Guidance

Central Administration of Pharmaceutical Care
General Administration For Drug Utilization &Pharmacy Practice

National Guidance for the Rational Use of Duplicate Antimicrobial Therapy 2024

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Contents

The Scope of the Guidance

To describe the appropriate use of duplicate antimicrobial therapy.
To describe best practices in antimicrobial prescribing including antimicrobial agents that are available in Egypt.
To serve as a clinical guide and not supersede the clinical judgment of physicians in the management of individual patients.

Abbreviations

ASP	Antimicrobial Stewardship Program
AST	Antibiotic Susceptibility Testing
CDC	The Centers for Disease Control and Prevention
CRE	Carbapenem-Resistant Enterobacteriaceae
C. difficile	Clostridioides difficile
CBA	Colistin Base Activity
CSF	Cerebro Spinal Fluid
DTR-PA	Difficult-to-Treat P.aeruginosa
DAC	Double Anaerobic Coverage
IV	Intravenous
KPC	Klebsiella pneumoniae carbapenemase producer
NVE	Native Valve Endocarditis
non-HLAR	non-High-Level Aminoglycoside Resistance
NDM	New Delhi metallo-β-lactamase - type
PVE	Prosthetic Valve Endocarditis
UTI	Urinary Tract Infection
MSSA	Methicillin-sensitive Staphylococcus aureus

Introduction

Combining two or more antibiotics may be necessary when treating certain types of infections. When combined, some antibiotics work synergistically to treat certain types of infections. Others are combined because a broader spectrum of coverage is needed in polymicrobial infections. For example, gentamicin is typically added to a beta-lactam antibiotic for the treatment of gram-positive endocarditis. Infections caused by Pseudomonas aeruginosa can be treated with a two-drug combination that includes an antipseudomonal beta-lactam (e.g., piperacillin/tazobactam) plus either an aminoglycoside, ciprofloxacin, or levofloxacin in certain conditions.[1] Combination therapy has also been used to treat multidrug-resistant Acinetobacter baumannii and Carbapenem-Resistant Enterobacteriaceae (CRE) in healthcare facilities globally. Although optimal therapy for these highly resistant infections has not been well defined, regimens usually include combinations of polymyxin and a secondary agent (e.g., tigecycline, aminoglycosides, or carbapenems), However, de-escalation should occur when microbiology data return in 48-72 hours, the duration of the redundant event should be short. [1]

The interest of the scientific community in combining different antibiotics started in the 1950s when the high incidence of relapse of endocarditis treated with penicillin G alone was largely reduced by simply adding streptomycin. Since then, the concepts of *synergy* and *antagonism* have sparked the curiosity of microbiologists, biochemists, and molecular biologists who began testing combinations of a wide range of antibiotics available at that time. In summary, the *theory of synergy* states that the effect of certain antibiotics used together is more potent than the sum of their individual effects. *Antagonism*, on the other hand, occurs when the combined effect of antimicrobial drugs is less than the sum of the independent effects measured separately. [2]

Combinations of antimicrobial agents that could constitute unnecessary therapy are a relatively easy target for stewardship intervention. Most commonly, this includes potentially redundant therapy or therapeutic duplication, whereby antimicrobials with an overlapping spectrum of activity are prescribed.[3] This refers to when two antibiotics are covering the same organism, yet only one antibiotic is needed for the job. Exposing a patient to two medications instead of just one can be considered inappropriate, as it needlessly increases a person's risk for adverse drug events and ecological consequences of antibiotic use (*e.g.*, risk for *Clostridium difficile* infection).[5],[6],[7]

Reports by the CDC indicate that 30% to 50% of antibiotic use in hospitals is unnecessary or unwarranted. [4]

There may be several potential reasons that clinicians choose to use redundant antimicrobials, some of which could be improved by the ASP: correcting inadvertent errors within the ordering process and review (e.g. provider forgot to discontinue an existing order when placing a new antibiotic order), correcting misunderstandings about the spectrum of activity, addressing the "more is better" mentality, and addressing concerns about resistant pathogens or source control.

CDC suggests that pharmacists should review unnecessarily duplicative antibiotic therapy, including the use of agents with overlapping spectra. [6]

Duplicate Antimicrobial Agents in The Common Practice

The following antibiotics (Table 1) are combinations of drugs that may represent unnecessary overlap in antimicrobial spectra and may require an intervention, but they may be used appropriately in certain conditions For example, piperacillin/tazobactam with intravenous metronidazole to treat a skin and soft tissue infection would generally be duplicate therapy. However, piperacillin/tazobactam together with oral metronidazole for C. difficile infection would be appropriate. [1]

Table1: Duplicate Antimicrobial in The Common Practice

Duplicate Antimicrobial	General Category of Duplicate Coverage
• Beta lactam antibiotics as the following examples [7],[8] • Ampicillin • Piperacillin-tazobactam • Cephalosporins (e.g., Cefazolin, Ceftriaxone, Cefepime) • Carbapenems (e.g., Meropenem, Ertapenem)	
• Metronidazole • Amoxicillin/clavulanate	Anaerobic [1],[3],[8]

