Carbapenem Utilization in a Tertiary Referral Teaching Hospital Over 8 Years: A Quasi-Experimental Study

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Abstract

Background: The high prevalence of resistance to broad-spectrum antibiotics in the hospital setting is a challenge worldwide. Inappropriate use of carbapenems has led to growing antimicrobial resistance, specifically in gram-negative pathogens. Evidence suggested that interventions might improve the appropriate use of carbapenems in hospitals. Therefore, we aimed to compare the appropriate use of carbapenems before and after guideline implementation and to investigate consumption trends over 8 years, following restriction policies.

Methods: This quasi-experimental study was conducted in a tertiary referral teaching hospital. Before and after the implementation of the carbapenem use guideline in the hospital, utilization of imipenem and meropenem was evaluated with respect to the appropriateness of indication, initial dose, maintenance dose, and obtaining cultures. Annual consumption of carbapenems in terms of Defined Daily Doses (DDDs) per 100 Occupied Bed-Days (OBDs) was estimated in the hospital from 2014 to 2021.

Results: The frequency of generally appropriate orders increased from 31.6% at baseline to 38% after the primary intervention (P=0.057). The number of cases with carbapenem use for more than 5 days without obtaining cultures decreased significantly in the second evaluation phase (from 15.8% to 8.1%, P=0.001). Despite fluctuations and a non-steady trend, carbapenem consumption increased from 39.30 to 71.37 DDDs/100 OBDs over 8 years with a statistically significant trend ($p < 0.001$, $R^2 = 0.93$).

Conclusion: The rising carbapenem consumption rate was slowed down following the interventions. Additionally, our study demonstrated that guideline implementation improved the appropriate choice of carbapenem and the timely obtaining of cultures. However, the practice change was temporary and limited before the commencement of the restriction policy and ASP. Prospective audit and feedback might be necessary to achieve sustainable changes in the appropriate use of carbapenem in hospitals.

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Keywords: Carbapenem; Antimicrobial Stewardship Program; Drug Utilization Evaluation; Antimicrobial Resistance; Clinical Pharmacy

Introduction

Antimicrobial resistance (AMR) is a global problem nowadays, and the high prevalence of resistance to broad-spectrum antibiotics, specifically in the hospital setting, is a challenge of greater importance (1). AMR is mainly due to the selective pressure following the inappropriate use of antibiotics (2). In other words, overuse of broad-spectrum antibiotics, excessive and unnecessary use of the

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antibiotics and/or using low and insufficient doses of them have a fundamental role in AMR (3, 4).

Carbapenems are among the most important last-line agents for the treatment of severe infections caused by multidrug-resistant (MDR) Gram-negative bacteria, particularly in tertiary care hospitals and intensive care units (ICUs) (5, 6). Inappropriate use of carbapenem has been reported in hospitalized patients (7-12). This has led to growing AMR and outbreaks of resistant gram-negative pathogens such as Pseudomonas aeruginosa and Enterobacterales (13, 14). Similarly, evidence from the hospitals in Iran shows high levels of carbapenem resistance in clinical isolates, highlighting the magnitude of the problem in this settings (15).

Optimal use of broad-spectrum antibiotics, including carbapenems, appears necessary to preserve current sensitivity to antibiotics, hamper the emergence of MDR pathogens, and prevent AMR outbreaks (16). Evidence suggested that interventions might improve appropriate use of antibiotics and reduce hospitalization without increasing the risk of death (2). Carbapenems have been targeted by interventional studies conducted in different settings around the world (10, 17-23).

Despite widespread inappropriate use, few interventional studies in Iran have been reported aiming at optimizing utilization of broad-spectrum antibiotics, including carbapenems (15, 24-26). Interventions in these studies included guideline implementation and restriction policies. A national antimicrobial stewardship program (ASP) was developed in 2016 and 2017 and its implementation has been required in the country's hospitals since 2018. The key policy was to restrict the administration of the eight specific antibiotics, including carbapenems, only to an infectious disease specialist (27). This restriction, however, was modified later.

In our university-affiliated referral tertiary hospital, efforts to improve appropriate utilization of medications, including carbapenems, were initiated in 2014. Carbapenem utilization evaluation, implementation of a carbapenem use guideline, education of the prescribers and ASPs, including restriction policies, were among them. In this quasi-experimental study, we aimed to compare the appropriate use of carbapenems before and after guideline implementation and to investigate consumption trends over 8 years, with respect to all the interventions mentioned.

