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ORIGINAL ARTICLE

The impact of clinical pharmacist and ID intervention in rationalization of antimicrobial use

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Abstract *What is known and objective:* There is little research on the impact of implementing and monitoring antimicrobial policy in Saudi hospitals. The purpose of this study is to measure the impact of the clinical pharmacist (CP) and infectious disease consultant (ID) interventions on the use of three antimicrobials (caspofungin, imipenem, meropenem) in hospitalized patients in the King Abdullah Medical City hospital.

Methods: The study was carried out in the King Abdullah Medical City, in Mekkah, Saudi Arabia. The hospital is a tertiary center that provides CCU, CSICU, Cardiac, Hematology, ICU, Medical, Neuroscience, Oncology, and specialized surgery services. The use of three antimicrobials (caspofungin, imipenem, meropenem) was reviewed by the clinical pharmacist for four periods, pre and post implementation of policy. Relevant data were collected in four periods. In the first period, before policy implementation, data were collected retrospectively to be used as baseline status reference, and in the three remaining periods that followed data were collected prospectively, and compared to baseline data, to evaluate the role of clinical pharmacist and ID interventions in optimizing antimicrobial therapy.

Results and discussion: Caspofungin duration of therapy was not affected significantly by the intervention. Statistically significant reduction in antimicrobial therapy duration was observed in imipenem (37%) and meropenem (37%) from baseline, which indicate a better control on antimicrobial use and reduction in antimicrobial resistance.

What is new and conclusion: The impact of the clinical pharmacist and ID interventions, in reducing antimicrobial therapy duration using imipenem and meropenem, is clear from the result presented above. However, lack of restriction and follow up in the antimicrobial policy in case

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of negative culture makes antimicrobial use uncontrollable in these cases. Establishing good and accepted policy may help reduce consumption and total cost of therapy.

1. What is known and objective

Little is known about the impact of implementing and monitoring an antimicrobial policy in Saudi hospitals. Most drug related problems in hospitals are caused by anti-infectives (Khdour et al., 2012). The rational of antimicrobial prescribing is to use the safest and most effective antimicrobial agent against relevant pathogens, with least impact on normal flora (Berild and Haug, 2008). Increased total consumption and use of broad spectrum antibiotics are associated with increased costs, medication errors and widespread antimicrobial resistance (Berild and Haug, 2008; Scheetz et al., 2009). Dynamics of resistance is a function of interacting variables (e.g., introduction of resistance, infection control practices, and antimicrobial use) (Nijssen et al., 2006). Rules and guidelines alone may not be enough to optimize antimicrobial prescribing practice (Charani et al., 2010). Need for intervention by clinical pharmacist (CP) and infectious disease (ID) consultants in managing the policy is well established. Clinical pharmacist interventions eliminate (37.4%) of treatment problems related to efficacy and monitoring of medications (Aburuz et al., 2013), promote efficacy of therapy (Jarab et al., 2012), and enhance desired health outcomes (Jarab et al., 2011). Frequent and prolonged use of broad-spectrum antimicrobial agents promote emergence of resistance (Velickovic-Radovanovic et al., 2012). Reserved antimicrobials should be used cautiously as the last resort. From this reserve we selected one antifungal (caspofungin), and two antibiotics (imipenem, and meropenem). These are of interest because of cost (as in caspofungin), emerging resistance, and being the last line of defense. Our study aimed at assessing the role of the clinical pharmacist and ID in optimizing antimicrobial therapy and preventing misuse of antimicrobials.

Caspofungin is an echinocandin that inhibits the synthesis of β(1,3)-D-glucan, an essential component of the cell wall of susceptible Aspergillus and Candida species. It has been approved by the FDA for use in adults and pediatric patients ($\geqslant$3 months of age) for empirical therapy for presumed fungal infections in febrile, neutropenic patients; treatment of candidemia and the Candida infections (intra-abdominal abscesses, peritonitis, and pleural space infections); treatment of esophageal candidiasis; and treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (e.g., amphotericin B, lipid formulations of amphotericin B, itraconazole) (Merck Sharp et al., 2013).

Imipenem is a Thienamycin that inhibits cell-wall synthesis. Cilastatin is a dehydropeptidase I inhibitor that prevents renal metabolism of imipenem. Imipenem has been approved by the FDA for the treatment of lower respiratory tract infections (LRTI), skin and skin structure infections (SSSI), and intra-abdominal and gynecologic infections caused by susceptible strains of microorganisms (Merck Sharp et al., 2013).

