

Clinical use of antimicrobial agents

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Before starting antimicrobial therapy, following questions should be asked:

1. Is an antimicrobial agent indicated on the basis of clinical findings?
2. Have appropriate clinical specimens been obtained to establish a microbiologic diagnosis?
3. What are the likely etiologic agents for the patient's illness?
4. What measures should be implemented to prevent further exposure?

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Further questions after the identification of a specific microbial pathogen based upon specific microbial tests

1. Can a narrower-spectrum agent be substituted for the initial empirical drug?
2. Is one agent or a combination necessary?
3. What is the optimal dose, route of administration, and duration of therapy?
4. What specific tests should be undertaken to identify patients who will not respond to treatment?
5. What adjunctive measures can be undertaken to eradicate the infection? (surgery, drainage of abscess. . .)

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Empirical antimicrobial therapy:

- The use of antimicrobial agents before the pathogen responsible for a particular illness or the susceptibility to a particular antimicrobial agent is known.

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Approach to empirical therapy I

- Clinician should conclude that there is anatomic evidence of infection (e.g. pneumonia).
- Specimens should be obtained for laboratory examination.
- A microbiologic diagnosis should be formulated with the history, physical examination, and immediately available laboratory results (e.g. Gram's stain)

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Approach to empirical therapy II

- The necessity for empirical therapy should be determined.
- Empirical therapy is indicated when there is a significant risk of serious morbidity.
- Treatment should be instituted taking into account the most likely pathogens responsible for the patient's illness.

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Table 51-2. Empiric antimicrobial therapy based on site of infection

Presumed Site of Infection	Common Pathogens	Drugs of First Choice	Alternative Drugs
Bacterial endocarditis			
Acute	Staphylococcus aureus	Penicillase-resistant penicillin + gentamicin	Vancomycin + gentamicin
Subacute	Viridans streptococci, enterococci	Penicillin + gentamicin	Vancomycin + gentamicin
Septic arthritis			
Child	<i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i>	Ceftriaxone	Ampicillin-sulbactam
Adult, nongonococcal	<i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i>	Ceftriaxone	Vancomycin, rifampin
Acute otitis media, sinusitis	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>	Amoxicillin	Amoxicillin-clavulanate, cefuroxime axetil, TMP-SMX
Celutitis	<i>Staphylococcus aureus</i> , group B streptococci	Penicillase-resistant penicillin, cephalosporin (first-generation)	Vancomycin
Meningitis			
Neonate	Group B streptococcus, <i>E coli</i> , listeria	Ampicillin + cephalosporin (third-generation)	Ampicillin + aminoglycoside (chloramphenicol)
Child	<i>Haemophilus pneumoniae</i> , meningococcus	Ceftriaxone or cefotaxime ± vancomycin ¹	Chloramphenicol
Adult	<i>Pneumococcus meningococcus</i>	Ceftriaxone, cefotaxime	Vancomycin + ceftriaxone or cefotaxime ¹
Peritonitis due to ruptured viscus	<i>Coliforms</i> , <i>S faecalis</i>	Metronidazole + cephalosporin (third-generation), piperacillin-tazobactam	Imipenem
Pneumonia			
Neonate	As in neonatal meningitis		
Child	<i>Pneumococcus</i> , <i>S aureus</i> , <i>H influenzae</i>	Ceftriaxone, cefuroxime, cefotaxime	Ampicillin-sulbactam
Adult (community-acquired)	<i>Pneumococcus</i> , mycoplasma, legionella, <i>H influenzae</i> , <i>S aureus</i> , <i>C pneumoniae</i> , coliforms	Outpatient: Erythromycin, amoxicillin, doxycycline Inpatient: Macrolide ⁴ + cefotaxime, ceftriaxone	Outpatient: Azithromycin, clarithromycin, quinolone Inpatient: Macrolide + piperacillin-tazobactam, ticarcillin-clavulanate, or cefuroxime, quinolone
Septicemia	Any	Vancomycin + aminoglycoside + cephalosporin (third-generation) or piperacillin + tazobactam	
Septicemia with gram-negative bacilli	Any	Antipseudomonal penicillin + aminoglycoside, cefepime, cefepime, consider addition of amphotericin B if fever persists beyond 3 days of empiric therapy	

