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Microbiology and Antimicrobial Therapy: An Integrated Approach Narrative Review

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Abstract: Clinical microbiology becomes clinically useful when microbial characteristics are connected to the patient's presentation, diagnostic evidence, and treatment decisions. This narrative review develops an integrated framework for medical students, beginning with recognition of an infectious syndrome and its anatomical source, followed by assessment of host factors, likely pathogens, and illness severity. It explains how Gram staining, culture, molecular assays, and susceptibility testing inform but do not independently establish causation or treatment suitability. Major bacterial pathogens, antimicrobial mechanisms, resistance determinants, pharmacokinetics and pharmacodynamics, drug toxicity, and source control are examined through common clinical syndromes. The review then links timely empiric treatment to diagnostic reassessment, targeted therapy, appropriate route and duration, and antimicrobial stewardship. The unifying principle is that effective infectious disease management requires not merely an active antibiotic, but a justified diagnosis, adequate drug exposure at the infection site, control of the infectious focus, and ongoing evaluation of clinical response.

Keywords: clinical microbiology, antimicrobial therapy, infectious diseases, antimicrobial resistance, diagnostic stewardship, medical education, source control.

INTRODUCTION

Infectious diseases remain a major cause of morbidity and mortality worldwide, underscoring the importance of clinical microbiology in medical education and patient care. A comprehensive global analysis estimated that 33 bacterial pathogens were associated with 7.7 million deaths in 2019, accounting for approximately 13.6% of all deaths worldwide.1

Remarkably, just five organisms, S. aureus, E. coli, S. pneumoniae, K. pneumoniae, and P. aeruginosa, accounted for 54.9% of deaths associated with the 33 bacterial pathogens studied.1 These findings demonstrate that, despite the enormous diversity of clinically relevant microorganisms, a relatively limited group of pathogens accounts for a substantial proportion of severe bacterial disease.

The growing burden of antimicrobial resistance further emphasizes the need to integrate microbiological knowledge with rational therapeutic decision-making. In 2021, bacterial antimicrobial resistance was estimated to be directly responsible for 1.14 million deaths and associated with 4.71 million deaths worldwide.2 These findings highlight the clinical consequences of resistance and the importance of accurate pathogen identification, appropriate antimicrobial selection, and antimicrobial stewardship.

Medical microbiology encompasses a broad range of microorganisms, pathogenic mechanisms, diagnostic methods, and antimicrobial agents. However, its clinical application requires more than memorizing microbial characteristics and antibiotic spectra. Physicians encounter patients presenting with infectious syndromes rather than established microbiological diagnoses. Clinical reasoning must therefore begin with recognition of the syndrome, identification of the probable anatomical source, and assessment of host characteristics and epidemiological factors that influence the likelihood of specific pathogens.