• Ampicillin/sulbactam • Cefoxitin • Clindamycin • Piperacillin/tazobactam • Ertapenem • Imipenem/cilastatin • Meropenem	
• Clindamycin • Amoxicillin/clavulanate • Ampicillin/sulbactam • Cefoxitin	Gram positive and anaerobes [1]
• Clindamycin • Cefazolin • Penicillin • Amoxicillin • Ampicillin • Vancomycin	Gram positive (but not anaerobes) [1]
• Clindamycin • Vancomycin • Linezolid • Daptomycin	Gram positive [1]
Macrolide + Fluoroquinolones as the following examples: • Levofloxacin • Ciprofloxacin • Azithromycin • Clarithromycin	Atypical bacteria [3]
Concurrent use of multiple agents with activity against resistant gram-negative organisms.	Antipseudomonus [1]
An echinocandin antifungal agent and fluconazole	Antifungal agents [3]

The appropriate use of dual beta-lactams

Beta lactams

Beta-lactam antibiotics are one of the most commonly prescribed drug classes with numerous clinical indications. Their advent starting from the 30s of the twentieth century drastically changed the fight against bacterial infectious diseases.[9]
In Egypt in 2021, beta-lactams make up 42.18% of the total antibiotics market. [10]
This class includes: [9]

- Penicillins. The group includes natural penicillins, beta lactam beta-lactamase-inhibitors, aminopenicillins, and ureidopenicillins (e.g., piperacillin).
- Cephalosporins: are traditionally divided into five classes or generations.
- Carbapenems.
- Monobactams.

History of the use of dual beta-lactams

Combination of dual beta lactam therapy, was broadly tested in the 1980s. Although results were, in general, favorable to its implementation, the actual need for this type of combination was scarce because physicians could achieve a great amount of success using large doses of single drugs with expanded spectrums. Moreover, "dual beta-lactam therapy" was considered to have an antagonist effect by some authors.(11)

Dual beta-lactam therapy has been used for quite some time as an empirical therapy for some severe infections such as endocarditis or meningitis. However, studies regarding the use of a beta-lactam combination stopped being made a long time ago, and it seems the scientific community has no interest in evaluating this as a treatment option. (11)

Drawbacks of using dual beta-lactams widely

The use of dual beta-lactam may not be suitable in all situations and should be tailored to each individual case to choose the optimal balance between efficacy and safety for patients. (11)

Dual beta-lactams shouldn`t be widely used for the following reasons:

1- There is potential for antagonism between some of the molecules. (12)

2- Disruption of the microbiome, which leads to changes in the abundance of certain genera. (12)

3- Increase in colonization with potentially pathogenic (e.g., Enterobacter) or opportunistic (e.g., Clostridioides, Candida spp.) microorganisms. (12)

4- Development of antibiotic resistance, many studies show that it may increase the abundance of multidrug-resistant gram-negative microorganisms. (12)

5- There is interaction between dual beta lactams e.g., ceftriaxone vs ampicillin sulbactam which is duplicate therapy interaction. (13)

Appropriate indications of dual betal-lactam therapy

1- Bacterial Meningitis

Table 2: Dual Beta lactams appropriately used in the management of bacterial meningitis

Dual Beta lactams	Indication
(Cefotaxime 2 g IV / 6 hours (14), (15) OR	• Empirically when suspected community-acquired bacterial meningitis for patients aged > 50 (≥ 60 in some references) years old. (14),(15),(17)

Ceftriaxone 2g IV /12 hours or 4 gm / 24 hr) [14], [15] + Amoxicillin/ Ampicillin 2g IV/ 4 hourly [14], [15]	• Age >18 and <50 years plus risk factors for Listeria monocytogenes e.g., Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions causing immunocompromise. [15], [16], [17] • If Gram-positive bacilli suggestive of Listeria monocytogenes are visible on Gram stain of CSF until culture confirmed. [14]
Age <1 week: Cefotaxime 50 mg/kg / 8 hours. [15] + Ampicillin/Amoxicillin 50 mg /kg / 8 hours. [15] Age 1–4 weeks: Cefotaxime 50mg/kg / 6–8h. [15] + Ampicillin 50 mg/kg / 6h. [15]	• Empirically for community-acquired bacterial meningitis for Neonates < 1-month-old. [15]
(Ceftriaxone or Cefotaxime) [15] + Meropenem 2 g every 8 hours [15]	• Directed therapy for community-acquired bacterial meningitis with Haemophilus influenzae β-Lactamase negative ampicillin resistant. [15]

2- Enterococcal infective endocarditis

Table 3: Dual Beta lactams appropriately used in the management of infective endocarditis	
Dual Beta lactams	**Indications**
Adults: (Ampicillin 2 g IV / 4 hours [18] or Amoxicillin 200 mg/kg/day IV. in 4–6 doses daily) for 6 weeks. [19] + Ceftriaxone 2 g IV every 12 h for 6 weeks. [18], [19] Pediatrics: Ampicillin 300 mg/kg/day IV in 4–6 equally divided doses/ day for 6 weeks. [19] +	• In patients with native valve endocarditis (NVE) due to non-high-level aminoglycoside resistance (non-HLAR) Enterococcus spp. [19] • In patients with Prosthetic valve endocarditis (PVE) and patients with complicated NVE or >3 months of symptoms due to non-HLAR Enterococcus spp. [19] • In patients with NVE or PVE due to HLAR Enterococcus spp. [19]

Ceftriaxone 100 mg/kg IV in 2 doses/day for 6 weeks. [19]	• It is recommended as an alternative for Ampicillin + Gentamicin for patients with initial creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during therapy with gentamicin-containing regimen. [18]