Meropenem is a carbapenem that penetrates bacterial cell walls to reach penicillin-binding-protein targets, thus inhibiting cell wall synthesis, resulting in cell death. The FDA has approved meropenem for the treatment of intra-abdominal infections (complicated appendicitis and peritonitis), bacterial meningitis, and complicated skin and skin structure infections (cSSSI) caused by susceptible strains of microorganisms. It is useful as presumptive therapy in the indicated condition prior to identification of causative organisms (AstraZeneca Pharmaceuticals LP, 2013).

2. Methods

2.1. Study design

This is a retrospective follow up chart review study. The study included 559 orders of antimicrobials in 357 patients in the King Abdullah Medical City, in Mekkah, Saudi Arabia. The hospital is a tertiary center that provides CCU, CSICU, Cardiac, Hematology, ICU, Medical, Neuroscience, Oncology, and specialized surgery services.

2.2. Measured outcome

Duration of antimicrobial therapy's pre- and post-policy implementation was measured, as well as, WHO-defined daily doses as per 100 bed days (DBD) as a marker for antimicrobial consumption. DBD calculate treatment period in a standardized fashion and allow inclusion of periods of shortage of either 70 mg or 50 mg dosage-forms resulting in the replacement of one dosage form for the other, and variation in doses used (Chandwani et al., 2009; Kotapati et al., 2004). Same approach can verify the captured actual duration of therapy parallels WHO-standardized defined daily doses (DDD) a patient should receive on average to achieve cure.

2.3. Inclusion and exclusion criteria

Our study included patients who received any of the three antimicrobials in-hospital, during the study period, regardless of their condition, age, sex, ward, or other variables. Patients not on any of these medications were excluded from the study.

2.4. Study methodology

On a daily basis, the CP reviewed medical chart, lab tests and culture reports and provided therapeutic interventions as needed to the treating physicians regarding doses, interactions and duration of antimicrobial therapy.

As a member of multidisciplinary team, the ID consultant has the authority to change or stop any antimicrobial agent and carries the responsibility of assuring proper antimicrobial use in terms of agent selection, appropriate indication and optimal duration of therapy.

Use of three antimicrobials (caspofungin, imipenem, meropenem) was reviewed by the clinical pharmacist for four periods, one period pre and three periods post implementation of the policy. The first period (Period I) started on 1st of March, 2011 and ended on 31st of August, 2011. The second period (Period II) started on 1st of September, 2011 and ended on 1st of December, 2011. The third period (Period III) started on 2nd December, 2011 and ended on 31st March, 2012. The fourth period (Period IV) started on 1st of April 2012 and ended on 31st of August, 2012. Data were collected retrospectively for the first period to serve as the control group. The following data were collected: file number, ward, culture result, quantity of consumption of antimicrobial, and duration of therapy.

Drug distribution system in the hospital was explained to enable proper interpretation of dates and calculation of time periods and quantities identified in the study.

The patient identifier included in the database is patient-file number, and this identifier was excluded from data presentation, and was only revealed for authorized pharmacy personnel when debating an issue of a dose given to a patient to clear the issue of appropriate dosing and enable identifying the patient and prescriber. Information revealed were never used to inflect penalty on identified people but rather to help resolve clinical decision making errors and clear information from human errors of entry into hospital information-system.

The clinical pharmacist and ID interventions were based on optimal duration of therapy based on Infectious Disease Society of America (IDSA) updated-guidelines.

2.5. Statistical analysis

Data were subjected to statistical analysis comparing duration of therapy, as well as DBD, among the four periods of the study using Oneway-ANOVA test using STATA/IC 12.0 for Windows. Microsoft Excel 2007 was used for data management.

Results were compared between the four periods based on culture-outcome as positive or negative.

3. Results and discussion

Duration of therapy analysis showed significant reduction in the average duration of use of imipenem and meropenem, in the second and fourth periods of the study. Average Caspofungin duration of therapy was (12.15, 7.70, 13.15, 10.97) days, for Periods I, II, III, and IV respectively ($F(3,93) = 0.84$, $p = 0.4756$), while average imipenem duration of therapy was (10.52, 7.61, 8.86, 6.68) days, for the same periods respectively ($F(3,214) = 3.60$, $p = 0.0144$). Meropenem duration of therapy was (12.74, 7.38, 10.35, 7.99) days for the same periods respectively ($F(3,240) = 3.95$, $p = 0.0089$). DBD analysis showed similar results for the same periods and drugs.