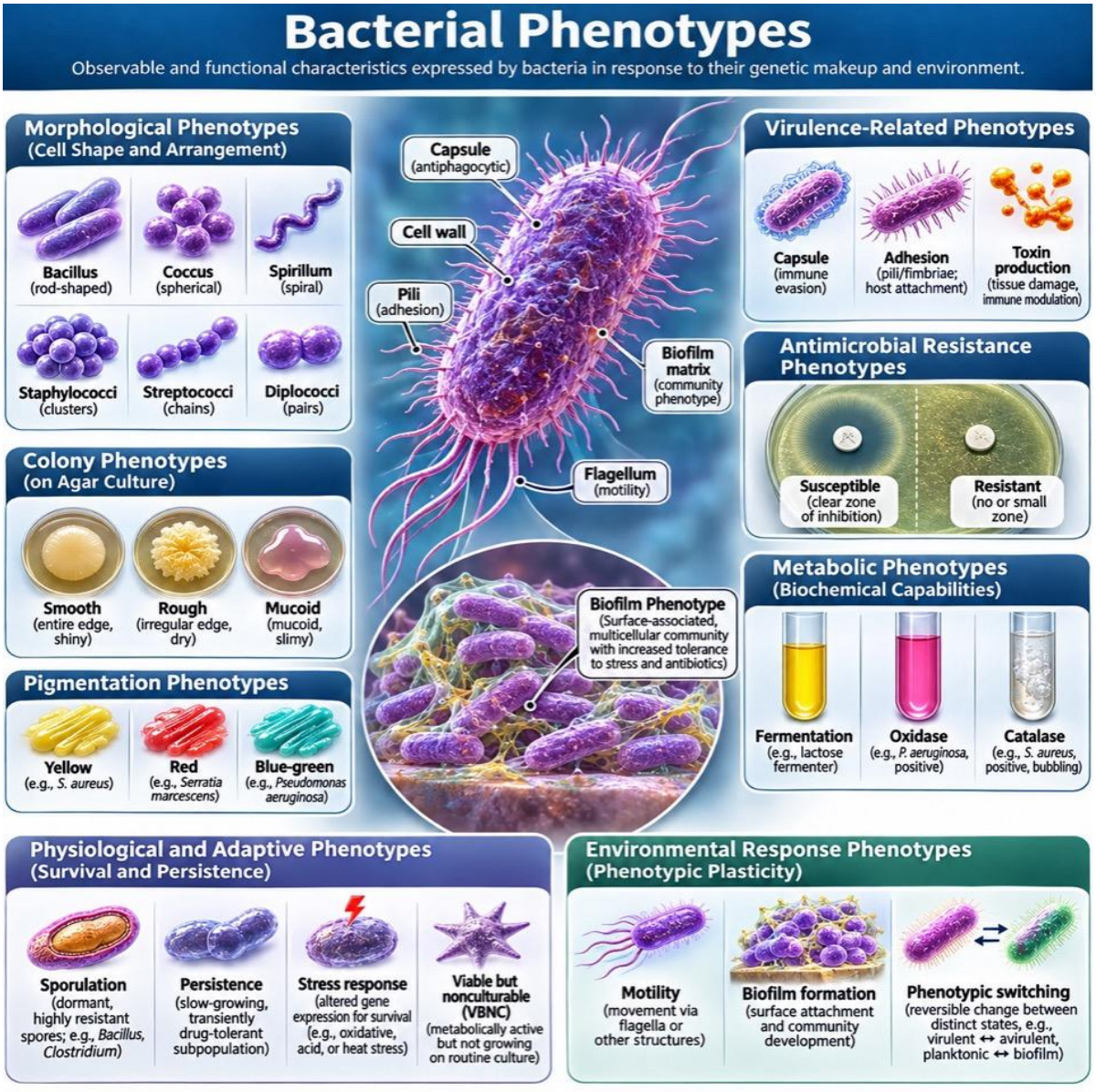


Figure 1

This approach provides the foundation for selecting appropriate diagnostic investigations and initiating empiric antimicrobial therapy when indicated. Subsequent organism identification and antimicrobial susceptibility testing permit refinement of treatment, but microbiological susceptibility alone does not guarantee clinical success.

Effective therapy also depends on antimicrobial pharmacokinetics and pharmacodynamics, adequate tissue penetration, patient-specific toxicity, and appropriate source control.3

This review presents an integrated, clinically oriented framework for medical students, connecting microbial classification and pathogenicity with diagnostic interpretation, antimicrobial mechanisms, resistance, and therapeutic decision-making. By organizing microbiology around the clinical progression from syndrome recognition to targeted treatment, it seeks to develop the knowledge and reasoning skills necessary for accurate diagnosis, effective antimicrobial therapy, and responsible prescribing. The bacterial phenotypes are shown in Figure 1.

CLINICAL SYNDROME AND MICROBIOLOGICAL DIAGNOSIS

Accurate microbiological diagnosis begins with recognition of the clinical syndrome and identification of the probable anatomical source of infection. Different anatomical compartments possess distinct microbial communities, protective barriers, and host defense mechanisms that influence pathogen distribution and disease manifestations.4 Consequently, the organisms responsible for community-acquired pneumonia differ from those associated with hospital-acquired pneumonia, just as uncomplicated cystitis, catheter-associated urinary tract infection, and bacterial meningitis require different diagnostic and therapeutic considerations.4,5

Anatomical localization establishes the initial differential diagnosis, which is subsequently refined by patient-specific and epidemiological factors. Age, immune status, underlying diseases, recent hospitalization, prior antimicrobial exposure, travel, invasive procedures, and implanted devices influence pathogen probability and the likelihood of antimicrobial resistance.6 For example, Streptococcus pneumoniae remains an important cause of community-acquired bacterial pneumonia and meningitis, whereas Pseudomonas aeruginosa becomes particularly relevant in patients with structural lung disease, selected healthcare exposures, or other risk factors for resistant Gram-negative infection.4,6

