ml$, imipenem $\leq 4\,\mu g/ml$, meropenem $\leq 4\,\mu g/ml$, piperacillin-tazobactam $\leq 16/4\,\mu g/ml$, tetracycline $\leq 4\,\mu g/ml$, tigecycline $\leq 2\,\mu g/ml$