3- Drug-resistant Acinetobacter baumannii

Table 4: Dual Beta lactams appropriately used in the management of Drug-resistant Acinetobacter baumannii

Dual Beta lactams	Indications
Colistin IV 2.5 mg Colistin Base Activity (CBA)/kg IV loading dose, then 1.5 mg CBA over 1 hour IV /12 hours. [20], [21], [22] + Meropenem 2 g IV every 8 hours, infused over 3 hours. [20], [21], [22] + Ampicillin/sulbactam (even if non-susceptible) [20], [21], [22] N.B., (high dose of ampicillin/ sulbactam used but no agreed consensus on the right dose) Potential infusion strategies include the following: - 9 grams of ampicillin-sulbactam (6 grams' ampicillin, 3 grams sulbactam) IV every 8 hours, infused over 4 hours. [20], [21], [22] - 27 grams of ampicillin-sulbactam (18 grams' ampicillin, 9 grams sulbactam) IV as a continuous infusion. [20], [21], [22]	Pneumonia, blood stram infections and complicated UTI infections due to carbapenem resistant Acinetobacter baumannii (resistance to at least any carbapenem (meropenem or imipenem)). [22] N.B., Sulbactam has antibacterial # (A. Baumannii) but is not available alone, so we are forced to use ampicillin-sulbactam. [22]

4- Drug resistant Enterobacterales

Table 5: Dual Beta lactams appropriately used in the management of Drug-resistant Enterobacterales

Dual Beta lactams	Indications

Meropenem 2 g IV every 8 hours, infused over 3 hours. [23] + Ertapenem 1 g/ 12- 24 hours (administered prior to a high-dose meropenem infusion). [23]	Critically ill patients with infections due to Klebsiella pneumoniae carbapenemase (KPC) producer or Metallo-carbapenemase producer (ie. (NDM), or, (IMP)). [23] N.B., use ertapenem infusion prior to a high-dose meropenem infusion as a salvage therapy for critically ill patients with CRE infections. [23]

5- **Drug resistant Pseudomonas aeruginosa/ Stenotrophomonas maltophilia**

Table 6: Dual Beta lactams appropriately used in the management of Drug-resistant Pseudomonas aeruginosa/ Stenotrophomonas maltophilia	
Dual Beta lactams	**Indications**
Ceftazidime-avibactam: 2.5 grams IV every 8 hours, infused over 3 hours. [24], [25] + Aztreonam: 2 grams IV every 6-8 hours (every 6-hour dosing preferred if possible), infused over 3 hours. [24], [25] Administered at the same time as ceftazidime-avibactam	• Metallo-carbapenemase producer (ie. (NDM), (VIM) or, (IMP)). [24] • Any clinical syndrome due to Difficult-to-Treat P.aeruginosa (DTR-PA) which resistant to Ceftazidime/avibactam. [25] • Stenotrophomonas maltophilia When significant clinical instability is evident or intolerance to or inactivity of other agents. [25]

6- Bacteremia due to Methicillin sensitive Staphylococcus aureus (MSSA)

Table 7: Dual Beta lactams appropriately used in the management of MSSA bacteremia	
Dual Beta lactams	**Indications**
Cefazolin 2 g / 8 hours. [26], [27] + Ertapenem 1 g/24 hours. [26], [27]	Treating refractory MSSA bacteremia where clearance cannot be achieved by removing an obvious focus, such as a catheter, abscess, or vegetation. [26]

The appropriate use of dual anti anaerobes

Table 8: Predominant anaerobic bacteria

Gram-positive cocci [28], [29]	<u>Peptococcus, Peptostreptococcus and Microaerophilic streptococci (not true anaerobes)</u> • They can be pathogenic and cause numerous infections such as chronic otitis media, chronic sinusitis, aspiration pneumonia, pelvic inflammatory disease, including tube-ovarian abscesses.
Gram-positive non spore-forming bacilli [28], [29]	<u>Propionibacterium spp</u> • The most significant member of this family is Propionibacterium Acne, which plays a role in the pathogenesis of acne vulgaris. <u>Bifidobacterium spp.</u> • It is usually non-pathogenic; however, pediatric infections have been documented in the form of chronic otitis media, abdominal abscesses, and peritonitis. <u>Actinomyces spp</u> • The 3 most common anatomic sites affected by Actinomyces are cervicofacial, thoracic, and abdominal. <u>Lactobacillus</u> • They have low pathogenic potential; however, cases of abdominal abscesses, aspiration pneumonia, and bacteremia, particularly in neonates, have been described. <u>Eubacterium</u>
Gram-positive spore-forming Bacilli [28], [29]	<u>Clostridium spp.</u> • Significant members of this family are: • Clostridium difficile, which causes C. difficile infection. Clostridium perfringens,which causes gas gangrene or soft tissue infections. • Clostridium septicum also causes gasgangrene.
Gram-negative bacilli [28], [29]	<u>Bacteroides fragilis group</u> • These organisms are most commonly the cause of intra-abdominal infections, particularly abscesses.