The clinical significance of microbial identification also depends on the relationship between the organism, anatomical site, and host. E. coli, a normal constituent of the intestinal microbiota, is the leading cause of uncomplicated bacterial urinary tract infection and an important cause of pyelonephritis, bacteremia, and intra-abdominal infection. Its detection in an appropriate clinical specimen may therefore indicate invasive disease, whereas its presence in the gastrointestinal tract ordinarily reflects colonization. Similarly, coagulase-negative staphylococci, which commonly inhabit human skin, frequently represent contamination when isolated from blood cultures but may cause clinically significant bloodstream or device-associated infections, particularly in patients with prosthetic valves, intravascular catheters, or other implanted materials.7,8 These distinctions are essential because increasingly sensitive microbiological methods can detect organisms that are not responsible for the patient's illness. A positive culture or molecular test must therefore be interpreted in conjunction with specimen quality, anatomical source, clinical presentation, and the probability of infection. Microbial detection establishes the presence of an organism or its components; it does not, by itself, establish causation. Distinguishing infection from colonization and contamination is fundamental to accurate diagnosis, avoidance of unnecessary antimicrobial treatment, and effective antimicrobial stewardship (Table 1).9

Table 1: Interpreting microbiological evidence in clinical context

Finding	Possible interpretation	Clinical question
Positive culture from a sterile site	May indicate invasive infection	Is the organism consistent with the syndrome and collection conditions?
Positive superficial or nonsterile-site sample	May reflect colonization or contamination	Does the specimen represent the infected tissue?
Positive molecular assay	Detects microbial nucleic acid, not necessarily viable organisms	Does the result fit the symptoms and other findings?
Negative culture	Does not always exclude infection	Was sampling adequate or performed after antibiotics?

Interpret every test in relation to pretest probability, specimen quality, and the clinical syndrome.

GRAM STAINING AND BACTERIAL CLASSIFICATION

Gram staining remains one of the most useful preliminary methods in clinical microbiology because it provides rapid information about bacterial cell-envelope structure, morphology, and arrangement, thereby narrowing the differential diagnosis and informing early antimicrobial decisions. Although molecular diagnostics offer increasingly rapid organism identification, Gram staining remains particularly valuable in the initial evaluation of positive blood cultures, cerebrospinal fluid, and other clinically significant specimens.10

The distinction between Gram-positive and Gram-negative bacteria reflects fundamental differences in cell-envelope architecture. Gram-positive organisms possess a thick peptidoglycan layer that retains the crystal violet–iodine complex during decolorization, producing a purple appearance. Gram-negative organisms have a thinner peptidoglycan layer surrounded by an outer membrane containing lipopolysaccharide and typically appear pink following counterstaining. The Gram-negative outer membrane also restricts entry of certain antimicrobial agents, while its lipopolysaccharide component contributes to host inflammatory responses. These structural differences have important implications for bacterial pathogenicity and antimicrobial susceptibility (Figure 2).11

Bacterial morphology and arrangement provide additional diagnostic clues. Gram-positive cocci in clusters suggest Staphylococcus species, whereas cocci in chains or pairs suggest Streptococcus or Enterococcus species. Gram-negative diplococci raise consideration of Neisseria species, including N. meningitidis in patients with suspected bacterial meningitis. Gram-negative bacilli encompass clinically important organisms such as E. coli, K. pneumoniae, and P. aeruginosa. However, these morphological patterns are presumptive rather than definitive, and interpretation must account for specimen source and clinical presentation.10

The immediate clinical value of Gram staining is particularly evident in serious infections. Identification of Gram-positive cocci in clusters in a positive blood culture raises concern for S. aureus bacteremia, whereas Gram-negative bacilli suggest a different spectrum of potential pathogens and antimicrobial requirements. Similarly, detection of Gram-negative diplococci in cerebrospinal fluid from a patient with acute meningitis

strongly supports consideration of meningococcal infection and may accelerate appropriate treatment and public health interventions.

Nevertheless, Gram staining cannot reliably establish species identity, distinguish susceptible from resistant strains, or exclude infection when results are negative. Definitive interpretation requires integration with culture, molecular identification, susceptibility testing, and clinical findings.10.12

