Evaluation of the Impact of Antimicrobial Stewardship Program (ASP) on Unrestricted Use of Meropenem at an Academic Medical Center

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Abstract

Objective
The primary objectives were to evaluate the prescriber acceptance rate of Antimicrobial Stewardship Program (ASP) pharmacist recommendation to de-escalate/discontinue meropenem, and estimate the difference in duration of meropenem therapy. The secondary objective was to determine incidence of adverse events in the two groups.

Methods
It was a retrospective study. All patients admitted to Gwinnett Medical Center and receiving meropenem from January-November 2015 were included in the study. Exclusion criteria were: patients admitted to intensive care unit, one-time dose, infectious disease consultation, and age <18 years. Electronic medical records were reviewed for data collection. The control group consisted of patients from January-July 2015 when there was no ASP pharmacist. The intervention group consisted of patients from August-November 2015 during which period the ASP pharmacist recommended de-escalation/discontinuation of meropenem based on culture and sensitivity results.

Results
A total of 41 patients were studied, 21 in the control group and 20 in the intervention group. There was no significant difference in baseline characteristics in the two groups and in terms of prior hospitalization or antibiotic use (within 90 days) and documented or suspected MDRO infection at the time of admission. De-escalation/discontinuation was suggested in 16/20 patients in the intervention group (80%), and intervention was accepted in 68%. The mean duration of therapy was significantly decreased in the intervention group (5.6 days vs. 8.1 days, p =0.0175). Two patients had thrombocytopenia (unrelated to meropenem), and none of the patients had seizure.

Conclusion
Targeted antibiotic review is an effective ASP strategy, which significantly decreases the duration of meropenem therapy.

Introduction
Antimicrobial resistance has emerged as a major healthcare problem in the 21st Century. According to the Centers for Disease Control and Prevention (CDC) in 2013, more than 2 million people in the United States became seriously infected with bacteria resistant to at least one antibiotic normally used to treat those infections, and at least 23,000 people died directly due to antibiotic-resistant infections. Rates of antimicrobial resistance among hospitals and community pathogens have increased considerably during the past decade. This growing issue of antimicrobial resistance has substantially contributed to the economic burden of the healthcare system. Antimicrobial resistance leads to multidrug resistant organisms (MDROs). Infection with MDRO leads to an increase in length of stay in the hospital by more than 8 million days annually. Average duration of hospitalization is prolonged by 6.4 to 12.7 days. According to the CDC data, total healthcare costs are estimated to be up to $55 billion, with costs related to loss of productivity contributing almost two-thirds.

The Infectious Diseases Society of America (IDSA) has listed groups of pathogens known as ‘ESKAPE’ pathogens that pose the highest threat, due to increments in prevalence and lack of effective therapeutics. These pathogens currently cause the majority of hospital infections and effectively ‘escape’ the effects of available antibacterial drugs. The ESKAPE pathogens are composed mostly of gram negative bacilli (GNB), such as Pseudomonas aeruginosa, Acinetobacter baumannii and common Enterobacteriaceae (Klebsiella pneumoniae, Enterobacter species, and Escherichia coli). Carbapenems are beta-lactem agents with established efficacy for treatment of GNBs. Due to their safety and established efficacy, carbapenems are usually the last resort option in hospitals’ drug armamentarium for treating MDR-GNB. The emergence and spread of resistance to carbapenems among common GNBs have led to multiple interdisciplinary efforts attempting to contain its spread.

Since one of the major reasons for antimicrobial resistance is widespread access combined with inappropriate use of broad spectrum antibiotics, establishing and strictly adhering to an antimicrobial stewardship program (ASP) can reduce the emergence of resistance. However, there is a dearth of scientific evidence to support the impact of stewardship practices on containing carbapenem-resistant GNB emergence and acquisition. Hence the primary objectives of this study were: i) to evaluate the prescriber acceptance rate of ASP pharmacist recommendations to de-escalate/discontinue meropenem, and ii) to estimate a difference in duration of meropenem therapy with ASP pharmacist intervention compared to no intervention. The secondary objective of this study was to determine the incidence of documented adverse drug reactions due to meropenem therapy, specifically seizures and thrombocytopenia.

Methods

Study setting and implementation of ASP at the site
This was a single center pilot study conducted at Gwinnett Medical Center – a 553-bed tertiary care hospital in Lawrenceville, Georgia. For the purpose of this study, an ASP pharmacist was appointed to review meropenem orders three times a week on selected medical floors.
Orders were reviewed by reviewing patients’ electronic charts to determine the condition for which the patient is being treated and the medical history. If an order was found to be inappropriate or suboptimal, the pharmacist contacted the prescriber directly, to either de-escalate/discontinue the meropenem therapy. De-escalation/discontinuation was based on the following: i) negative cultures at 72 hours, and ii) final culture and sensitivity results. All recommendations were communicated to the primary care team through documentation in the patient’s chart and frequently included telephone or in-person discussions. There was no extra cost for this set-up, and the pharmacist who normally worked on the floors took up this responsibility. The pharmacist did have some help at times from pharmacy residents and students when on rotation.