	• The majority of these abscesses are mixed infections. • They can also cause extra-abdominal infections such as aspiration pneumonia, and brain abscesses. <u>Prevotella spp</u> • In children, they are frequently associated with head and neck infections such as peritonsillar abscesses, and retropharyngeal abscesses as well as perineal or perianal infections such as pilonidal abscesses. <u>Fusobacterium spp.</u> • One of the species from this group of anaerobes, Fusobacterium necrophorum, which is a common cause of peritonsillar abscesses associated with a complication of internal jugular vein thrombosis, known as Lemierre syndrome. <u>Sutterella spp</u>

Table 9: Antimicrobial agents with anaerobic activity		
Nearly always active	**Usually active**	**Variable**
Metronidazole	Clindamycin	Penicillin
Imipenem	Piperacillin/tazobactam	Cephalosporins (other than Cefamycin)
Ertapenem	Cefamycin.g., Cefoxitin and Cefotetan	Tetracycline
Meropenem		Vancomycin
Amoxicillin/clavulanate		Macrolides
Ampicillin/sulbactam		Moxifloxacin
		Tigecycline

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Almost half of the prescriptions of metronidazole in combination with other anti-anaerobic agents are unnecessary [30]

Table 10: Anti- anaerobic agents and their characteristics	
Anti-anaerobic agent	**The most common characteristics**

Metronidazole	• Drug of choice for most anaerobes, but with a notable lack of activity against Propionibacterium acnes, Actinomyces, and Lactobacillus. • Classically best for infections "below the diaphragm" – mainly due to excellent activity vs Bacteroides, and less reliable activity vs Peptostreptococcus (gram-positive oral anaerobe) and total lack of activity vs microaerophilic streptococci. For this reason, it should never be used as monotherapy against above-the-diaphragm infections like lung abscesses, etc. (but fine to combine with beta-lactam, levofloxacin, etc).
Clindamycin	• It is used for infections above the diaphragm, as it has activity vs microaerophilic streptococci. • Avoid in intraabdominal infections due to high rates of resistance among Bacteroides species (up to 40% or more).
Combined Beta-lactam /Beta-Lactamase inhibitors (Amoxicillin/clavulanic, Ampicillin/sulbactam, Piperacillin/tazobactam)	• All have excellent anaerobic activity, so no need to add Metronidazole (unless for C. diff). • Ampicillin/sulbactam is better for anaerobic infections above the waist, but not preferred for intraabdominal infections (due to the high rate of resistance in E. coli).
Carbapenems (Meropenem, Imipenem, Ertapenem)	All have excellent anaerobic activity
2nd Generation Cephalosporins (Cefamycin) e.g., cefoxitin and cefotetan	There is increasing resistance of Bacteroides (Cefoxitin is better than Cefotetan, but avoid both for serious intraabdominal infections)
Moxifloxacin	There is data to support its use in intraabdominal infections, but there is increasing resistance among Bacteroides (up to 40%!)
Tigecycline	Excellent anaerobic activity.

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Treatment of anaerobic infection

Treatment of anaerobic infection is complicated by:

- Their slow growth in culture, technical and financial constraints associated with the identification and culture of anaerobic bacteria, microbiology, and antibiotic susceptibility testing (AST) of anaerobes isolates are rarely routinely performed in clinical microbiology laboratories. Therefore, the treatment of anaerobic infections has long been empirical. [31], [32]
- Their growing resistance to antimicrobials. [32], [33]

- Their polymicrobial nature, [32], [33] as their isolation is mixed with aerobes, so the antimicrobial chosen should provide adequate coverage of both. [34]

N.B., important clues of anaerobic infection include the presence of a condition predisposing an individual to an anaerobic infection, for example, tissue necrosis, a foul-smelling discharge, infection leading to thrombophlebitis, no improvement with antibiotics in suspected anaerobic activity. [28]

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. [34]

Table 11: Anaerobic bacteria isolated in various types of infection

Site of infection	**The anaerobe detection rate in local infections (frequency)** [35]	**Recommended anti-anaerobic therapy to be combined with other regimens according the different types of infectious diseases (**if the agent being used to treat the causative micro-organisms lacks such activity**).** [29]	Notes
Intracranial [29], [35]	• Brain abscess and subdural empyemas (Very frequently) • CNS shunt infections (Rarely) • Meningitis (Very rarely)	• Metronidazole.	• There are no anaerobic colonizing bacteria at CNS sites in healthy individuals.
Dental or Oral cavity [29],[35]	• Odontogenic infections (Very frequently) • Necrotizing periodontal disease or ulcerative gingivitis, also called Vincent angina ("trench mouth", an erosive polymicrobial infection) (Always) • Noma (cancrum oris) (Always) • Dental abscesses • Peritonsillar abscess	**First choices** • Clindamycin • Amoxicillin/ clavulanic acid **Alternatives** • Metronidazole + Ampicillin/ Amoxicillin • Ampicillin/ sulbactam	• Major pathogens include Peptostreptococcus, microaerophilic streptococci, Fusobacterium, and others. [31]

	• Deep neck space		
Upper Respiratory Tract Infection (29),(35)	• Otitis media (Frequently) • Mastoiditis (Frequently) • Chronic sinusitis (Very frequently) • Acute sinusitis (Rarely) • Peritonsillar and retropharyngeal abscess (Very frequently)	**First choices** • Clindamycin • Amoxicillin/ clavulanic acid **Alternatives** • Ampicillin/sulbactam • Metronidazole+ Macrolide	
Pulmonary (29), (35), (36)	• Lung abscess (Very frequently) • Aspiration and/or necrotizing pneumonia (Very frequently) • Pleural empyema (Very frequently) • Bronchiectasis (Occasionally)	**First choices** • Clindamycin + macrolide • Clindamycin + flouroquinolones **Alternatives** • Metronidazole+ Macrolide • Amoxicillin/ clavulanic acid	• Same pathogens as oral infections (31) • The ATS/IDSA guidelines recommend that anaerobic coverage should not be routinely added for suspected aspiration pneumonia unless lung abscess or empyema is suspected. This is mainly based on observational studies reporting a decrease in the detection of anaerobes as causative organisms, with no additional mortality benefit, but leads to an increased risk of C difficile colitis. (36),(37)