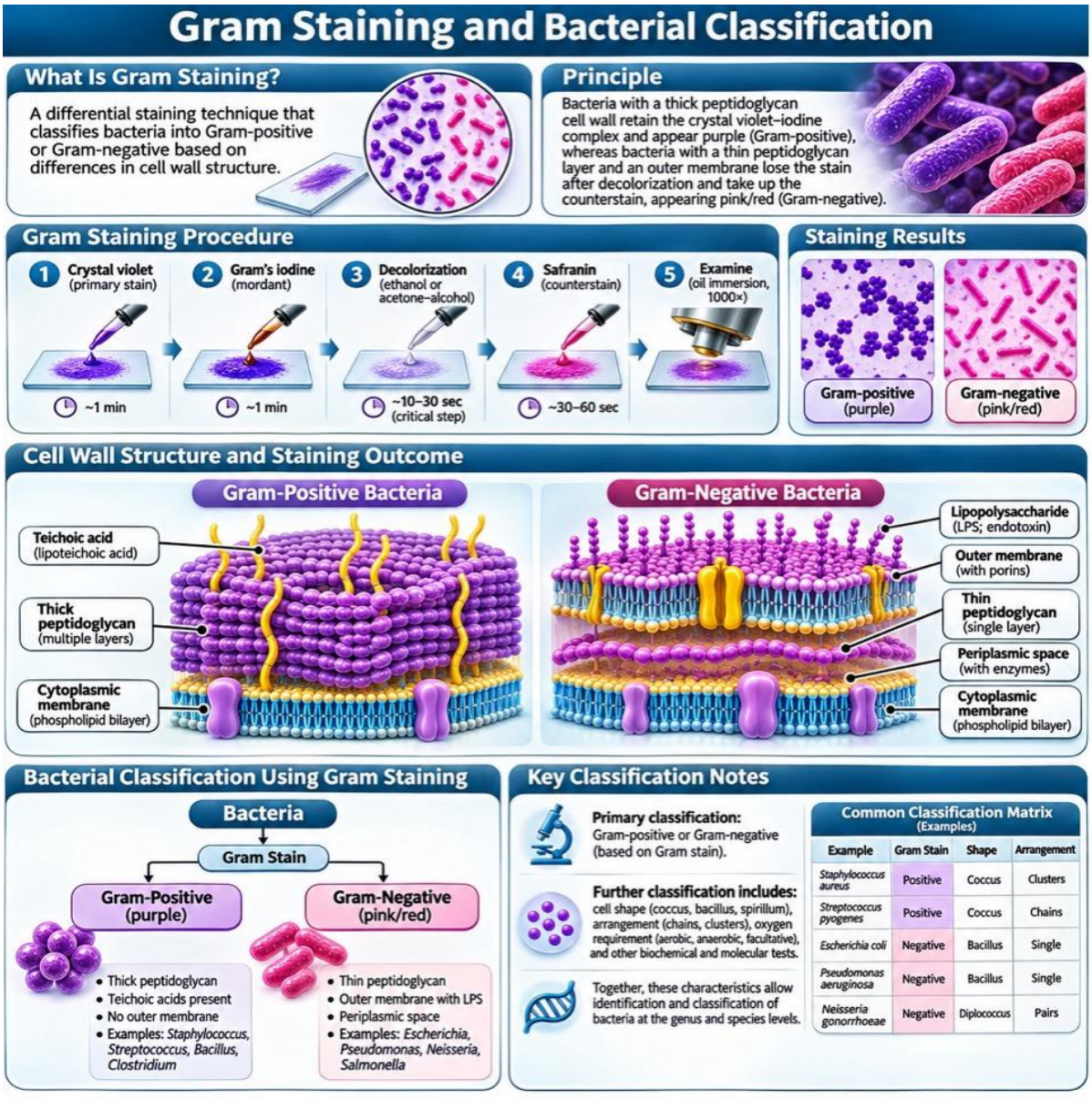


Figure 2

Thus, Gram staining serves as an important bridge between fundamental bacterial biology and clinical decision-making. Its principal value lies not in morphological classification alone but in using rapidly available microbiological evidence to refine diagnostic probability and guide appropriate initial treatment while more definitive results are pending.

CLINICALLY IMPORTANT GRAM-POSITIVE BACTERIA

Gram-positive bacteria are responsible for a substantial burden of community-acquired and healthcare-associated infections. Among the most clinically important are S. aureus, Streptococcus species, and Enterococcus species, which differ considerably in pathogenicity, clinical manifestations, and antimicrobial susceptibility. Understanding these distinctions is essential for accurate diagnosis and appropriate treatment.