Methods

This quasi-experimental study was conducted in a tertiary hospital affiliated with Tehran University of Medical Sciences (TUMS). This referral and teaching hospital with 834 licensed beds has various medical and surgical wards, including cardiology, pulmonary, nephrology, gastrointestinal, endocrine, neurology, rheumatology, hematology, oncology, hematopoietic stem cell transplantation (HSCT), urology, maxillofacial, orthopedic, general surgery, neurosurgery, and intensive care. This study was approved by the ethics committee of TUMS (Approval number: 15118).

In this study, carbapenem consumption was studied before and after interventions over 8 years. The primary hospital-wide intervention consisted of the carbapenem (imipenem and meropenem) use guideline. Before the primary intervention, baseline carbapenem utilization was evaluated in January-March 2015. For each new carbapenem order, data including indication, dose, treatment duration, patient demographic information, and other relevant clinical information were collected from patients' medical records, nursing files, and pharmacy database.

In order to develop and approve the guideline for our hospital, we considered the following steps. Initially, a literature review was performed to gather up-to-date available evidence and previously published institutional guidelines. Thereafter, a guideline was drafted, and the hospital infectious disease specialists were asked to review the initial version. After making final revisions according to the experts' comments, the hospital drug and therapeutics committee (DTC) approved the guideline.

After completing the baseline evaluation, the approved guideline was printed in pocket-sized booklets and sent to all hospital wards in April 2015. Additionally, one session was held in each hospital ward to present the guideline to the physicians, including post-graduate medical students, during May and June 2015. We did not consider any restrictive measures at this step until the ASP commencement. Following completion of the sessions, the second carbapenem utilization evaluation was conducted in July-September 2015, considering the same approach as the previous phase before intervention.

Carbapenem use for studied orders was evaluated considering two approaches. First, the appropriateness of every different important aspect of use (i.e., indication, initial dose, maintenance dose, and obtaining cultures) was determined, described, and compared. Second, generally appropriate uses of carbapenem were determined for each of the studied orders. An order that had all aspects appropriately was considered generally appropriate.

Appropriate indication, initial dose, and maintenance dose were determined considering the implemented guideline. All the cases with a duration of use of more than 5 days for which culture was obtained were considered appropriate for the culture aspect. Considering the recorded duration of carbapenem use for study patients, days of therapy (DOTs) and DOTs per patient were also calculated in two evaluation

phases. DOTs were calculated by summing up carbapenem treatment duration for all patients in each phase.

The antimicrobial stewardship program (ASP) has been required in the hospital since September 2016, following the implementation of a global university-level policy. This program required confirmation of all new carbapenem orders by the infectious disease specialists and postgraduate students. The ASP commenced approximately 2-3 months later.

To study the changes in carbapenem utilization in the hospital over 8 years, annual consumption was estimated. According to the World Health Organization (WHO) defined daily dose (DDD) (2018), and using hospital pharmacy sales data, carbapenem consumption was calculated as DDDs per 100 occupied bed days (OBDs). In calculating OBDs, we considered patients who stayed less than 24 hours in the hospital.

Continuous variables were described by mean (SD), while categorical variables were described by frequency (%). Chi-square was used to compare the appropriateness of different aspects of carbapenem use before and after intervention. Linear regression was used for trend analysis. A p-value<0.05 was considered a significant level, and all analyses were performed by SPSS 18.

Results

In the two evaluation phases (e.g., baseline and after the primary intervention), 412 (382) and 418 (371) orders (patients) were recorded, respectively. The demographic and clinical characteristics of patients are described in Table 1.

Table 1. Demographic and clinical characteristics of the patients

Patients' characteristics	Baseline Evaluation	Second Evaluation
Gender, Male, N (%)	194(51.9)	214(58)
Carbapenem type, N (%)		
Meropenem	174(46.5)	158(42.8)
Imipenem	200(53.5)	211(57.2)
Age (years), Mean (SD)	49.2(21.2)	48.9(21.2)
Carbapenem use duration (days), Mean (SD)	12.5(11.9)	11.7(10.2)
Hospital stay (days), Mean (SD)	27.9(37.8)	25.0 (20.9)

N: Number, SD: Standard Deviation

The different indications for carbapenem use across the two evaluation phases are summarized in Figure 1. Before the intervention, the most common infections were pneumonia (30.7%) and septicemia/sepsis (30.7%), followed by neutropenic fever (13.4%) and intra-abdominal infection (10.6%). The proportions of indications changed after the intervention: the frequency (%) of pneumonia decreased to 19.4%, whereas the proportions of septicemia/sepsis and intra-abdominal infection increased to 42.3% and 12.2%, respectively.