Intra-abdominal (29),(35),(38),(39)	▪ Intra-abdominal abscess (Very frequently) ▪ Appendicular abscess (Very frequently) ▪ Appendicitis/peritonitis (Very frequently) ▪ Post-surgical intra-abdominal infections (Very frequently) ▪ Liver abscess (Frequently) ▪ Biliary tract infections (Occasionally)	**First choices** • Metronidazole+ Aminoglycoside • Metronidazole+ Flourouquinolones **Alternatives** • Imipenem • Meropenem • Ertapenem • Piperacillin-tazobactam • Tigecycline • Clindamycin (a second-line anti-anaerobic agent in combination regimens, and also it is an option if metronidazole cannot be used). (39	• The major anaerobic pathogen is Bacteroides species. (31) • The anaerobic bacterial component of intra-abdominal infections is often not determined but assumed and treated empirically. (38) • Coverage for anaerobes is often continued for the duration of the antibiotic course even when anaerobes are not isolated from cultures, particularly if the cultures were obtained only after initiation of antibiotics that are active against anaerobes. (38)
Pelvic (29),(35),(31)	▪ Pelvic inflammatory disease (Very frequently) ▪ Pelvic abscess (Very frequently) ▪ Endometritis (Very frequently) ▪ Vaginal cuff abscess (Very frequently) ▪ Bacterial vaginosis (Very frequently) ▪ Urinary tract infections (Very rare)	**First choice** (Clindamycin or cefoxitin) + Doxycycline **Alternatives** <u>Any one of the following</u> Piperacillin-tazobactam, Ampicillin/sulbactam, Metronidazole, Amoxicillin/clavulanic acid + Doxycycline	• Major pathogens include Prevotella species and others. (31)

Skin and soft tissue (29),(35)	▪ Impetigo (Occasionally) ▪ Infected/gas gangrene (Very frequently; especially in the setting of diabetes) ▪ Breast abscess (Very frequently) ▪ Perianal, perirectal, pilonidal abscess (Very frequently) ▪ Necrotizing cellulitis (Very frequently) ▪ Infections after trauma (Very frequently) ▪ Acne vulgaris (Very frequently) ▪ Wound infections (Frequently) ▪ Other abscesses (Frequently) ▪ Cellulitis and necrotizing fasciitis (Frequently) ▪ Bite wounds (Frequently) ▪ Diabetic foot infections (Frequently) ▪ Infected decubitus ulcers (Frequently)	**First choice** • Clindamycin • Cefoxitin • Amoxicillin/ clavulanic acid **Alternatives** • Metronidazole+ Vancomycin • Tigecycline	
Bone and Joints (29), (35)	▪ Orthopedic device infections (Frequently) ▪ Native joint septic arthritis or osteomyelitis (Occasionally)	**First choice** • Clindamycin • Imipenem • Meropenem **Alternatives** • Metronidazole+ Vancomycin	

	▪ Prosthetic joint infections (Rarely)	• Piperacillin-tazobactam	
Blood [29], [35]	▪ Intra-abdominal sepsis (Very frequently) ▪ Septic abortion (Very frequently) ▪ Bacteremia after oral surgery or tooth extraction (Occasionally) ▪ Bacteremia due to endocarditis (Rarely)	**If bacteremia, with b-lactamase-producing bacteria** • Imipenem • Meropenem • Metronidazole **If bacteremia, without b-lactamase-producing bacteria** • Clindamycin • Metronidazole	• There are no anaerobic colonizing bacteria in the bloodstream in healthy individuals)

N.B., This table just highlights the most common infectious diseases requiring anti-anaerobic coverage but to get the precise therapeutic regimens, you should refer to the respective international or national guidance (if available) for each infectious disease.

The use of dual anti anaerobes

No data or guidelines support the use of two anti-anaerobic drugs in clinical practice, with the following clinical exceptions [31],[40], [41], [42],[43]

- Metronidazole can be added to another agent with anaerobic activity when being used to treat Clostridium difficile infection.
  (in rare instances a patient might be receiving a broad-spectrum agent with antianaerobic coverage to treat one infection along with metronidazole (usually orally) to treat concomitant Clostridium difficile (C. difficile), in the majority of instances the use of two antibiotics with anti-anaerobic activity is unnecessary).
- Clindamycin can be added to another agent with anaerobic activity when being used for the treatment of necrotizing fasciitis (for its antitoxin effects and not anaerobic activity)

Drawbacks of using dual antianaerobes widely

The use of double anaerobic coverage (DAC) has been associated with:

- Increased risks of drug resistance [44]
- Adverse reactions [44]
- Increased hospital costs. [44]
- longer length of hospital stays [44]
- In-hospital postoperative complications. [44]
- In critically ill patients, early treatment with anti-anaerobic antibiotics is associated with increased mortality. Mechanisms may include enrichment of the gut with respiratory pathogens, but increased mortality is incompletely explained by infections alone. Given consistent clinical and experimental evidence of harm, the widespread use of anti-anaerobic antibiotics should be reconsidered. [45]