**Sample size calculation**

To observe an acceptance rate of at least 40% (with an alpha error rate of 5%), a sample size of 18 will provide a statistical power of 95%. Similarly, to observe a decrease in mean duration of meropenem therapy by 1.5 days (with an alpha error rate of 5%), a sample size of 17 will provide a statistical power of 95%.

**Data collection**

Data was collected from January to November 2015. Inclusion criteria were: patients admitted to the hospital and receiving meropenem therapy. Exclusion criteria were: patients admitted to intensive care unit (ICU), one-time meropenem administration, infectious disease consultant on the case, or age <18 years.

The control group consisted of patients who received meropenem therapy according to hospital practice without ASP pharmacist intervention (Jan – July 2015).

The intervention group consisted of patients who were started on meropenem therapy and the order was reviewed by an ASP pharmacist to make necessary recommendations to de-escalate/discontinue meropenem therapy (August – November 2015). Patients in both groups were identified by VigilLanz® software program. VigilLanz® is a clinical decision support software that can identify patients based on the search criteria specified. All data were collected using electronic medical records. After reviewing 60 consecutive patients’ data, a total of 41 patients were included in the final analysis (20 in the control group and 21 in the intervention group). Nineteen patients were excluded due to the following reasons: ICU patients (n=8), one-time meropenem administration (n=2), infectious disease consultation (n=7) and age <18 years (n=2).

Data collection included demographics, risk factors for MDRO infection (previous infection or colonization with MDRO, recent use of broad-spectrum antibiotics, invasive procedures or the use of medical devices (e.g., urinary catheters, endotracheal tubes, vascular catheters), comorbid conditions such as diabetes or chronic kidney disease, receiving hemodialysis, residents of nursing homes or long-term care facilities, and those receiving immunosuppression therapy), indications for initiating meropenem therapy, duration of meropenem therapy, intervention rationale, and whether or not the intervention was accepted. In the intervention group, data on recommended therapy in lieu of meropenem was also gathered. A gram-negative isolate was considered an MDRO if it was non-susceptible to ≥1 agent in ≥3 antimicrobial classes.

Our primary outcome measures were the prescriber acceptance rate of ASP pharmacist recommendation and the difference in duration of meropenem therapy with ASP pharmacist intervention compared to no intervention. The prescriber acceptance rate was calculated (intervention accepted /total reviewed interventions) for the intervention group.

The secondary outcome of this study was the incidence of documented adverse drug reactions secondary to meropenem use, especially seizure and thrombocytopenia. Information on adverse drug reactions secondary to meropenem was abstracted from the patients’ electronic medical records.

A chi-square test was used to compare the categorical variables between the two groups and a students’ t-test was used to compare the continuous variables between the two groups. The student’s t-test was also used to detect the difference in the duration of meropenem therapy between the two groups. The hospital’s Institutional Review Board (IRB) approved the study. The alpha level used for statistical tests was 0.05.

**Results**

The median age in the control group was 64 years (interquartile range (IQR) 40-100 years) vs. 59 years (IQR 34-90 years) in the intervention group (p=0.21). A total of 51.2% of the population was male (9 in the control group, 12 in the intervention group). There was no statistically significant difference in the ethnicity or clinical conditions like hypertension and diabetes between the two groups (Table 1).

**Risk factors for MDRO infection and indicators for meropenem therapy**

A total of 5 patients (23.8%) in the control group had risk factors for MDRO infection compared to 7 patients (35%) in the intervention group (p=0.27). There was no statistically significant difference in the computerized physician order entry (CPOE) indications for initiating meropenem in both the groups (Table 1). Suspected MDRO infection was found to be the major CPOE indication for initiating meropenem therapy (16 in the control group, 15 in the intervention group.) Among the total 31 patients who had suspected MDRO infection as CPOE indication for starting meropenem therapy, only 7 had cultures positive for MDRO (22.5%).

**ASP pharmacist’s recommendations and meropenem de-escalation/discontinuation**

In the intervention group, the de-escalation/discontinuation of meropenem was recommended in 16 patients (80%). The intervention was accepted in 11 out those 16 patients (68% acceptance rate). Reasons for non-acceptance of ASP interventions were classified as follows: 1) physician’s clinical decision, 2) patient still sick, do not wish to de-escalate/discontinue, 3) patient improving with current antibiotics. Interventions recommended were discontinuation of meropenem in 6 patients (37.5%) - negative cultures at 72 hours and de-escalation to other antibiotics in 10 patients (62.5%) - based on final culture and sensitivity results (Figure 1). Ertapenem was the most frequently recommended antibiotic for de-escalation (50%) followed by ceftriaxone (20%), and ciprofloxacin (10%) (Figure 2). The mean duration of meropenem therapy was significantly decreased in the intervention group (5.6 ± 1.8 days) compared to the control group (8.1 ± 2.9), p=0.0175.
Table 1.

