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Frequently Asked Question 2: Antimicrobial Double Coverage

Background:

Antimicrobial double coverage is defined as prescribing two antimicrobials to treat the same microorganism. The use of double coverage is often justified by a desire to ensure adequate empiric therapy, achieve synergy, or prevent the development of resistance. However, double coverage for pathogens is rarely indicated, and double coverage can be associated with adverse events. The following organizations endorse pharmacy review of double coverage to improve patient care: Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA), and the Centers for Disease Control and Prevention (CDC).[1,2] The purpose of this FAQ is to review the literature for antimicrobial double coverage, outline the benefits and harms associated with double coverage, and describe when double coverage should be considered.

Summary of Evidence:

Antimicrobial double coverage can be classified into two separate categories: empiric and definitive therapy. Empiric therapy is use when culture results are not yet known. Definitive therapy is when culture results have already resulted.

Empiric Therapy: Improved outcomes are associated with appropriate initial therapy, especially in critically ill patients. Use of local antibiogram data, along with knowledge of patient specific risk factors for antimicrobial resistance should guide empiric therapy choices. Double-coverage of suspected Gram-negative pathogens is rarely indicated.[3-8] For example, Gram-negative monotherapy is appropriate if the antibiotic is expected to be active against ≥90% of Gram-negative bacilli. For example, if your antibiogram shows that most Gram-negative pathogens remain susceptible to cefepime, then empiric gram-negative double coverage is not necessary under most circumstances. Furthermore, it is unlikely that a pathogen resistant to a broad-spectrum beta-lactam, like cefepime, will remain susceptible to a fluoroquinolone.[3] Similarly, most anaerobic bacteria remain susceptible to beta-lactam/beta-lactamase combinations and metronidazole. Combining two anaerobic agents for empiric therapy is not recommended.

Definitive Therapy: In circumstances where empiric double coverage is employed, de-escalation to a single agent is recommended once susceptibility data are available.[1] *For most conditions, there is no evidence to support routine use of combination therapy once susceptibility data are known.* Clinicians will occasionally prescribe two antibiotics for synergy. The data behind synergy is limited, and there are few settings where synergy is recommended (e.g. certain types of streptococcal endocarditis, cryptococcal meningitis, treatment of some mycobacterial infections, treatment of HIV, management of necrotizing fasciitis, and treatment of some prosthetic joint infections). Synergy between drug classes is not well documented, and *some combinations of antibiotics may be antagonistic*, rather than synergistic.[3,5] An infectious diseases consult is strongly recommended if double coverage for the purpose of synergy is considered for definitive therapy.

Antimicrobial Stewardship Program

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Overview of the Risks and Benefits of Double Coverage:

Benefits: There are limited benefits for double coverage. Situations where double coverage should be considered include:

- Known or suspected multidrug-resistant bacterial infections
- Treatment of prosthetic joints infections with retained hardware
- Treatment of infections where resistance is known to develop on therapy

Risks: There are several risks associated with unnecessary double coverage. These risks include:

- Increased complexity of treatment regimen
    - Particularly significant in patients receiving multiple intravenous medications
- Increased risk of toxicity (including seizures)
- Potential antagonism
- Increased cost of therapy
- Increased risk of superinfections

Summary and Recommendations:

Antimicrobial double coverage for empiric and definitive treatment of patients is rarely warranted and can be associated with adverse events. Pharmacy evaluation of patients receiving double antimicrobial coverage is the standard of care and endorsed by several professional societies.[1,2] Providers who are interested in prescribing two or more antimicrobials should discuss the case with an antimicrobial stewardship pharmacist and/or an infectious disease physician. These providers can help optimize antimicrobial coverage while minimizing patient harm.

CONSIDER GRAM NEGATIVE DOUBLE COVERAGE:

1. Empiric treatment of serious, suspected multidrug resistant Gram-negative, infections (presenting with hypotension, pressor requirement, or mechanical ventilation) *until microbiology data are available*.
2. Documented infection with a resistant Gram-negative organism with very limited treatment options.
3. Documented infection with a resistant Gram-negative organism after synergy testing has shown benefit.

NOTE: The two agents should be from different antimicrobial classes (i.e. beta-lactam + aminoglycoside or beta-lactam + quinolone) and chosen based on local, or pathogen specific, susceptibility data.

CONSIDER ANAEROBIC DOUBLE COVERAGE:

1. Metronidazole or vancomycin may be added to another agent with anaerobic coverage to treat a *clostridium difficile* infection.
2. Clindamycin may be added to therapy when treating necrotizing fasciitis.

References:

1. Dellit TH, Owens RC, McGowan JE, Jr., et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007;44(2):159-177.
2. Centers for Disease Control and Prevention. Core Elements of Hospital Antibiotic Stewardship Programs. 2017; https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html. Accessed May 8, 2018.
3. Johnson SJ, Ernst EJ, Moores KG. Is double coverage of gram-negative organisms necessary? *Am J Health-Syst Pharm.* 2011;68(2):119-124.
4. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* 2016;63(5):e61-e111.
5. Barriere SL. Monotherapy versus combination antimicrobial therapy: a review. *Pharmacotherapy.* 1991;11(2 (Pt 2)):64S-71S.
6. Leibovici L, Paul M, Poznanski O, et al. Monotherapy Versus Beta-Lactam-Aminoglycoside Combination Treatment for Gram-Negative Bacteremia: a Prospective Observational Study. *Antimicrob Agents Chemother.* 1997;41(5):1127-1133.
7. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ.* 2004;328(7441):668.
8. Paul M, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ.* 2003;326(7399):1111.