- Clindamycin use is one of the well-known predisposing factors for the development of Clostridium difficile infection. [41]

The appropriate use of dual anti pseudomonal

Among infections caused by Gram-negative rods, *Pseudomonas aeruginosa* has a leading role, especially in critically ill and immunocompromised patients. Antimicrobial resistance has led to a serious restriction in treatment options for *P. aeruginosa* infections, which has become a critical and deadly issue. [46]

Antibiotics used for the treatment of *Pseudomonas aeruginosa* infections (which are registered at EDA-products used systemically)

Table 12: Antibiotics used for treatment of Pseudomonas aeruginosa infections

Class	Agent	Notes
Penicillin-beta-lactamase combinations	Piperacillin/tazobactam	
Cephalosporins	• Ceftazidime • Cefoperazone • Cefepime	
Monobactams	Aztreonam	
Fluoroquinolones	• Ciprofloxacin • Levofloxacin	• This is the only class of antibiotics with antipseudomonal activity that have an oral formulation. • Levofloxacin has no advantage over ciprofloxacin for infections due to P. aeruginosa since its additional spectrum of coverage is usually unnecessary and potentially harmful. • Levofloxacin is primarily indicated for treatment of respiratory tract infections when additional empiric P. aeruginosa coverage is warranted and in rare situations such as a culture-positive polymicrobial infection that includes susceptible strains of streptococci and P. aeruginosa
Carbapenems	• Meropenem. • Imipenem/cilastatin.	• Meropenem is preferred over imipenem because imipenem has a higher propensity to induce resistance during treatment. • All carbapenems have been associated with emergent resistance during therapy; thus we

		reserve their use for the treatment of P. aeruginosa infections resistant to other agents or in polymicrobial infections.
Advanced beta-lactamase inhibitor combinations	• Ceftazidime/avibactam • Ceftolozane/tazobactam	
Aminoglycosides	• Amikacin • Gentamicin • Tobramycin (inhalation only)	• Aminoglycosides are generally not used as single agents because of inadequate clinical efficacy at most sites. (47) • Aminoglycosides should not be used as monotherapy for pneumonia because they perform poorly in an acidic environment. • Aminoglycosides should not be used as monotherapy for bacteremia as they are associated with high mortality rates. (47) • Aminoglycosides are frequently used in combination with other antibiotics for empiric therapy, pending susceptibility results or for the treatment of select serious infections. (47) • Aminoglycosides can be used as a single agent for the treatment of lower urinary tract infections (eg, cystitis).(47)
Polymyxins	Colistin	• Polymyxins are generally used as part of a combination regimen when treating *Pseudomonas* infection

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Indications for dual antipseudomonal

Combination of two agents from different classes with in-vitro activity against P. aeruginosa for empiric treatment of serious infections known or suspected to be caused by P. aeruginosa in the following conditions (47):

- When signs of severe sepsis or septic shock are present
- Neutropenic patients with bacteremia

- Burn patients (who have a high incidence of multidrug-resistant P. aeruginosa infections) with serious infections.
- In other settings where the incidence of resistance to the chosen antibiotic class is high (e.g., >10 to 15 %)

In other circumstances, empiric treatment using only one antipseudomonal agent is appropriate.

Empiric combination therapy

Combination therapy is used by many clinicians for empiric coverage of known or suspected pseudomonal infections, and is usually discontinued once susceptibility results become available. (47)

A commonly cited reason for use of combination therapy is the potential for synergistic activity against *P. aeruginosa* with two agents, which in turn may result in better outcomes than single-drug therapy. However, there is no compelling evidence that two agents offer improved survival outcomes for treating *P. aeruginosa* infections. (47)