| Patient Characteristics       | Control Group (n=21) | Intervention Group (n=20) | P value |
|-------------------------------|----------------------|---------------------------|---------|
| Age in years, median (range)  | 64 (40 - 100)        | 59 (34 - 90)              | 0.21    |
| Males                         | 9                    | 12                        | 0.51    |
| Ethnicity                     |                      |                           |         |
| Caucasians                    | 12                   | 11                        | 0.39    |
| African-Americans             | 6                    | 5                         | 0.54    |
| Others                        | 3                    | 4                         | 0.45    |
| Hypertension                  |                      |                           |         |
| Diabetes Mellitus             |                      |                           |         |
| Risk factors for MDRO infections |                    |                           |         |
| Prior hospitalization (within 90 days) | 2                | 3                         | 0.28    |
| Prior antibiotic administration (within 90 days) | 2                | 3                         | 0.31    |
| Resident of nursing home or LTCF | 1                  | 1                         | 0.80    |
| CPOE indication               |                      |                           |         |
| Allergy to cephalosporin      | 2                    | 1                         | 0.64    |
| Documented MDRO               | 3                    | 4                         | 0.58    |
| Suspected MDRO                | 16                   | 15                        | 0.71    |
**Adverse drug reactions**

Out of the entire study population, 2 patients (9%) had thrombocytopenia, which was found to be unrelated to meropenem therapy. There were no episodes of seizure in any of the patients. All meropenem doses were adjusted for renal function.

**Discussion**

In our pilot study, we found that ASP pharmacist intervention was successful in significantly decreasing the mean duration of meropenem therapy by 2.5 days. One contributing factor to the low acceptance rate of our ASP interventions (68%) could have been the novelty of an ASP that targeted meropenem utilization.
in our institution. However, with continued efforts it is likely to improve. A study by Lew et al. showed a similar acceptance rate (68%) for de-escalation of carbapenem utilizing an ASP setting. They also showed a decrease in mean duration of carbapenem therapy by 2 days with lower rates of adverse drug reactions in the ASP intervention group.10 Another interesting finding of our study was that 75.6% (n=31) of patients were started on meropenem therapy due to suspected MDRO infection. However, only 7 (22.5%) had positive cultures for MDRO. This proves that most patients with suspected MDRO infection actually do not have MDRO infection.

Established risk factors for MDRO infection are previous infection or colonization with MDRO, recent use of broad-spectrum antibiotics, invasive procedures or the use of medical devices (e.g., urinary catheters, endotracheal tubes, vascular catheters), comorbid conditions such as diabetes or chronic kidney disease, receiving hemodialysis, residents of nursing homes or long term care facilities, and those receiving immunosuppression therapy.11(1) However, there is lack of understanding for the potential dangers of inappropriate use of broad-spectrum antibiotics. This along with widespread access to antimicrobials has led to the current state of antimicrobial resistance.12(2) Also, up to 50% of antibiotics used are inappropriate.13(3) Educating the hospital staff including physicians and nurses regarding MDRO infection risk factors can help create awareness and thus increase acceptance rate of ASP pharmacist intervention.

Since this was a pilot study, we did not look at hospital length of stay and cost analysis. Currently the extension of this study is ongoing at our institution to estimate an impact on length of stay and cost savings due to ASP pharmacist intervention. Future studies should definitely look at cost analysis, length of stay and readmissions data. Such data is extremely important for hospital administrators and policy makers, and will help them implement programs like ASP in a full-fledged manner. We only looked at meropenem in this project, but large-scale studies should look at all the antibiotics. Impact on length of stay and cost savings would be much higher if an ASP pharmacist intervenes on unnecessary administration of all possible antibiotics. Future studies should also focus on the impact of stewardship programs on the incidence of MDRO infections.

Few limitations of our study need to be acknowledged. First, this was a retrospective study and data were obtained from electronic medical records. There are inherent limitations of this methodology like lack of proper documentation in some cases. Second, the sample size was small since this was a pilot project. Finally, the ASP pharmacist was available only 3 days a week to review patient charts on selected floors to make the recommendations. However, we believe that this could have underestimated the difference in duration of meropenem therapy. If the ASP pharmacist were available every day of the week, there would have been more possibilities of earlier intervention (at least in some cases), which would have further decreased the duration of meropenem therapy. Studies have shown significant reduction in utilization of broad-spectrum antibiotics with hospital-wide implementation of ASP.13(14)

Conclusion

A high number of patients (80%) who were initially started on meropenem therapy did not need it, and with ASP pharmacist intervention, it was discontinued/de-escalated in 68% of patients. This significantly decreased the mean duration of meropenem therapy by 2.5 days in the studied population. This study shows that not every patient who is suspected to have MDRO infection actually has an MDRO infection. Targeted antibiotic review is an effective ASP strategy to decrease unnecessary usage of broad-spectrum antibiotics like meropenem.

About the Author

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