Double Anaerobic Coverage: What is the role in clinical practice?

BACKGROUND

Anaerobic pathogens are normal flora of the oral cavity and the gastrointestinal tract. While oral anaerobic flora are mostly gram-positive organisms such as *Peptococcus* and *Peptostreptococcus spp.,* the principal anaerobic intestinal flora are gram-negative bacilli such as *Bacteroides fragilis*, *Prevotella melaninogenica*, and *Fusobacterium spp.* Gram-positive oral anaerobes are widely covered by most of the orally-available agents, including penicillin. However, antibiotic activity against the most common intestinal anaerobic bacteria, *Bacteroides spp.*, is variable.

Anaerobic coverage is indicated in a variety of infectious processes, including but not limited to aspiration pneumonia, intra-abdominal infection, gynecologic infection, and diabetic foot ulcer infection. Antimicrobial agents with appreciable anaerobic activity include the following:

- Amoxicillin/clavulanate
- Ampicillin/sulbactam
- Cefotetan
- Cefoxitin
- Clindamycin
- Doripenem
- Ertapenem
- Imipenem
- Meropenem
- Metronidazole
- Moxifloxacin
- Piperacillin/tazobactam
- Ticarcillin/clavulanate
- Tigecycline

Double anaerobic coverage is the use of any combination of the above agents, which is prevalent at The Nebraska Medical Center. Redundant anaerobic coverage is the third most common problem intervened upon by the Antimicrobial Stewardship Program, accounting for approximately 20% of the interventions.

Available susceptibility and clinical data do not support this practice. The following susceptibility data from 2005-2007 were observed for the *B. fragilis* group, the most common pathogenic gram-negative anaerobes:[1]

RESISTANCE RATES OF VARIOUS ANTIBIOTIC AGENTS AMONG *B. FRAGILIS* GROUP ISOLATES

Antibiotic Agent (No. of Isolates Tested)	Resistance breakpoint (mg/L)	% Resistant[a]
Metronidazole (6574)	≥32	<0.1
Piperacillin-tazobactam (1351)	≥128	0.3
Ampicillin-sulbactam (1351)	≥32	5.5
Cefoxitin (1351)	≥64	9.1
Meropenem (1351)	≥16	0.4
Ertapenem (1351)	≥16	0.9
Clindamycin (1351)	≥8	36
Moxifloxacin (1351)	≥8	40.7
Tigecycline (1351)	≥16	4.3

[a]Isolates categorized according to CLSI breakpoints. Adapted and modified from Snydman DR, Jacobus NV, McDermott LA, et al. Lessons learned from the anaerobe survey: historical perspective and review of the most recent data (2005-2007). *Clin Infect Dis*. 2010;50 Suppl 1:S26-33.

With regard to gram-positive anaerobes, all the agents listed above maintain excellent activity.[2] For example, moxifloxacin was shown to have excellent activity against gram-positive anaerobic cocci such as *Peptostreptococcus* spp with MICs as low as 0.25mg/L (range 0.25-1mg/L).[3-5]

None of the available treatment guidelines published by the Infectious Diseases Society of America (IDSA) recommend the use of double anaerobic coverage.

CLINICAL SYNDROMES

Aspiration Pneumonia

Aspiration pneumonia and pneumonitis are common clinical syndromes. In the case of aspiration pneumonia, oral gram-positive anaerobic flora and gram-negative enterics are the pathogens of interest as opposed to those traditionally associated with intra-abdominal infections. Amoxicillin/clavulanate, clindamycin, or moxifloxacin provide excellent anaerobic coverage for aspiration pneumonia. Aspiration pneumonitis follows the aspiration of gastric contents, and often no organism is implicated.

Intra-abdominal Infection

The recent intra-abdominal guidelines published by the Infectious Diseases Society of America and the Surgical Infection Society recommend metronidazole as the anaerobic agent of choice for combination therapy with agents devoid of clinically-significant anaerobic activity (i.e., agents other than those listed above), whereas beta-lactam monotherapy such as piperacillin/tazobactam or a carbapenem is reserved for complicated cases of intra-abdominal infection.[6] Table 1 summarizes the guideline recommendations for community-acquired intra-abdominal infections.

