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Evaluating the use of Ertapenem (Invanz®) in a Hospital System-Epidemiologic and Financial Implications

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ABSTRACT

Purpose: Carbapenems may represent the last effective antibiotics for many multi-drug-resistant gram-negative infections, warranting judicious use in order to curb resistance. In an effort to examine use of a last-line antimicrobial agent and minimize antimicrobial expenditures, ertapenem utilization and wholesale acquisition cost (WAC) expenditures were described at three facilities in San Antonio, Texas.

Methods: This multicenter, retrospective study included 1,448 patients who received ertapenem between July 1, 2013 and December 31, 2013. Patients were analyzed based on number of doses, treatment indication, prescribing physician's specialty, and available microbiology lab results. WAC information was obtained from Amerisource Bergen® and RED BOOK® for projection of cost savings with an alternative therapeutic option (cefazolin+metronidazole) from the organizational perspective.

Results: In total, 3,301 doses of ertapenem were administered, representing an average monthly use of 51.1 doses per 1,000 patient days and a WAC of $270,259 ($81.87/day). Internal medicine practitioners were responsible for the highest utilization, with 1,138 doses (34%) administered during the study period. General surgery, colorectal surgery, emergency medicine, and family medicine followed, with 480 (15%), 413 (13%), 414 (13%), and 290 (9%) ertapenem doses administered, respectively. By comparison, use of cefazolin+metronidazole in the study population resulted in an estimated WAC of $29,808 ($9.03/day). This represented a potential cost savings of $240,451.

Conclusion: Analysis of ertapenem utilization at three regional hospitals over a 6-month period revealed substantial usage, which may negatively influence local resistance patterns. Additionally, use of cefazolin+metronidazole offers a noteworthy cost-savings potential.

INTRODUCTION

Antimicrobial stewardship programs, which often track antibiotic prescribing trends and assess for optimal use, have demonstrated the ability to improve patient safety, reverse antimicrobial resistance rates, and decrease healthcare expenditures [1-14]. Pharmacists often lead these initiatives, given their unique perspective as drug information specialists and thorough knowledge of antimicrobials [1,12]. With the urgent threat from carbapenem-resistant organisms, the utilization of carbapenems and other broad-spectrum antibiotics has drawn attention [15]. Ertapenem for injection (Invanz®) is an appropriate choice for a system-wide drug use review, given its broad spectrum activity, convenient use in many indications, potential impact on collateral resistance, and considerable cost.

Ertapenem is a 1β-methyl carbapenem approved for complicated intra-abdominal infections (cIAI), prophylaxis of surgical site infection in elective colorectal surgery, amongst other indications. This agent has broad spectrum coverage, including efficacy against extended-spectrum B-lactamase (ESBL) and AmpC-producing Enterobacteriaceae, as well as anaerobic bacteria. With a 24-hour dosing interval, ertapenem represents an attractive choice for surgical prophylaxis, eliminating the concern for re-dosing during procedures [16,17].

The Infectious Diseases Society of America (IDSA) guidelines for cIAI list ertapenem as an option for empiric treatment of a mild-to-moderate infection [18]. In addition, multidisciplinary guidelines for antimicrobial prophylaxis in surgery list ertapenem as an option for colorectal surgeries [19]. Ertapenem was previously shown to be more effective than cefotetan and demonstrated cost savings due to the decrease in prophylactic failures and shorter length of stay [20]. Despite convenience, ertapenem remains a controversial option for surgical prophylaxis, due to the availability of alternative therapies, the increasing threat of carbapenem-resistant organisms, and significant cost [21,22].

Carbapenem antibiotics are often considered a last resort and may represent the last effective antibiotic for many multi-drug resistant gram-negative infections, warranting judicious use. As a relatively expensive agent compared to alternative regimens listed in guidelines, ertapenem avoidance presents a potential cost-savings opportunity, particularly in the setting of prophylaxis during colorectal surgery. Ertapenem for injection (Invanz®) use was reviewed at a three regional Methodist Healthcare System sites in order to promote diligent carbapenem utilization efforts regionally and minimize excessive antibiotic expenditures.

