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Gastrointestinal Selective Capacity of Doripenem, Meropenem, and Imipenem for Carbapenem-Resistant Gram-Negative Bacilli in Treated Patients with Pneumonia

To the Editor—Multidrug-resistant gram-negative bacilli (GNB) have emerged as major infectious threats and therapeutic challenges for physicians worldwide.[1,2] Infections with these multidrug-resistant pathogens have been associated with poor patient outcomes.[3,4] Data on the emergence of carbapenem-resistant (CR) GNB in gastrointestinal flora and the selective capacity of carbapenem exposure are limited. We conducted a feasibility trial to evaluate the gastrointestinal selective capacity of 3 carbapenems for CR *Acinetobacter baumannii*, CR *Pseudomonas aeruginosa*, and CR *Stenotrophomonas maltophilia* among patients treated for healthcare-associated pneumonia. These findings on the emergence of multidrug-resistant GNB contribute to the current understanding of the selective capacity of gastrointestinal flora after carbapenem exposure.

From October 31, 2009, through August 31, 2010, all patients who were admitted to the medical intensive care unit (ICU) at Thammasat University Hospital with healthcare-associated pneumonia were approached for study participation. Consecutive consenting adults were enrolled. By means of a computer-generated list, patients were randomly assigned at a 1 : 1 : 1 ratio to receive imipenem, meropenem, or doripenem at admission after enrollment. Clinical criteria for healthcare-associated pneumonia were the same as described elsewhere.[5] Rectal swab specimens for culture were obtained at admission, on day 14, and on day 28. Patients who tested positive for enteric CR-GNB at admission or patients who died before day 14 were excluded. Prestudy baseline ICU rates of CR *A. baumannii*, CR *P. aeruginosa*, and CR *S. maltophilia* colonization or infection were 0.85, 0.14, and 0.05 cases per 1,000 patient-days, respectively. Rectal swab specimens were transported and processed within 1 hour of procurement for culture on MacConkey agar plates. Bacterial colonies suspected of being *A. baumannii*, *P. aeruginosa*, or *S. maltophilia* were identified using standard microbiological techniques. The minimum inhibitory concentrations (MICs) of all representative isolates were determined for the 3 study drugs by E-test (AB bioMérieux), in accordance with the manufacturer's protocol. Susceptibility results were interpreted according to Clinical and Laboratory Standards Institute breakpoints.[6] Laboratory personnel were masked to treatment assignments.

During the study period, 69 patients were screened for study participation, and 60 met the study criteria for participation and follow-up (20 patients per drug group). Excluded patients included 4 who tested positive for enteric CR-GNB at admission (2 positive for CR *A. baumannii* and 2 positive

TABLE 1. Characteristics of 60 Study Subjects with Healthcare-Associated Pneumonia and the Emergence of Carbapenem-Resistant (CR) Enteric Flora after Exposure to Carbapenems

Variable	Imipenem (n = 20)	Meropenem (n = 20)	Doripenem (n = 20)
Characteristics			
Age, years	51 (31–65)	50 (25–69)	49 (28–67)
Male sex	12 (60)	13 (65)	13 (65)
Comorbid conditions			
Diabetes	6 (30)	5 (25)	6 (30)
COPD	5 (25)	4 (20)	5 (25)
Chronic liver disease	4 (20)	4 (20)	3 (15)
Chronic kidney disease	5 (25)	5 (25)	4 (20)
Neurological disease	3 (15)	3 (15)	2 (10)
APACHE II score, median	17	16	19
Duration of study therapy, days	7 (6–16)	6 (5–16)	7 (6–15)
Outcomes			
Day 14 after treatment			
CR *Acinetobacter baumannii*	4 (20)	4 (20)	3 (15)
CR *Pseudomonas aeruginosa*	6 (30)	6 (30)	0 (0)[a]
CR *Stenotrophomonas maltophilia*	1 (5)	1 (5)	1 (5)
Day 28 after treatment			
CR *A. baumannii*	4 (20)	4 (20)	3 (15)
CR *P. aeruginosa*	5 (25)	5 (25)	0 (0)[a]
CR *S. maltophilia*	1 (5)	1 (5)	1 (5)

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for CR *P. aeruginosa*) and 5 who died before day 14. The median age of patients was 51 years (range, 31–69 years), the median duration of carbapenem therapy was 7 days (range, 5–16 days), and no enrolled patients had enteric CR-GNB infection or colonization at admission. Patient characteristics are summarized in Table 1. On day 14, CR *A. baumannii*, CR *P. aeruginosa*, and CR *S. maltophilia* were detected in 4 subjects (20%), 6 subjects (30%), and 1 subject (5%), respectively, in the imipenem group, compared with 4 subjects (20%), 6 subjects (30%), and 1 subject (5%), respectively, in the meropenem group and 3 subjects (15%), 0 subjects (0%), and 1 subject (5%), respectively, in the doripenem group. On day 28, CR *A. baumannii*, CR *P. aeruginosa*, and CR *S. maltophilia* were detected in 4 subjects (20%), 5 subjects (25%), and 1 subject (5%), respectively, in the imipenem group, compared with 4 subjects (20%), 5 subjects (25%), and 1 subject (5%) in the meropenem group and 3 subjects (15%), 0 subjects (0%), and 1 subject (5%) in the doripenem group.

Overall, there were no differences in the gastrointestinal selective capacity of the 3 carbapenems for the emergence and detection of CR *A. baumannii* or CR *S. maltophilia* 14 and 28 days after treatment (Table 1). However, on day 14, selection for CR *P. aeruginosa* was found less frequently in the doripenem group than in the imipenem group (0% vs 30%; $P = .01$) and the meropenem group (0% vs 30%; $P = .01$). On day 28, selection for CR *P. aeruginosa* was found less frequently in the doripenem group than in the imipenem group (0% vs 25%; $P = .04$) and the meropenem group (0% vs 25%; $P = .04$) (Table 1). The MIC_{90} values for carbapenems were >32 mg/L for both CR *A. baumannii* and CR *S. maltophilia* isolates in all 3 groups. They were 16 and 8 mg/L 14 days after treatment and 16 and 8 mg/L 28 days after treatment for CR *P. aeruginosa* in the imipenem and meropenem groups, respectively; MIC data were not available for the doripenem group on days 14 and 28.

Although limited by a small sample size and the selected patient population, our study findings suggest that there are no differences in the emergence of CR *A. baumannii* or CR *S. maltophilia* after exposure to imipenem, meropenem, or doripenem for treatment of healthcare-associated pneumonia. However, the emergence of CR *P. aeruginosa* was less frequent among subjects who received doripenem. Additional studies will be important to promote understanding of the gastrointestinal selective capacity of carbapenems and other anti-infective agents for the emergence of multidrug-resistant gram-negative pathogens and their contributory role in the transmission dynamics of drug resistance.

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Intervention to Reduce the Incidence of Healthcare-Associated Methicillin-Resistant *Staphylococcus aureus* Infection in a Tertiary Care Hospital in Saudi Arabia

To the Editor—The greatest success in controlling methicillin-resistant *Staphylococcus aureus* (MRSA) has been in places that adhere to rigorous transmission-based control policies that include active surveillance culture testing to identify colonized patients and strict application of barrier precautions

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