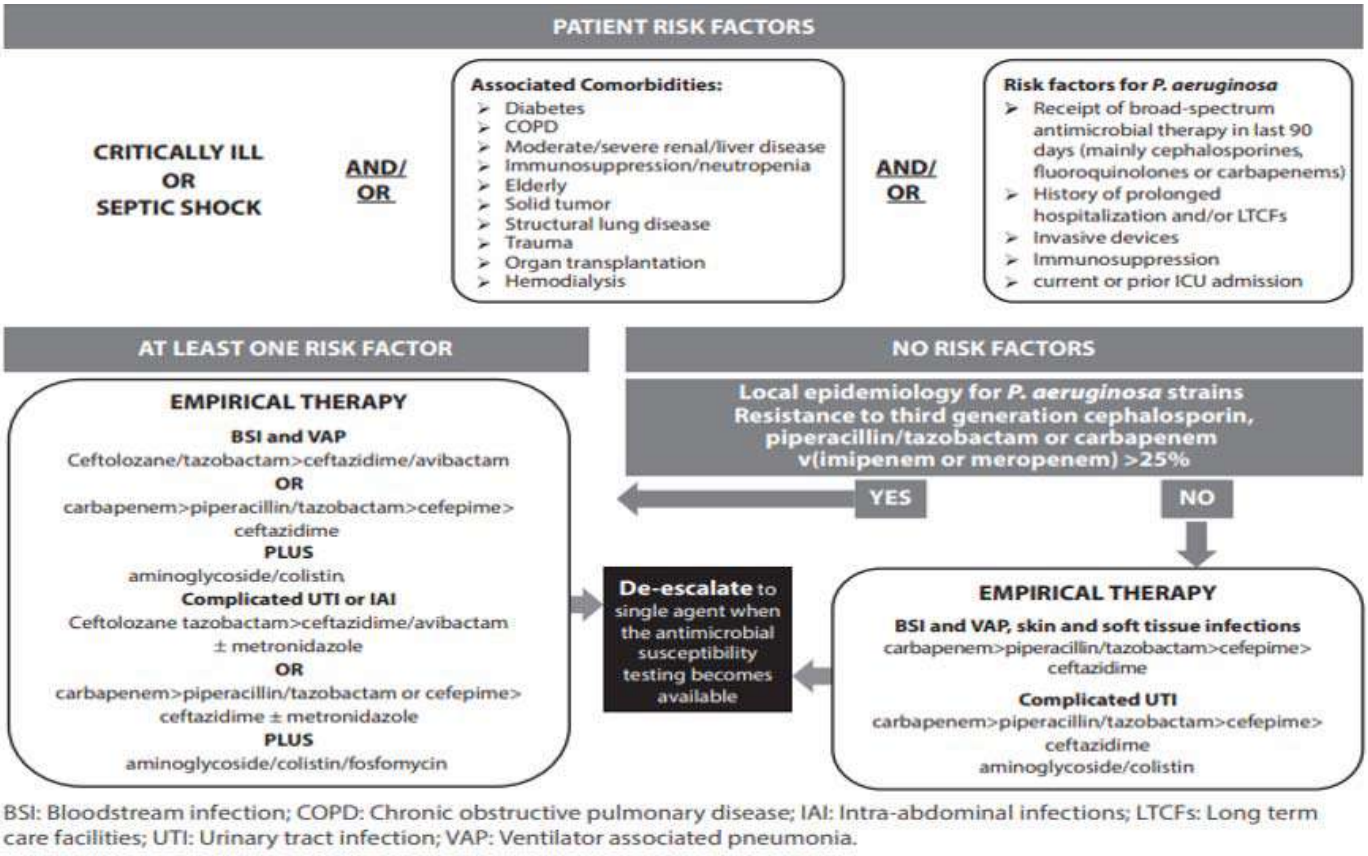
Directed combination therapy

Definitive therapy can be tailored to the results of susceptibility tests once they are available. Definitive therapy with a single active agent is appropriate for most infections. (47)

Nevertheless, combination therapy is often used in situations in which the risk of emergent resistance or significant morbidity or mortality is high. For example (47):

- *P.* aeruginosa endocarditis, it is recommended that combination therapy with two intravenous antipseudomonal antibiotics from different classes to which the isolate is susceptible (one of them should be an aminoglycoside unless the use is precluded by nephrotoxicity).
- Bacteremia in high-risk hosts for neutropenic patients, it is recommended to use a single active agent and continue it for at least 14 days and until the neutrophil count has recovered. However, some experts continue to use two intravenous antipseudomonal antibiotics from different classes to which the isolate is susceptible for the first three to five days of treatment to ensure clinical improvement because of the high mortality risk, despite the absence of data to support the practice.

Figure 1: Clinical approach to patients with suspected P. aeruginosa infection



BSI: Bloodstream infection; COPD: Chronic obstructive pulmonary disease; IAI: Intra-abdominal infections; LTCFs: Long term care facilities; UTI: Urinary tract infection; VAP: Ventilator associated pneumonia.

Adopted from: Bassetti M, Vena A, et al. How to manage Pseudomonas aeruginosa infections. Drugs Context. 2018 May 29; 7:212527.

N.B., for more details about infections due to Pseudomonas aeruginosa (PA) and Difficult-to-Treat P.aeruginosa (DTR-PA), you can refer to "National Guidance for Antimicrobial Use in Infections with Multi-Drug Resistant Organisms (MDROs)" which is available at https://edaegypt.gov.eg/media/me5bwkal/guide-line-national-guidance-for-antimicrobial-use-in-infections-mdros.pdf

Policy & Procedures

Antimicrobial Stewardship is crucial to address the prescribing of multiple antimicrobial agents (e.g., dual beta-lactams, dual anti-anaerobic agents, and dual antipseudomonal agents) and can impact patient outcomes and associated costs. One of the required elements involves the implementation of either preauthorization for specific antibiotics or prospective review and feedback regarding antibiotic prescribing practices.

Procedures to restrict and control the use of unnecessary duplicate antimicrobials

1- The head of pharmacy assigns a team of clinical pharmacists to do the following tasks:
- Develop a list of possible duplicate antimicrobial agents (you can use the table mentioned in the guide and tailor it according to the available antimicrobials at your hospital).

- Develop a list containing the indications of the appropriate use of dual beta-lactams, dual anaerobic coverage, and dual antipseudomonal antibiotics (refer to the National Guidance for Antimicrobial Use in Infections with Multi-Drug Resistant Organisms (MDROs)).