METHODS

Inpatient data was retrospectively collected from three community hospitals in San Antonio, Texas from July 1, 2013 to December 31, 2013. Patients ≥ 18 years of age receiving at least one dose of ertapenem for injection were selected as part of a standardized drug utilization report within the electronic health record and were analyzed based on number of doses, treatment indication, hospital unit, prescribing physician's specialty, and available microbiology lab results. Drug utilization was calculated as the aggregate sum of administered ertapenem doses per month for each facility, across all sites, and by physician specialty. Monthly days of therapy were also calculated for each facility (total doses administered/total adjusted patient days × 1000) and across all sites.

In order to further describe the financial impact of ertapenem use in the study sites, cefazolin and metronidazole, in combination, were selected as an alternative therapeutic option, given their appropriateness in many patient cases. Proprietary wholesale acquisition cost (WAC) information was obtained from Amerisource Bergen® in December 2014, although data presented in this publication reflect RED BOOK® WAC pricing from June 2015 [23] WAC for ertapenem 1 gram daily ($81.872) was compared to a 24-hour regimen of intravenous (IV) cefazolin 1 gram q8h + IV metronidazole 500 mg q8h ($9.03) for each month and across specialties.

RESULTS

Overall, drug utilization data was extracted for 1,448 patients across all three facilities. As shown in **Table 1**, a total of 3,301 doses of ertapenem were administered over the study period, with highest utilization in September 2013 (610 total doses). This represents an average monthly use of 51.1 doses per 1,000 patient days, with a max of 58.4 doses per 1,000 patient days in July **(Table 2).**

Table 1. Monthly ertapenem doses administered from July to December 2013.

	July	August	September	October	November	December	Total
Hospital 1	362	371	416	319	337	272	2077
Hospital 2	59	78	56	51	53	73	370
Hospital 3	185	111	138	130	175	115	854
Total	606	560	610	500	565	460	3301

Table 2. Monthly ertapenem days of therapy per 1,000 patient days from July to December 2013.

	July	August	September	October	November	December
Hospital 1	15.3	16.5	17.3	13.1	15.3	11.0
Hospital 2	6.2	8.2	5.8	5.5	6.0	7.5
Hospital 3	36.9	23.4	29.2	29.3	37.1	23.3
Total	58.4	48.1	52.3	47.9	58.4	41.7

Internal medicine, general surgery, colorectal surgery, emergency medicine, and family medicine were the highest-utilizing specialties with 1,138 (34%), 480 (15%), 413 (13%), 414 (13%), and 290 (9%) doses administered during the study period, respectively. Combined, the surgery and colorectal surgery specialties were responsible for 893 doses (28%). Internal medicine and general surgery saw their highest use in November, with 230 and 98 doses, respectively, while colorectal surgery reached its peak in July with 92 doses administered **(Table 3).**

Table 3. Monthly ertapenem doses administered among top 5 physician specialties.

	July	August	September	October	November	December
Internal Medicine	214	163	215	179	230	137
General Surgery	43	96	90	95	98	58
Colorectal Surgery	92	66	76	53	44	82
Emergency Medicine	72	96	82	61	58	45
Family Medicine	66	36	51	32	42	63
Total	487	457	514	420	472	385

Ertapenem WAC estimates for the 6-month period total $270,259.47, with a September WAC of $49,941.92. The WAC for the internal medicine specialty totaled $93,170.34, while combined general and colorectal surgery specialties totaled $73,111.70 during the study period. Combined general and colorectal surgery specialties reached the highest WAC in September, totaling $13,590.75. The five highest utilizing specialties totaled $223,919.92 during the study period.