Non-significance of reduction of caspofungin DBD resulted from the drug being used in culture-negative patients, as illustrated in Fig. 1, and failing to de-escalate therapy appropriately (Levy et al., 2012). Off-label (Mukattash et al., 2011) and prophylactic prescribing may impair control of caspofungin. In these cases causative organisms were not identified and drug therapy was empirical. The analysis was not expanded to the number of microorganisms and number of infection sites which could affect the result of the analysis (Jourdan et al., 2003).

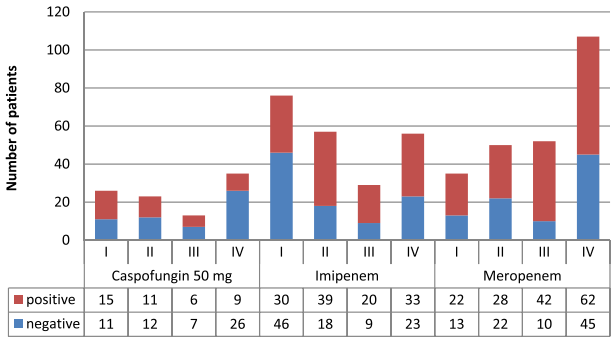

Figure 1 Culture result for the three antimicrobials in the four periods.

Table 1 Doses and World Health Organization defined daily doses for the three antimicrobials used in this study.

	LD[a]	MD[b]	Duration (days)	WHO-DDD[c]
Caspofungin	70 mg stat	50 mg OD	14	50 mg OD
Imipenem		500 mg BID	14	500 mg QID
Meropenem		500 mg TID		500 mg QID

[a] LD: loading dose.
[b] MD: maintenance dose.
[c] WHO-DDD: World Health Organization Define Daily Dose.

Results from implementing and fostering antimicrobial policy by clinical pharmacist and ID resulted in (37%) reduction in consumption of imipenem and meropenem, which correlate with reduction in antimicrobial resistance and associated costs. Velickovic-Radovanovic et al. (2012) reported a similar result (37.8%) (see Table 1).

Table 2 provides the analysis of antimicrobial use in all wards and captures the prescribing habits in these wards. Once wards with high consumption rate were identified a more focused approach was done to dictate the use of the antimicrobial under study to verify rational use of the drug and minimize prolonged unnecessary use of the antimicrobial. For example, the ICU was consuming the highest amount of all three antimicrobials. The open structure of ICU ward allows a higher consumption of antimicrobials with less control to antibiotic prescription (Murunga et al., 2005). This pattern is of concern as the ICU is associated with increased emergence of resistance to treated organisms (Fish et al., 1995). In the first period, major sites of prolonged therapy were: medical ward for all three antimicrobials, CCU for caspofungin, and the cardiac ward for meropenem. In the second period, prolonged therapy peaked in: specialized surgery consumption for caspofungin and meropenem, hematology, ICU, and medical for imipenem, and Oncology for meropenem. The third period showed prolonged therapy in: ICU using caspofungin, hematology, ICU, and medical ward using imipenem, and CSICU using meropenem. In the last period prolonged

Table 2 Defined daily doses per 100 bed days divided by the number of patients for caspofungin, imipenem, and meropenem during the four periods of the study.

Drug	Ward	Period §				Weighted Average
		I	II	III	IV	
Caspofungin	Cardiac ward	0.11	NA	NA	0.31	0.24
	CCU	0.23	0.1	NA	NA	0.14
	CSICU	NA	NA	NA	0.06	0.06
	Hematology unit	NA	NA	NA	0.11	0.11
	ICU	0.12	0.06	0.18	0.13	0.12
	Medical ward	0.26	0.09	0.08	0.04	0.1
	Neuroscience unit	NA	NA	NA	0.05	0.05
	Oncology ward	0.1	0.09	0.05	0.06	0.08
	Specialized Surgical unit	0.18	0.28	0.14	0.24	0.22
Weighted average	0.14	0.1	0.14	0.14	0.13	
Imipenem	–	0.02	NA	NA	NA	0.02
	Cardiac ward	0.09	0.06	0.04	0.04	0.05
	CCU	0.08	0.06	NA	0.03	0.05
	CSICU	NA	0.01	NA	NA	0.01
	Hematology unit	NA	0.08	0.15	0.23	0.17
	ICU	0.13	0.08	0.14	0.09	0.1
	Medical ward	0.19	0.08	0.13	0.08	0.11
	Oncology ward	0.14	0.1	0.03	0.04	0.1
	Specialized Surgical unit	0.11	0.1	0.14	0.04	0.1
Weighted average	0.13	0.08	0.11	0.07	0.1	
Meropenem	–	0.03	NA	NA	NA	0.03
	Cardiac ward	0.36	0.04	0.13	0.17	0.15
	CCU	0.15	0.08	0.03	0.05	0.08
	CSICU	NA	0.04	0.22	0.13	0.11
	Hematology unit	NA	NA	0.14	0.13	0.14
	ICU	0.24	0.14	0.14	0.13	0.16
	Medical ward	0.35	0.1	0.16	0.07	0.12
	Neuroscience unit	NA	NA	NA	0.15	0.15
	Oncology ward	0.19	0.16	0.1	0.09	0.13
	Specialized Surgical unit	0.09	0.12	0.24	0.16	0.16
Weighted average	0.21	0.11	0.15	0.12	0.14	