Table 1 Empiric antibiotic therapy for community-acquired intra-abdominal infection

Regimen	Adults: mild to moderate (e.g. perforated or abscessed appendicitis)	Adults: High risk or severe (severe physiologic disturbance, advanced age, immunocompromised state)	Pediatrics
Single agent	Cefoxitin, ertapenem, moxifloxacin, tigecycline	Meropenem, piperacillin/tazobactam	Ertapenem, meropenem, piperacillin/tazobactam
Combination	Cefazolin, cefuroxime, ceftriaxone, ciprofloxacin **PLUS** Metronidazole	Cefepime, ceftazidime, ciprofloxacin **PLUS** Metronidazole	Ceftriaxone, cefotaxime, cefepime, ceftazidime **PLUS** Metronidazole **OR** Gentamicin or tobramycin **PLUS** Metronidazole or clindamycin **±** Ampicillin

Healthcare-associated intra-abdominal infection includes a spectrum of adult patients who have close association with acute care hospitals or reside in chronic care settings. These patients are typically at risk for infection with multidrug resistant (MDR) flora, *P. aeruginosa* and *Acinetobacter* species, extended-spectrum beta-lactamase (ESBL)–producing *Klebsiella* and *E. coli*, *Enterobacter* species, *Proteus* species, methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococci*, and *Candida* species. Some identified risk factors for healthcare-associated intra-abdominal infection include: (1) presence of an invasive device at time of admission; (2) history of MRSA infection or colonization; or (3) history of surgery, hospitalization, dialysis, or residence in a long-term care facility in the 12 months preceding the

culture date. The decision regarding an appropriate empiric regimen in these cases should be guided by local susceptibility data. Reasonable empiric therapy options for healthcare-associated intra-abdominal infections include piperacillin/tazobactam, meropenem, or a combination of cefepime plus metronidazole. Vancomycin may be added if MRSA is a concern.

Pelvic Inflammatory Disease

In pelvic inflammatory disease (PID), the most common pathogens are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, but other pathogens such as anaerobes, *G. vaginalis, Haemophilus influenzae,* enteric Gram-negative bacilli, *Streptococcus agalactiae,* mycoplasmal bacteria (*M. hominis* and *M. genitalium)*, and *U. urealyticum* have also been associated with PID.[7,8] Treatments are generally targeted toward these pathogens.[7,8] Anaerobic coverage is indicated if tubo-ovarian abscess is present. The Centers for Disease Control and Prevention (CDC) guidelines do not recommend double anaerobic coverage, and no evidence exists to show that double anaerobic coverage in PID results in better clinical or microbiologic cure rates. The CDC's treatment recommendations are summarized in table 2.[7] Haggerty et al. have summarized several PID trials in a recent article.[9] The therapies and their respective clinical cure rates were: ofloxacin (95%) vs. cefoxitin plus doxycycline (93%); clindamycin plus ciprofloxacin (97%) vs. ceftriaxone and doxycycline (95%); moxifloxacin (90%) vs. ofloxacin plus metronidazole (91%); doxycycline plus metronidazole (91%) or ciprofloxacin plus tinidazole (96%); azithromycin alone (97%) or azithromycin plus metronidazole (96%) vs. metronidazole plus doxycycline plus cefoxitin plus probenecid (95%) or doxycycline plus amoxicillin/clavulanate (95%); doxycycline plus metronidazole (35%); meropenem (88%) vs. clindamycin plus gentamicin (90%). The microbiologic eradication rate was also high, with a median of over 90% (range 88-100%). Interestingly, regimens with or without an anti-anaerobic agent produced similar clinical cure rates and microbiologic eradication rates. However, the CDC still suggests the optional addition of metronidazole to ofloxacin therapy given higher treatment failure in non-gonococcal, non-chlyamydial PID in the ofloxacin trial.[7,8] The trial that used metronidazole plus doxycycline plus cefoxitin reported higher rate of adverse events and discontinuations.[10] Based on these trials, the use of double anaerobic coverage in PID is unfounded.

Table 2. Treatment recommendations for PID

Options	Regimen A	Regimen B	Alternative
Parenteral therapy	Cefoxitin **PLUS** Doxycycline	Clindamycin **PLUS** Gentamicin	Ampicillin/sulbactam + doxycycline
Oral therapy	Ceftriaxone IM **PLUS** Doxycycline **±** Metronidazole **OR** Cefoxitin IM **plus** Probenecid x1 dose **PLUS** Doxycycline **±** metronidazole **OR** Cefotaxime **PLUS** Doxycycline ± metronidazole		Levofloxacin ± metronidazole **OR** Ofloxacin ± metronidazole **OR** Amoxicillin/clavulanate + doxycycline **OR** Azithromycin + metronidazole

Avoid fluoroquinolone-based regimen if *N. gonorrheae* is suspected and antimicrobial susceptibility data are unavailable. Discontinue parenteral therapy after 24 hours of clinical improvement. Duration of therapy is 14 days and may be completed orally with doxycycline alone or the addition of clindamycin or metronidazole to doxycycline if PID is complicated by tubo-ovarian abscess.

CONCLUSIONS

Use of multiple drugs active against anaerobes is not necessary and puts the patients at risk for additional drug toxicities. No data or guidelines support the use of two anti-anaerobic drugs in clinical practice, with two clinical exceptions (see below).

Exceptions:

1. Metronidazole can be added to another agent with anaerobic activity when being used to treat *Clostridium difficile* infection.
2. Clindamycin can be added to another agent with anaerobic activity when being used for the treatment of necrotizing fasciitis.

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