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# The Duke Antimicrobial Stewardship Outreach Network (DASON) Newsletter

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### Avoiding Ertapenem for Colorectal Surgery Perioperative Prophylaxis

**Background**

Surgical site infections (SSI) are a common problem following colorectal surgery. A 2013 retrospective study involving more than 2,000 patients reported an overall SSI rate following colorectal surgery of approximately 1 in 10 [1]. Optimizing the choice and timing of perioperative prophylactic antibiotics is an important goal for the prevention of SSI. Multiple intravenous antibiotics provide adequate antimicrobial activity for these surgeries, but no compelling data exist to declare a single antibiotic regimen superior to other agents.

The Centers for Medicare and Medicaid Services (CMS) designates approved prophylactic antibiotics for common surgeries through the Surgical Care Improvement Project (SCIP). Ertapenem is one of more than ten approved antibiotic regimens for colorectal procedures [2]. Ertapenem is a beta-lactam antibiotic of the carbapenem class (which also includes meropenem, imipenem, and doripenem). Carbapenems provide broad antibacterial coverage against most Gram-positive and Gram-negative bacteria. We and most other specialists in infectious diseases and epidemiology **do not** recommend carbapenems for routine daily use for an important but often overlooked reason: ***These agents are considered drugs of "last resort" because they are the only remaining commercially-available antibiotics that can be used to treat serious infections due to bacteria that contain extended-spectrum beta-lactamases (ESBL)***.

This newsletter will review current data and evaluate the risks and benefits of use of ertapenem for surgical prophylaxis prior to colorectal procedures. We will provide recommendations for best practice which meet both infection prevention and antibiotic stewardship goals.

**How does ertapenem compare to other antibiotics used for colorectal surgery prophylaxis?**

Only limited data exist comparing ertapenem to other antibiotics in the setting of perioperative prophylaxis for colorectal surgery. A randomized trial published in 2006 analyzed the rate of SSI following 901 colorectal procedures in patients receiving either ertapenem or cefotetan [3]. Ertapenem

was superior to cefotetan in this study: 17% of patients who received ertapenem developed SSIs, while 26% of patients given cefotetan developed these infections. Rates of SSI were higher in both groups in this trial than in other populations that have been studied after colorectal surgery. More patients who received ertapenem developed *Clostridium difficile* infection (1.6%) than those given cefotetan (0.6%), but this difference did not reach statistical significance. Although cefotetan is now considered an inferior regimen for colorectal prophylaxis, ertapenem has not been directly compared to other antibiotics proven to be safe and effective for colorectal surgery prophylaxis.

**Ertapenem offers broad coverage and seems effective for a surgery with a high baseline SSI rate. So why are there concerns about the wisdom of its use for perioperative prophylaxis?**

With the exception of cefotetan, ertapenem has not been shown to be superior to other agents widely used for colorectal surgery prophylaxis [4], including a regimen of cefazolin combined with metronidazole (that is recommended as the regimen of choice by DASON). We believe that preferential or routine use of ertapenem for prophylaxis will not produce better outcomes in individual patients, and importantly, such use may endanger hospitalized patients and individuals in the community by promoting the emergence of multi-drug resistant (MDR) organisms. This is not a purely hypothetical argument: there is no question or scientific disagreement that widespread use of any antimicrobial agent promotes the development of resistance to that agent.

The CDC has recently declared that Carbapenem-resistant Enterobacteriaceae (CRE) are a real and urgent threat to public health. Resistance to carbapenems has consequences that are more serious and far-reaching than resistance to other antibiotics. Carbapenems are the best and often the only antibiotics available to treat life-threatening serious infections due to multiply-resistant Gram-negative bacteria. As the prevalence of CRE continues to increase, particularly in the Eastern United States, both in hospitals and post-acute care facilities, more and more patients are dying because they have infections with no effective treatment [5].

Although the possibility exists that the risk of promoting resistance is lower for widespread ertapenem use than for other carbapenems, this is not a compelling reason to preferentially use ertapenem for routine surgical prophylaxis. A single study found that bowel colonization with carbapenem-resistant Gram-negative bacteria is uncommon after treating intra-abdominal infections with ertapenem [6]; however, resistance is difficult to detect in short-term studies. Furthermore, extensive use of ertapenem, like that of any antibiotic, is expected to promote carbapenem resistance [7]. This effect may be amplified if the course of prophylactic antibiotics extends beyond the day of surgery, a practice that is discouraged with support of a high level of evidence [8].

Resistance to carbapenems is most commonly encountered in non-lactose fermenting gram-negative enteric bacteria. *Pseudomonas* and *Acinetobacter* species are intrinsically resistant to ertapenem; however, they usually remain susceptible to the other carbapenems. In contrast, ertapenem-resistant enteric bacteria are resistant to all carbapenems and are also typically resistant to all or most other common antibiotics. The reasons for this cross-resistance are well understood. Carbapenems are

potent inducers of chromosomal beta-lactamases, such as AmpC, which also induce high-grade resistance to 3rd generation cephalosporins and beta-lactam/beta-lactamase inhibitor combinations [9]. Emergence of AmpC-mediated drug resistance can occur as fast as 2-3 days after treatment with an inducing antibiotic.

Ertapenem prophylaxis for colorectal procedures also produces a risk of *Clostridium difficile* infection (CDI) that may be higher than the risk for other antibiotics because it has a longer half-life than other commonly used agents. Indeed, even a single dose of ertapenem may result in CDI. In the trial described above, more patients receiving ertapenem prophylaxis developed *C. difficile* than those given cefotetan.

Finally, ertapenem is an expensive antibiotic compared with other preferred agents. Exact costs vary by hospital, but per wholesale pricing, costs of 24 hours of treatment with ertapenem compared with the combination of cefazolin and metronidazole are approximately 3-times as high and $50 more per case.

**Summary of Pros and Cons of Prophylactic Ertapenem for Colorectal Surgery**

**Pros:**

- Excellent coverage of Gram-positive and Gram-negative, aerobic and anaerobic bowel flora
- More effective than cefotetan (cefotetan is not a preferred agent)
- Good safety profile for individual patient
- Does not require combination therapy with other antibiotics
- Intraoperative re-dosing unnecessary given long half-life
- One of several SCIP-approved antibiotics for this indication

**Cons:**

- Not proven to be more effective than preferred agents recommended prior to colorectal surgery
- Approximately 3-times as expensive as preferred agents
- May increase risk of *C. difficile* colitis relative to other antibiotics
- **Increases risk of development of drug-resistance**
    - Serious infections with CRE have a 40%-50% mortality rate [10].
    - CRE has implications in the hospital, other healthcare facilities, and the community.

**DASON Recommendations for Antibiotic Prophylaxis Before Colorectal Surgery**

Ertapenem should not be routinely or preferentially used as perioperative prophylaxis prior to colorectal surgeries. The risk of increasing carbapenem resistance and rates of serious, untreatable infections with drug-resistant organisms outweighs the benefit of preferentially using ertapenem instead of other

standard, safe, and effective regimens. Also, ertapenem is three-times as expensive as the recommended agents and may increase the risk of CDI.

Please see the recently updated Prevention Initiative on the DICON Members website (https://diconmembers.medicine.duke.edu/wysiwyg/downloads/Colerectal_project--revised_9-27-13.pdf) for our comprehensive recommendations on methods to reduce the risk of SSI after colorectal surgery. "Appendix A" within this document provides detailed recommendations regarding antibiotic prophylaxis prior to colorectal surgery.

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