The cells in orange represent wards that are identified as putting patients on prolonged therapy of the relevant antimicrobial in the related period of the study.

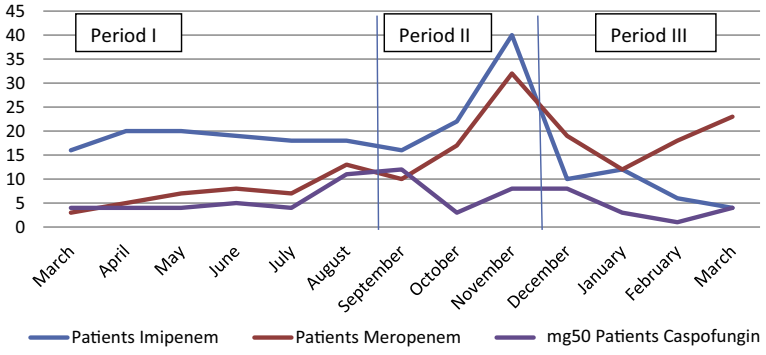

Figure 2 Monthly patient number 2011–2012.

therapy was in: cardiac ward with caspofungin and meropenem, hematology with imipenem, and specialized surgery with meropenem.

During Hajj time millions of pilgrims are received in Mekkah; this necessitates high patient turn over. Figs. 2 and 3 show control of drug ordering habits during the period of peak admission of patients, period II (September–December, 2011), the Hajj time.

This drug utilization review (DUR) enabled auditing use of caspofungin, imipenem, and meropenem in real time and was conducted prospectively longitudinally. The interim reports of this study provided surrogate markers for the result of efforts of the ID and clinical pharmacist services in the whole hospital vicinity.

This DUR included time of Hajj in Mekkah, during this period maintaining antimicrobial control is a challenge, be-

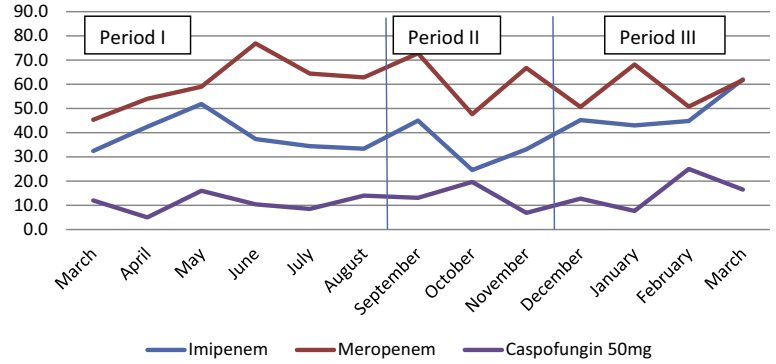

Figure 3 Monthly unit/patient ratio 2011–2012.

cause of increased number of admitted patients and increased antimicrobial use.

The study served as a quality monitor of the hospital pharmacist activity that pertains to clinical pharmacy service provision. This allowed correction of some potential error sources and inspection of faulty entries to promote higher standards of operation; thus some provision in medication safety practice.

This study was presented in the 2nd Mekkah International Conference in its early phases, and this article provides an update and continuation of the same study in its period VI.

Limitations of the study included:

1. Inclusion of subgroup analysis for culture result.
2. Differences in indications and concomitant complications.
3. Resistance patterns of the different strains of the infective organisms.

4. What is new and conclusion

This study showed improvement in antimicrobial use after the intervention of the clinical pharmacist and ID. Involvement of the clinical pharmacist and ID is highly recommended to optimize the use of antimicrobials, and decrease antimicrobial resistance in hospitalized patients. We recommend continuation of the study to maintain supervision over quality, decrease resistance (Regal et al., 2003), and monitor the need for intervention in the different wards. Surveillance of consumption of reserved antibiotics should be done according to local guidelines, as well as for external comparison. This can save medical staff the burden of managing patients chronically, or having deteriorating patients in the wards.

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