2- The head of the pharmacy presents both lists in the relevant committee meeting e.g., antimicrobial stewardship committee/rational antimicrobial use committee/drug and therapeutics committee.
3- The responsible committee members discuss the suggested procedures to implement the policy and approve it.
4- Distribute both lists to each clinical department, and a poster or flyer of antianaerobic agents Spectra of activity to the inpatient and outpatient pharmacy.
5- AMS team should develop a training program for all hospital pharmacists and healthcare providers about the policy to restrict the inappropriate use of duplicate antimicrobials (through training sessions or discussion on handover meetings between shifts).
6- Front-line pharmacists (clinical pharmacists) should screen patients receiving duplicate antimicrobials for the handful of scenarios where it may be appropriate to assess for combinations of antibiotics that are likely to be unnecessary through a post-prescription review of antibiotics, combined with audit and feedback.
7- Dispensing pharmacists (inpatient and outpatient) can also review orders to verify appropriateness for double check.
8- If there is any inappropriate dual combination, clinical pharmacists or dispensing pharmacists should recommend streamlining therapy (de-escalation) to monotherapy instead of dual therapy by providing oral or written feedback.
9- Calculate KPIs to measure the success of the policy (monthly or quarterly).
10- Discuss the KPIs results with the ASP committee, and make decisions for improvement according to the KPIs results.
11- Nominate the department with the highest adherence degree to the implementation of the policy, and try to reward the nominated department whether through financial incentives or honoring.

Performance Metrics (KPIs)

The following KPIs can be used to assess the performance and impact of restricting and controlling the use of unnecessary duplicate antimicrobials

- Rate of prescriping of dual beta lactams in appropriate indications (per month).
  (Number of prescriptions containing dual beta lactams in appropriate indications/ total number of prescriptions containing any antibiotic).
- Rate of prescriping of dual beta lactams in inappropriate indications (per month).
  (Number of prescriptions containing dual beta lactams in inappropriate indications/Total number of prescriptions containing any antibiotic)
- Rate of prescriping antibiotics with dual anaerobic coverage in appropriate indications (per month).
  (Number of prescriptions with antibiotics with dual anaerobic coverage in inappropriate indications/Total number of prescriptions containing any antibiotic).
- Percentage of medication errors due to prescribing dual beta lactam antibiotics inappropriately.

(Number of medication errors due to prescribing dual beta lactam antibiotics inappropriately/ Total number of medication errors).

- Percentage of medication errors due to antianaerobic coverage redundancy inappropriately.
  (Number of of medication errors due to antianaerobic coverage redundancy inappropriately/ Total number of medication errors)

Key Messages

1- Dual Beta- lactams can be used appropriately in the following indications:

- Bacterial Meningitis
- Enterococcal infective endocarditis
- Drug-resistantAcinetobacter baumannii
- Drug resistant Enterobacterales
- Drug resistant Pseudomonas aeruginosa/ Stenotrophomonas maltophilia
- Bacteremia due to Methicillin sensitive Staphylococcus aureus (MSSA)

2- Dual anti anaerobes can be used appropriately in the following indications:

- Metronidazole can be added to another agent with anaerobic activity when being used to treat Clostridium difficile infection.
- Clindamycin can be added to another agent with anaerobic activity when being used for the treatment of necrotizing fasciitis (for its antitoxin effects and not anaerobic activity).

3- Combination of two agents from different classes with in vitro activity against P. aeruginosa for empiric treatment of serious infections known or suspected to be caused by P. aeruginosa in the following conditions:

- When signs of severe sepsis or septic shock are present
- Neutropenic patients with bacteremia
- Burn patients (who have a high incidence of multidrug-resistant P. aeruginosa infections) with serious infections.

In other settings where the incidence of resistance to the chosen antibiotic class is high (e.g., >10 to 15 %)

Appendix 1

Anti-anaerobic agents Spectra of activity

Antibiotic Classes	Penicillins							Carba-penems					Quinolones			Cephalosporins									Macro-lides								
Antibiotic / Bacteria	Penicillin G	Penicillin V	Ampicillin	Amoxicillin	Amox-clav	Amp-sulb	Pip-tazo	Ertapenem	Imp-cilastatin	Meropenem	Metronidazole	Clindamycin	Ciprofloxacin	Levofloxacin	Moxifloxacin	Cefazolin	Cefotetan	Cefoxitin	Cefuroxime	Cefoperazone	Ceftriaxone	Cefotaxime	Ceftazidime	Cefepime	Ceftaz-avibactam	Ceftaroline	Azithromycin	Clarithromycin	Doxycycline	Tigecycline	Vancomycin	Ticoplanin	Linezolid	Colistin	TMP/SXT
Anaerobic gram-negative bacilli																																			
B. fragilis	0	0	0	0	++	+	++	++	++	++	++	0	0	0	±	0	±	±	0	+	0	0	0	0	0	0	0	0	±	+	0	0	0	0	0
F. necrophorum	±	±	±	±	+	+	+	+	+	+	++	+	0	0	0	0	+	+	0	+	+	+	0	0	0	0	0	0	+	+	0	0	0	0	0
Prevotella sp.	±	±	±	±	+	+	+	+	+	+	++	+	0	±	+	0	+	+	0	+	0	0	0	0	0	0	±	±	+	+	0	0	0	0	0
Anaerobic gram-positive																																			
Actinomyces sp.	++	++	++	++	+	+	+	+	+	+	0	++	0	0	0	0	0	+	0	0	+	+	0	0	0	0	+	+	+	0	0	0	+	0	0
C. perfringes	++	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	+	+	0	0	+	+	0	0	0	0	+	+	+	+	+	+	+	0	0
P.acnes	++	+	+	+	+	+	+	+	+	+	0	±	±	±	±	+	+	+	+	0	+	+	+	+	+	+	±	±	+	+	+	+	+	0	±
Peptostreptococci	++	++	++	++	+	+	+	+	+	+	±	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	±	±	+	+	+	+	+	0	0

++	Preferred agent (first line therapy)	+	Alternative
±	Limited activity	0	Not recommended

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