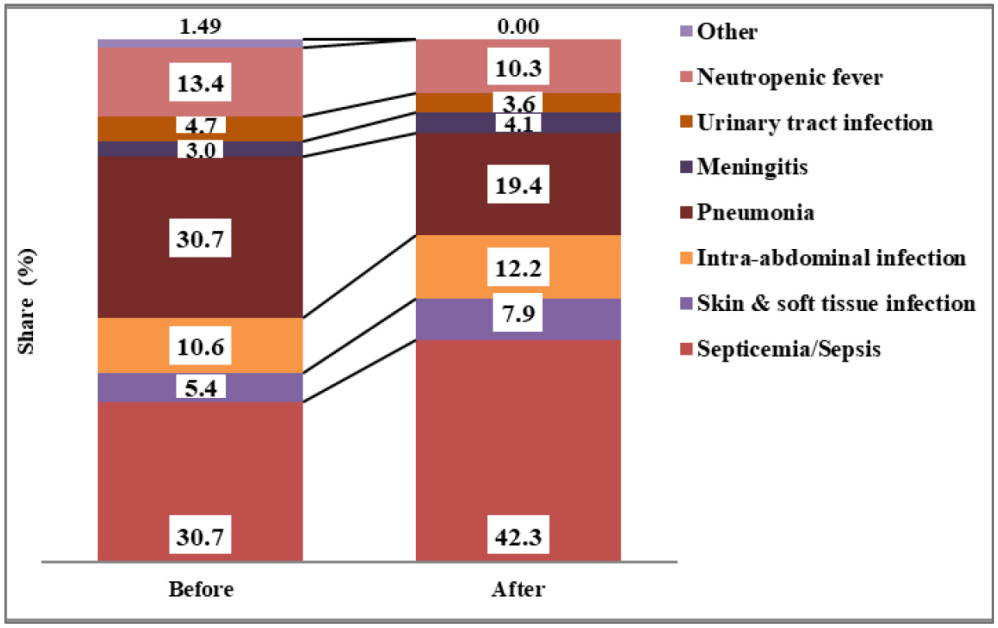


Figure 1. Indications of carbapenems in two evaluation phases

Considering the appropriateness of carbapenem use, the frequency of generally appropriate orders increased from 31.6% at baseline to 38% after the primary intervention (P=0.057). The frequencies of inappropriate indication, initial dose, maintenance dose, and timely culture obtaining were compared in two evaluation phases (Table 2). Inappropriate indications decreased significantly in the 45-day evaluation after the primary intervention. Considering the frequency of inappropriate initial and maintenance doses, we did not observe any significant difference between the two evaluation phases. The number of cases with carbapenem use for more than 5 days without obtaining cultures decreased significantly in the second evaluation phase (from 15.8% to 8.1%, P=0.001).

Table 2. Frequency of inappropriate carbapenem use before and after guideline immplementation

Aspect of Carbapenem Use	Inappropriate cases (%)		P value
	Baseline Evaluation	Second Evaluation	
Indication	25.0	12.9	<0.001
Initial dose	38.3	42.5	0.241
Maintenance dose	39.7	45.5	0.097
Use for > 5 days without obtaining culture	15.8	8.1	0.001

We compared aspects of carbapenem use in the indication subgroups between the two phases. Among the mentioned comparisons, we observed only one statistically significant difference. The frequency of cases with intra-abdominal infections for whom carbapenem was used for more than 5 days without obtaining culture decreased significantly in the second evaluation phase (from 39.5% to 0%, P<0.001).

Carbapenem use in terms of DOTs and DOTs per patient across the two evaluation phases is illustrated in Figure 2. Carbapenem DDDs/100OBDs were 33.88 and 32.48 in the baseline and second evaluation phases, respectively.