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Meningitis

Neonate	Group B streptococcus, <i>E coli</i> , listeria	Ampicillin + cephalosporin (third-generation)	Ampicillin + aminoglycoside, chloramphenicol
Child	<i>H influenzae</i> , pneumococcus, meningococcus	Ceftriaxone or cefotaxime ± vancomycin ¹	Chloramphenicol
Adult	<i>Pneumococcus</i> , meningococcus	Ceftriaxone, cefotaxime	Vancomycin + ceftriaxone or cefotaxime ¹

Pneumonia

Neonate	As in neonatal meningitis		
Child	<i>Pneumococcus</i> , <i>S aureus</i> , <i>H influenzae</i>	Ceftriaxone, cefuroxime, cefotaxime	Ampicillin-sulbactam
Adult (community-acquired)	<i>Pneumococcus</i> , mycoplasma, legionella, <i>H influenzae</i> , <i>S aureus</i> , <i>C pneumoniae</i> , coliforms	Outpatient: Erythromycin, amoxicillin, doxycycline Inpatient: Macrolide ⁴ + cefotaxime, ceftriaxone	Outpatient: Azithromycin, clarithromycin, quinolone Inpatient: Macrolide + piperacillin-tazobactam, ticarcillin-clavulanate, or cefuroxime, quinolone

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Antimicrobial therapy of infections with known etiology

Properly obtained and processed specimens for culture yield reliable information about the cause of infection frequently.

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Table 51-1. Empiric antimicrobial therapy based on microbiologic etiology.

Suspected or Proved Disease or Pathogen	Drugs of First Choice	Alternative Drugs
Gram-negative cocci (aerobic) <i>Moraxella (Branhamella) catarrhalis</i>	TMP-SMZ, ¹ cephalosporin (second- or third-generation)	Erythromycin, quinolone, clarithromycin, azithromycin
<i>Neisseria gonorrhoeae</i>	Ceftriaxone, cefixime, quinolone	Spectinomycin, cefoxitin
<i>Neisseria meningitidis</i>	Penicillin G	Chloramphenicol, cephalosporin (third generation) ²

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In the case of following conditions microbial confirmation may not be obtained:

- Sample error
- Noncultivable or slow-growing organism
- Requesting bacterial cultures when infection is due to other organisms
- Not recognizing the need for special media or isolation techniques
- The present culture technique may be inadequate to identify all cases of the disease.

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Guiding antimicrobial therapy of established infections

- Susceptibility testing
- Specialized assay methods (β -lactamase assay, synergy studies).

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Pharmacokinetic aspects

Bactericidal agents can be divided into two groups.
Agents that exhibit:

- Concentration-dependent killing (aminoglycosides, quinolones)
- Time dependent killing (β -lactams, vancomycin).

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Table 51-5. Antimicrobial agents that require dosage adjustment or are contraindicated in patients with renal or hepatic impairment.

Dosage Adjustment Needed in Renal Impairment	Contraindicated in Renal Impairment	Dosage Adjustment Needed in Hepatic Impairment
Acyclovir, adefovir, amantadine, aminoglycosides, aztreonam, cephalosporins, ¹ clarithromycin, cycloserine, didanosine, ethambutol, famciclovir, fluconazole, flucytosine, foscamet, ganciclovir, imipenem, lamivudine, meropenem, penicillins, ³ quinolones, ⁴ rimantadine, stavudine, terbinafine, trimethoprim-sulfamethoxazole, valacyclovir, vancomycin, zalcitabine, zidovudine	Cidofovir, itraconazole (IV), methenamine, nalidixic acid, nitrofurantoin, ribavirin, sulfonamides (long-acting), tetracyclines ²	Amprenavir, caspofungin, chloramphenicol, clindamycin, erythromycin, indinavir, metronidazole, rimantadine, voriconazole

¹Except cefoperazone and ceftriaxone.