Staphylococcus aureus

S. aureus is a particularly important human pathogen because of its capacity to cause both localized and life-threatening invasive infections. It commonly produces skin and soft-tissue infections, including abscesses and cellulitis, but may also cause bacteremia, infective endocarditis, pneumonia, osteomyelitis, septic arthritis, and metastatic infection. Its clinical importance is reflected in a global analysis estimating that S. aureus was associated with approximately 1.1 million deaths in 2019, making it the leading bacterial pathogen associated with mortality worldwide.13

The isolation of S. aureus from blood cultures should generally be regarded as clinically significant rather than be dismissed as contamination. Bacteremia warrants prompt evaluation for the primary infection source, persistent bloodstream infection, endocarditis, and metastatic complications. Management may require repeat blood cultures, echocardiography, prolonged antimicrobial therapy, and removal or drainage of infected foci.14

The distinction between methicillin-susceptible S. aureus (MSSA) and methicillin-resistant S. aureus (MRSA) has major therapeutic implications. Methicillin resistance is primarily mediated by the mecA gene, which encodes penicillin-binding protein 2a (PBP2a), an altered target with reduced affinity for most conventional beta-lactam antibiotics. Serious MSSA infections are generally treated preferentially with antistaphylococcal beta-lactams, such as cefazolin or nafcillin, because these agents provide more favorable clinical outcomes than vancomycin when the organism is susceptible.

MRSA requires agents with reliable activity against the resistant phenotype, with selection determined by infection site, severity, susceptibility, and patient-specific considerations. For example, vancomycin or daptomycin may be used for MRSA bacteremia, whereas daptomycin is inappropriate for pneumonia because pulmonary surfactant inhibits its antibacterial activity.14,15

Streptococcus Species

Streptococci species encompass several clinically important pathogens with distinct patterns of disease. S. pyogenes (group A streptococcus) causes pharyngitis, impetigo, erysipelas, cellulitis, and invasive infections, including necrotizing fasciitis and streptococcal toxic shock syndrome. It may also trigger immune-mediated complications, notably acute rheumatic fever and poststreptococcal glomerulonephritis. Severe invasive infection requires prompt antimicrobial treatment and, when indicated, urgent surgical intervention. Penicillin remains a principal treatment because clinically significant resistance of S. pyogenes to penicillin has not been documented.16

S. agalactiae (group B streptococcus) is an important cause of neonatal sepsis and meningitis and can also cause invasive infections in pregnant individuals, older adults, and patients with underlying medical conditions. Maternal screening and intrapartum antibiotic prophylaxis have substantially reduced early-onset neonatal group B streptococcal disease, illustrating the importance of integrating microbiology with preventive clinical care.17

S. pneumoniae is a major cause of community-acquired pneumonia, bacterial meningitis, bacteremia, acute otitis media, and sinusitis. Its polysaccharide capsule is a major virulence determinant because it impairs phagocytic clearance. Patients with anatomical or functional asplenia are particularly vulnerable to invasive pneumococcal infection, emphasizing the importance of host defenses and vaccination. Antimicrobial selection depends on infection site and susceptibility, particularly in meningitis, where resistance and cerebrospinal fluid penetration are critical considerations.18

Enterococcus Species

E. faecalis and E. faecium normally inhabit the gastrointestinal tract but can cause urinary tract infections, bacteremia, infective endocarditis, and intra-abdominal or device-associated infections, particularly among hospitalized or medically complex patients. Enterococci are clinically important because of their intrinsic resistance to several antimicrobial classes and their capacity to acquire additional resistance determinants. E. faecium is generally more resistant than E. faecalis, while vancomycin-resistant enterococci (VRE) present additional therapeutic challenges. Vancomycin resistance commonly results from alteration of the peptidoglycan precursor targeted by the drug, reducing its binding affinity. Treatment must therefore be guided by species identification, susceptibility testing, infection site, and disease severity.19

GRAM-NEGATIVE BACTERIA AND ANTIMICROBIAL RESISTANCE

Gram-negative bacteria are among the leading causes of urinary tract infections, pneumonia, intra-abdominal infections, and bacteremia. Their clinical importance reflects both their capacity to cause severe invasive disease and their increasing resistance to commonly used antimicrobial agents. The Gram-negative outer membrane restricts penetration of certain antibiotics, while beta-lactamases, efflux pumps, altered antimicrobial targets, and reduced membrane permeability contribute to intrinsic and acquired resistance. These mechanisms are particularly concerning because they may coexist within the same organism, substantially limiting therapeutic options.20

Escherichia coli

E. coli is a predominant constituent of the normal intestinal microbiota but also one of the most important bacterial pathogens worldwide. It is responsible for approximately 75% to 95% of uncomplicated urinary tract infections and is a major cause of pyelonephritis, bacteremia, intra-abdominal infection, neonatal meningitis, and several distinct diarrheal syndromes.21 Its diverse clinical manifestations reflect differences in virulence factors, anatomical site, and host susceptibility.

