Antimicrobial Stewardship News
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Anaerobic Infections and Double Anaerobic Coverage

Introduction

Anaerobic bacteria are normal flora of the oral cavity and gastrointestinal (GI) tract that are pathogenic in a variety of clinical syndromes.[1,2] In clinical practice, anaerobic pathogens are rarely isolated from cultures, and antimicrobial susceptibility testing is not routinely performed in the community hospital setting. Therefore, treatment of infections in which anaerobic bacteria are suspected is often empiric.

The purpose of this newsletter is to outline appropriate anaerobic therapy for select clinical syndromes and to discuss avoidance of double anaerobic coverage.

Anaerobic Pathogens and Antibiotics with Anaerobic Activity

Anaerobic bacteria are causative pathogens in a variety of clinical syndromes. Clinical clues to anaerobic infection include: abscess formation; putrid odors; polymicrobial flora on Gram stain; and infection involving invasion of normal flora from adjacent mucosal surfaces (e.g. oral, gut, or vaginal flora). Anaerobes isolated from the oral cavity are mostly Gram-positive organisms, such as *Peptostreptococcus spp.,* and susceptible to most oral antibiotics including penicillin. Anaerobes isolated from the GI tract, however, are often Gram-negative bacilli, such as *Bacteroides fragilis*, *Prevotella melaninogenica*, and *Fusobacterium spp*., and have variable susceptibility patterns.

Table 1. Select Antibiotics with Anaerobic Activity[3]

Class	Agents (Route)	*B. fragilis* susceptibility[4-7]
Beta-lactam beta-lactamase inhibitor combinations	amoxicillin/clav (PO) ampicillin/sulb (IV) piperacillin/tazo (IV)	90-97% 97% > 99%
Cephalosporin	cefotetan (IV) cefoxitin (IV)	N/A 83-90%
Carbapenem	doripenem (IV) ertapenem (IV/IM) meropenem (IV) imipenem (IV)	> 99%
Fluoroquinolone	moxifloxacin (IV/PO)	66-70%
Other	clindamycin (IV/PO) metronidazole (IV/PO) tigecycline (IV)	66-70% > 99% 81-96%

Double Anaerobic Coverage

Double anaerobic coverage occurs when any of the agents listed in **Table 1** are prescribed in combination. Combinations of antibiotics that include redundant or duplicate antimicrobial therapy place patients at risk for harm and can contribute to antimicrobial resistance. Double anaerobic coverage occurs too frequently in many hospital settings. In fact, nearly one quarter of all metronidazole use in a large retrospective study at 128 hospitals in the Veteran Affairs (VA) healthcare system was considered to be redundant.[8] In addition to placing patients at risk for harm, redundant therapy results in excess costs. In a recent study at 505 nonfederal US hospitals, double anaerobic coverage represented greater than $12 million in potentially avoidable healthcare costs.[9] In both studies, the most common combination of redundant anaerobic coverage was piperacillin-tazobactam plus metronidazole.[8,9] These studies suggest double anaerobic coverage is common and represents a “low hanging fruit” opportunity for intervention for antibiotic stewards.

Many agents that we use to treat common infections include coverage for anaerobic pathogens, such as ampicillin with or without sulbactam. Many other broad spectrum antimicrobials, such as piperacillin-tazobactam and carbapenems, have good anaerobic activity as well and do not need an additional agent when therapy is directed against anaerobes.[10] In the setting of treatment failure with anaerobic infections, appropriate source control should be pursued before considering failure of anti-anaerobic agents.

Do NOT add metronidazole to amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, or a carbapenem to cover anaerobes.

There are no data or national guidelines to support double anaerobic coverage. In our experience, there are two clinical exceptions:

1. Metronidazole may be indicated for treatment of *Clostridium difficile* infection (CDI) in addition to another anti-anaerobic agent required for a second primary infection. In this rare clinical scenario, the benefits of providing appropriate therapy for CDI outweigh the risks of duplicative therapy with overlapping spectrums of activity. However, it should be noted that redundant therapy should be minimized when possible, and the most appropriate agent should be selected to treat each infection.
2. Clindamycin may be indicated with another anti-anaerobic agent when used for the treatment of necrotizing fasciitis. In this rare clinical scenario, clindamycin is selected due to its ability to reduce the production of toxins by staphylococcus and streptococcus.[11] The anti-toxin benefits of clindamycin in severe cases that are rapidly progressive outweigh the risks of duplicative therapy with overlapping spectrums of activity.

Appropriate Anti-Anaerobic Agent Use in Treatment of Clinical Syndromes

Empiric treatment with anaerobic coverage is warranted in a variety of clinical syndromes, including aspiration pneumonia, intra-abdominal infection, diabetic foot infection, and pelvic inflammatory disease.[12-15] In each of these clinical syndromes, anaerobic bacteria are treated empirically because anaerobic pathogens are rarely isolated from cultures and susceptibility testing is not routinely performed. Fortunately, multicenter susceptibility surveys of clinically important anaerobic bacteria continue to report excellent susceptibilities for beta-lactam beta-lactamase inhibitor combinations and the carbapenems; therefore, double anaerobic coverage is not recommended.[10]

Why is Double Anaerobic Coverage So Prevalent?

The exact reasons for the redundant use of antimicrobial agents with anaerobic activity remain unclear. One potential explanation is that many prescribers are unaware of the overlapping spectra of antibiotic activity. When addressing this knowledge gap, it's important to know that most clinically important anaerobic pathogens remain susceptible to commonly used agents (**Table 1**).[8] For example, some clinicians may be unaware that beta-lactam beta-lactamase inhibitor combinations and carbapenems adequately cover anaerobes as a single agent because they confuse their antibiotic spectrum with other anti-pseudomonal agents (e.g. cefepime and ceftazidime). Another potential explanation is the pervasive belief that little harm comes from using multiple antibiotics, and that "more is better." This, in fact, is not the case, and prescribing antibiotics with this mindset is dangerous. Lastly, some redundant use of metronidazole might represent *C. difficile* "prophylaxis," which is not supported by the current guidelines.[16]

Overall, redundant anti-anaerobic use in hospitals is too common. Misperceptions about the potential harm of duplicative therapy as well as the antimicrobial susceptibility patterns of anaerobic bacteria contribute to antibiotic overuse. Redundant anaerobic coverage represents a "low hanging fruit" opportunity for stewardship programs to intervene, educate, and promote the judicious use of antimicrobials.

Take Home Message:

1. Anaerobic bacteria are difficult to isolate, and treatment is often empiric.
2. Double anaerobic coverage should not be routinely provided outside of the following two clinical scenarios:
    a. Metronidazole can be added to another agent with anaerobic activity when being used to treat *Clostridium difficile* infection and a second primary infection.
    b. Clindamycin can be added to another agent with anaerobic activity when being used for the treatment of necrotizing fasciitis.
3. Stewardship champions should target redundant anti-anaerobic antibiotics through education of local providers and stewardship interventions.

dason news

- MARK YOUR CALENDARS! The DASON Continuing Education series program on Urinary Tract Infections will be broadcasted on February 9th from 12-1pm
- Please join us in welcoming April Dyer! She has joined our team of Liaison Clinical Pharmacists!

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