In comparison, a matched cefazolin + metronidazole regimen would represent a WAC of $29,808.03 over the study period, with potential savings of $240,451.44 over six months if replacing ertapenem in 100% of cases **(Table 4).** The alternative regimen would total $10.276.14 for the internal medicine specialty, with savings of $82,894.20. Combined general and colorectal surgery specialties would result in an alternative WAC total of $8,063.79, which is $65,047.91 less than that of ertapenem. Overall, replacement of ertapenem therapy with matched cefazolin + metronidazole results in an 88.97% reduction in WAC.

Table 4. Monthly ertapenem and proposed alternative (cefazolin + metronidazole) WAC expenditures ($) from July to December 2013.

	Ertapenem WAC	Cefazolin + metronidazole WAC	Proposed savings
July	49,614.43	5,472.18	44,142.25
August	45,848.32	5,056.80	40,791.52
September	49,941.92	5,508.30	44,433.62
October	40,936.00	4,515.00	36,421.00
November	46,257.68	5,101.95	41,155.73
December	37,661.12	4,153.80	33,507.32
Total	270,259.47	29,808.03	240,451.44

DISCUSSION

After the evaluation of ertapenem use at three regional hospitals in San Antonio, Texas, widespread prescribing is apparent, illustrated by the high number of doses per 1,000 patient days over the 6-month period. Utilization was led by the internal medicine, general surgery, colorectal surgery, emergency medicine, and family medicine specialties, which were responsible for over 80% of the WAC estimates. Surprisingly, over 25% of expenditures were due to surgical use. Across all specialties, an alternative regimen of cefazolin+metronidazole represents a viable option with significant WAC savings.

As mentioned previously, ertapenem represents an attractive choice for many indications, with a once-daily dosing interval and broad coverage. The lack of concern regarding re-dosing during surgical procedures, in particular, provides incentive to physicians in general and colorectal surgery specialties. Considering the high use in emergency and internal medicine services, the broad coverage of this agent also provides motivation in cases where more detailed susceptibility information is not yet available. The agent is also useful when treating a patient with a complicated intra-abdominal infectious process who may be a surgical candidate. However, examination of select patients who received several days of ertapenem therapy following microbiological lab results revealed limited de-escalation of therapy, leading to prolonged broad-coverage therapy and excessive expenditures.

In situations where ESBL or AmpC-producing bacterial infections are suspected, carbapenems have been considered first-line, with much evidence supporting success [17,24,25]. However, it is generally accepted that widespread use of any antibiotic will eventually lead to resistance, supporting the reservation of broad-spectrum, last-line agents for necessary cases [21]. In vitro studies have shown that ertapenem may select for resistant Pseudomonal isolates and cross-resistance to imipenem and meropenem, although this has never been proven in vivo [26-29]. Carbapenem use, in general, has been shown to increase the risk of carbapenem-resistant *Klebsiella pneumoniae* infections in inpatients, further illustrating the need for prudent use [30,31].

There are significant limitations to this analysis, given its retrospective nature and absent use of diagnosis and microbiological lab information. Although the authors are unable to comment on the appropriateness of therapeutic alternatives for each patient case, it is reasonable to conclude that cefazolin+metronidazole provides a reasonable coverage pattern that would suit many cases where ertapenem is an option. WAC pricing in this publication was also collected at a later time point, after determination that proprietary cost data is unavailable for publication. Cost calculations do not take other direct or indirect medical expenditures into account. Costs of preparation, administration, and other expenditures may impact the overall value of each treatment method. In the future, an assessment of clinical outcomes for the cefazolin+metronidazole combination versus ertapenem will be necessary to ensure optimal patient safety in a variety of indications.

In summary, it was found that ertapenem has maintained widespread popularity across a variety of physician specialties

within three regional hospitals in San Antonio, Texas. With the increasing threat of carbapenem resistance, judicious use of important broad-spectrum agents should be a major priority. As in the case of ertapenem, antimicrobial stewardship pharmacists should play a significant role in antibiotic-sparing initiatives, using existing knowledge of drug safety profiles, antibiotic resistance rates, and cost information to guide medication use when possible.

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