Uptake of higher intravenous colistin methanesulfonate dosing in hospitals in the Gulf Cooperation Council states. *A web-based survey study*

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Infections caused by carbapenem-resistant gram-negative bacteria are becoming increasingly more common, resulting in a parallel increase in the clinical use of intravenous colistin methanesulfonate (CMS), commonly known as colistin.[1] Delayed appropriate antimicrobial therapy for patients with severe infections results in increased morbidity, cost, length of hospital stay and mortality.[2] Data from recent pharmacokinetic studies have shown that standard CMS dosing regimens of 6 million units (480 mg) per day results in sub-optimal serum and target organ concentrations.[3] Moreover, without a high intravenous CMS loading dose of 9-12 million units (720-960 mg), it can take over 48 hours for colistin serum levels to reach a steady state.[4] Many centers around the world have adopted higher intravenous CMS dosing protocols in order to optimize antimicrobial treatment for patients with infections caused by carbapenem-resistant gram-negative bacteria.[5] The aim of this study is to explore variations in CMS dosing regimens used in hospitals in the Gulf Cooperation Council (GCC) states, and the extent to which practice has changed in the light of the emerging CMS pharmacokinetic data.

This study was conducted in May to June 2012. An online questionnaire was prepared using SurveyMonkey® tools, and distributed by e-mail to infectious diseases specialists, intensive care physicians, clinical microbiologists, and clinical pharmacists in major hospitals within the GCC states of the Kingdom of Saudi Arabia (KSA), United Arab Emirates (UAE), Bahrain, Qatar, Kuwait, and Oman. All responses were exported to a Microsoft Excel for analysis.

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Sixty-three complete responses were received out of a total of 110 sent (57.3%). Responses from hospitals in KSA predominated (85.7%), followed by Qatar (7.9%), UAE (3.2%), and Bahrain (3.2%). The majority of respondents were clinical pharmacists (46.0%), followed by infectious diseases physicians (44.4%), intensive care physicians (6.3%), and clinical microbiologists (3.2%). Respondents were mainly from hospitals with 500 beds, or more (72%). Only 3.2% of respondents stated that an intravenous CMS loading dose is administered routinely in their hospitals. Nineteen per cent prescribe a CMS loading dose for selected groups of patients, while 78% never do (**Figure 1**). The most common intravenous CMS maintenance dose for patients with normal renal function is 6 million units (480 mg) per day (92.1%). Regimens of 9 million units (720 mg) per day are used by only 7.9%.

The results outline intravenous CMS dosing practices in major GCC hospitals at the time of the survey. When starting a course of intravenous CMS therapy, the majority of patients neither receive an intravenous loading dose, nor a higher maintenance dose. A commonly cited concern against using higher CMS doses is the risk of increased adverse effects, especially nephrotoxicity. Evidence continues to accumulate in favor of safety and efficacy of CMS dosing regimens utilizing high loading and maintenance doses.[6] One key determinant of CMS nephrotoxicity appears to be the cumulative dose received, rather than individual high doses over the course of therapy.[7] It can therefore be argued that administering a shorter course of a higher dose of intravenous CMS may improve clinical efficacy, without necessarily an associated increased risk of

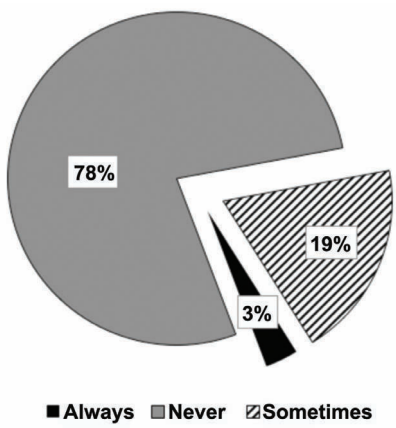

Figure 1 - Responses on the use of intravenous colistin methanesulfonate loading dose of the studied population (N=63 responses).

nephrotoxicity. Comparative data from appropriately designed, prospective studies of both dosing regimens are not available. Responses were received from approximately three-fifths of the surveyed population, and therefore may not be fully representative. We sent named invitations to encourage participation and follow-up reminders to all non-responders. Such rate of unresponsiveness is, however not uncommon in questionnaire-based studies. Moreover, the responses received were overwhelmingly from KSA-based healthcare professionals. This is reflective of the population size and number of secondary healthcare institutions in KSA relative to other GCC states.

In conclusion, intravenous CMS dosing regimens involving a loading dose and higher maintenance doses do not seem to have been taken up widely in the GCC region. Direct comparative clinical studies confirming safety and superior clinical efficacy are probably required for wider implementation of higher intravenous CMS dosing regimens.

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