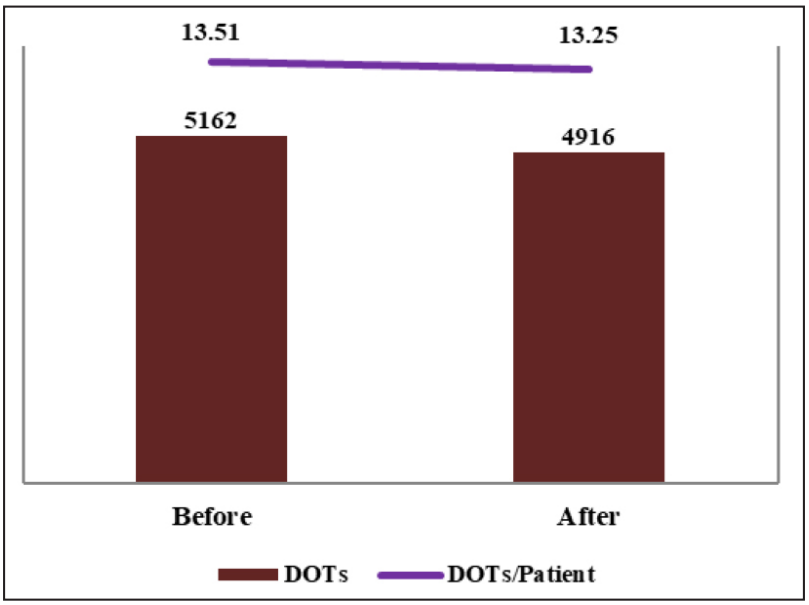
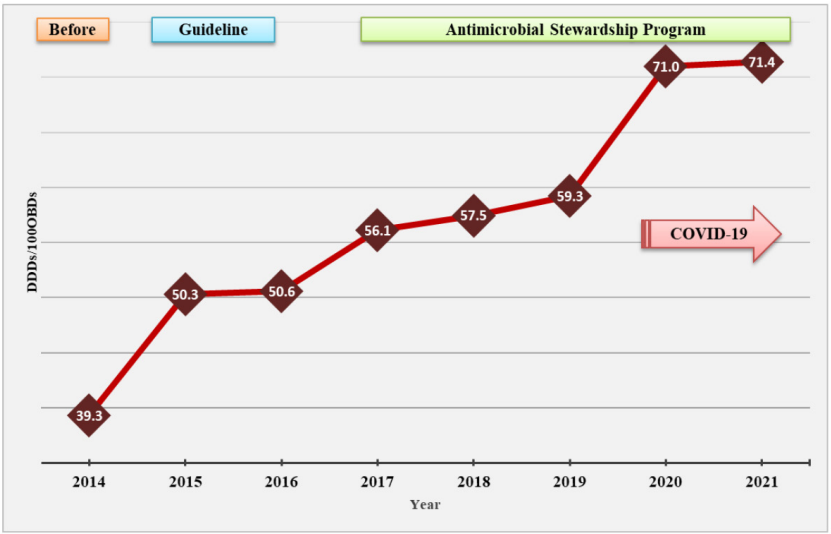


Figure 2. Carbapenem days of therapy (DOTs) and days of therapy per patient (DOTs/Patients) in two evaluation phases

Carbapenem consumption over 8 years increased substantially from 39.30 to 71.37 DDD/100 OBDs (Figure 3). This represents a total relative increase of 81.6% from 2014 to 2021. A simple linear regression showed a statistically significant upward trend ($p < 0.001$, $R^2 = 0.93$).

Figure 3. Carbapenem consumption (Defined Daily Doses (DDDs)/100 Occupied Bed Days (OBDs) in the hospital from 2014 to 2021



Discussion

In the present study, patterns and consumption of carbapenems fluctuated following attempts to optimize their use, considering education, implementation of an evidence-based institutional guideline, and restriction policies.

The pattern of carbapenem use changed after education and guideline implementation in our hospital. Although a 7% increase in generally appropriate uses following intervention was not statistically significant (P=0.057), this change is not negligible. Adherence to the guideline was less than anticipated. Although the guideline was introduced to the physicians during a dedicated session, its specific details were not discussed in depth to mitigate potential disagreements and minimize confusion among prescribers. This may have inadvertently contributed to the lower-than-expected adherence. The effectiveness of institutional guidelines or leaflets alone in improving prescribing has been doubted (28). In other words, a focused educational program including direct and long-term training contact with the prescribers showed sustained improvement in prescribing antibiotics (29).