²Except doxycycline and possibly minocycline.

³Except antistaphylococcal penicillins (eg, nafcillin and dicloxacillin).

⁴Except trovafloxacin and moxifloxacin.

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Table 51–6. Cerebrospinal fluid (CSF) penetration of selected antimicrobials.

Antimicrobial Agent	CSF Concentration (Uninflamed Meninges) as Percent of Serum Concentration	CSF Concentration (Inflamed Meninges) as Percent of Serum Concentration
Ampicillin	2–3	2–100
Aztreonam	2	5
Cefotaxime	22.5	27–36
Ceftazidime	0.7	20–40
Ceftriaxone	0.8–1.6	16
Cefuroxime	20	17–88
Ciprofloxacin	6–27	26–37
Imipenem	3.1	11–41
Meropenem	0–7	1–52
Nafcillin	2–15	5–27
Penicillin G	1–2	8–18
Sulfamethoxazole	40	12–47
Trimethoprim	< 41	12–69
Vancomycin	0	1–53

Post antibiotic effect (PAE)

- Persistent suppression of bacterial growth after limited exposure to an antimicrobial agent.
- Most antimicrobials possess significant in vitro postantibiotic effects (≥ 1.5 h) against susceptible Gram-positive cocci.
- In vivo PAE's are usually longer than in vitro PAE's due to postantibiotic leukocyte enhancement.
- Drug concentrations of the agents that lack postantibiotic effect should be maintained above the minimal inhibiting concentration for the entire dosage interval.

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Table 51–4. Antibacterial agents with in vitro postantibiotic effects ≥ 1.5 hours.

Against gram-positive cocci	Against gram-negative bacilli
Aminoglycosides	Aminoglycosides
Carbapenems	Carbapenems
Cephalosporins	Chloramphenicol
Chloramphenicol	Quinolones
Clindamycin	Rifampin
Macrolides	Tetracyclines
Oxazolidinones	
Penicillins	
Quinolones	
Quinupristin-dalfopristin	
Rifampin	
Sulfonamides	
Tetracyclines	
Trimethoprim	
Vancomycin	

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Antimicrobial Agent Combinations

Antimicrobial combinations should be selected for one or more of the following reasons:

1. To provide broad-spectrum empirical therapy in seriously ill patients.
2. To treat polymicrobial infections.
3. To decrease the emergence of resistant strains.
4. To decrease dose-related toxicity by using reduced doses of one or more components of the drug regimen.
5. To obtain enhanced inhibition or killing.

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Antimicrobial agents may be synergistic by:

- Blockade of sequential steps in a metabolic sequence (trimetoprim + sulfamethoxazole)
- Inhibition of enzymatic inactivation (β -lactamases)
- Enhancement of antimicrobial agent uptake (penicillins + aminoglycosides)

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Mechanisms of antagonistic action

- Inhibition of -cidal activity by -static agents
- Induction of enzymatic inactivation

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Table 51–3. Bacteriostatic and bactericidal antibacterial agents.

Bactericidal agents	Bacteriostatic agents
Aminoglycosides	Chloramphenicol
Bacitracin	Clindamycin
Beta-lactam antibiotics	Ethambutol
Isoniazid	Macrolides
Metronidazole	Nitrofurantoin
Polymyxins	Novobiocin
Pyrazinamide	Oxazolidinones
Quinolones	Sulfonamides
Quinupristin-dalfopristin	Tetracyclines
Rifampin	Trimethoprim
Vancomycin	

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Antimicrobial prophylaxis

The use of antimicrobial agents in preventing infections.

- Surgical prophylaxis
- Nonsurgical prophylaxis

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Thank you...

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