It should be noted that the session primarily targeted post-graduate medical students and junior physicians, with limited engagement of senior physicians and attending professors. Within this academic training environment, prescribing decisions by trainees and junior physicians are influenced by the supervising attending physician. It has been shown that the most important factors affecting antibiotic choice in teaching hospitals were medical school education and guidance from senior physicians (30).

In our study, appropriate choice of carbapenems, as one of the important aspects of carbapenem use, improved significantly and inappropriate indications reduced to half after guideline implementation. Although the hospital case mix did not change between the two study phases, we observed a seasonal pattern for carbapenem indications. Reasons for carbapenem use changed after intervention; its use for septicemia /sepsis increased while the frequency of pneumonia cases decreased in the second phase. This observation is compatible with the seasonal prevalence of pneumonia (31).

On the other hand, pneumonia, the most frequent indication in the first phase, was one of the main inappropriate indications of carbapenem in our hospital. Therefore, we tried to provide a detailed and clear guide for rational choice of carbapenem in different types of pneumonia in our guideline. Although, this approach improved the rational choice of carbapenem for pneumonia, nearly half of the carbapenem orders for this indication remains inappropriate. Moreover, it is not clear whether decreased use of carbapenems for pneumonia was a seasonal pattern or due to the effect of intervention.

Our intervention could not affect dosing of carbapenem significantly. Nearly 40-50% of initial and maintenance doses were inappropriate in before and after evaluation phases. In spite of detailed dosing guide in the guideline it was not considered by the prescribers. Another important aspect of carbapenem use that is mainly targeted by antimicrobial stewardship programs, is timely adjustment of antibiotic therapy based on obtained cultures. We determined the frequency of carbapenem use for more than 5 days without obtaining culture and the results revealed significant decrease in frequency of these cases in the second phase. Moreover, we observed very small decrease in DOT/patient over the second evaluation phase.

Broad-spectrum antibiotics like imipenem and meropenem are often used in critically ill patients and are rarely

discontinued unless culture results show de-escalation is safe. This is due to clinicians' concerns about therapeutic effectiveness rather than antimicrobial resistance when making decisions (32). Guideline implementation in our study could not optimize the duration of carbapenem use in the hospital. Published studies showed that while guideline implementation and education provided a necessary foundation, they were insufficient to modify prolonged carbapenem use (33).

Carbapenem consumption increased from 39.30 to 71.37 DDDs/100 OBDs over 8 years with a statistically significant trend. Despite this ascending trend, the increase slowed down following interventions. The negligible change from 2015 to 2016 and the minimal increase from 2017 to 2019 in carbapenem consumption signal the effectiveness of the interventions. However, the guideline implementation without continuous active interventions did not result in a sustained effect, which was shown as an increase in carbapenem consumption in 2017 versus 2016. Following the commencement of the restriction policy in the hospital in early 2017, the growing consumption was hampered.

As observed in our study, guideline implementation without restrictions may be insufficient to induce prominent changes in the use of highly prescribed and critical antibiotics such as carbapenems. Restrictive policies could empower the implementation of guidelines for the improvement of the rational use of antibiotics (34). Ozkurt et al. found that an antibiotic restriction policy significantly improved cost, consumption, and the rational use of antibiotics in hospitals (35). Similarly, a carbapenem use restriction program that was developed by Pakyz et al. decreased carbapenem consumption, and the frequency of carbapenem-resistant P. aeruginosa isolates significantly (36). During the COVID-19 pandemic, carbapenem consumption surged. Despite the ASP, higher severity, prolonged stays, and empiric broad-spectrum prescribing during the pandemic substantially amplified carbapenem use after 2019.

This study suffered from some limitations. The most important one was the lack of interactive and effective education and prospective audit and feedback. Moreover, due to the teaching nature of the hospital, a remarkable number of the prescribers were post-graduate medical students who were rotating between university hospitals. This might affect the effectiveness of intermittent educational interventions.

Conclusion

The rising carbapenem consumption rate was slowed down following the interventions. Additionally, our study demonstrated that guideline implementation improved the appropriate choice of carbapenem and the timely obtaining of cultures. However, the practice change was temporary and limited before the commencement of the restriction policy and ASP. Prospective audit and feedback might be necessary to achieve sustainable changes in the appropriate use of carbapenem in hospitals.

Conflict of Interest

Authors have nothing to declare.

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