Uropathogenic E. coli possesses adhesins and other virulence determinants that facilitate attachment to urinary epithelial cells, persistence, and ascending infection. In contrast, diarrheagenic strains employ distinct mechanisms, including toxin production, epithelial invasion, or disruption of intestinal epithelial function. The distinction is clinically important because identification of E. coli alone does not establish the pathogenic mechanism or determine the appropriate treatment.

Increasing resistance among E. coli isolates, particularly to fluoroquinolones, trimethoprim-sulfamethoxazole, and extended-spectrum cephalosporins, complicates empiric treatment. Antimicrobial selection must therefore account for infection severity, local resistance patterns, prior culture results, and susceptibility testing.22

Klebsiella pneumoniae and Proteus mirabilis

K. pneumoniae is an important cause of urinary tract infection, pneumonia, bacteremia, and intra-abdominal infection, particularly among hospitalized patients and individuals with significant comorbidities. Its polysaccharide capsule contributes to resistance against host immune defenses, while acquisition of extended-spectrum beta-lactamases (ESBLs) and carbapenemases has made certain strains particularly difficult to treat. Hypervirulent K. pneumoniae strains may additionally cause invasive community-acquired infections, including pyogenic liver abscesses with metastatic complications.23

P. mirabilis is particularly associated with complicated urinary tract infections, catheter-associated infections, and urinary calculi. Its production of urease hydrolyzes urea into ammonia, increasing urinary pH and promoting precipitation of magnesium ammonium phosphate (struvite) and calcium phosphate crystals. These processes contribute to urinary stone formation, catheter encrustation, obstruction, and recurrent infection.24 This relationship illustrates how a specific microbial metabolic property can directly influence disease pathogenesis and the need for anatomical intervention.

Pseudomonas aeruginosa

P. aeruginosa is a clinically important opportunistic pathogen associated with hospital-acquired pneumonia, bloodstream infection, complicated urinary tract infection, burn wound infection, and chronic respiratory infection in patients with structural lung disease, particularly cystic fibrosis. Its pathogenicity is supported by biofilm formation, multiple virulence factors, and substantial metabolic adaptability.

The organism exhibits intrinsic resistance to numerous antibiotics through low outer-membrane permeability, multidrug efflux systems, and chromosomally encoded beta-lactamases. Additional resistance may develop through target mutations, porin alterations, and acquisition of resistance genes. Consequently, treatment options may become severely restricted, especially in infections caused by multidrug-resistant or difficult-to-treat resistant strains.20 Nevertheless, empiric antipseudomonal coverage is not routinely indicated for all serious infections. Its use should be guided by clinical syndrome, prior microbiological findings, recent antimicrobial exposure, healthcare-associated risk factors, and local epidemiology. Unnecessary broad-spectrum coverage increases antimicrobial selection pressure without necessarily improving clinical outcomes.25

Major Resistance Mechanisms and Therapeutic Implications

Resistance in Gram-negative bacteria is especially consequential because a single mechanism may compromise multiple agents within an antimicrobial class. Distinguishing the underlying mechanism helps clinicians interpret susceptibility results and select effective treatment.

Extended-spectrum beta-lactamases commonly confer resistance to third-generation cephalosporins and aztreonam, although their effects vary by enzyme and organism. AmpC beta-lactamases can compromise several penicillins and cephalosporins and may be inducible in organisms such as E. cloacae complex, K. aerogenes, and C. freundii.

Carbapenem resistance may result from carbapenemase production, including KPC, NDM, VIM, IMP, and OXA-48-like enzymes, or from combinations of other beta-lactamases with reduced membrane permeability.20

These distinctions have direct therapeutic consequences. For example, carbapenems are generally preferred for serious invasive infections caused by ESBL-producing Enterobacterales, whereas treatment of carbapenem-resistant infections depends on the specific resistance mechanism and susceptibility to available agents. Newer beta-lactam/beta-lactamase inhibitor combinations and other targeted agents have expanded treatment options, but their activity is not interchangeable across different carbapenemases.20 Importantly, the resistance phenotype must be interpreted alongside the anatomical site and severity of infection. An antimicrobial appropriate for uncomplicated cystitis may be unsuitable for bacteremia or pyelonephritis because of inadequate systemic or renal tissue concentrations. Similarly, microbiological susceptibility does not eliminate the need for source control when obstruction, abscess formation, or infected devices contribute to persistent infection.

ANAEROBIC, ATYPICAL, AND INTRACELLULAR PATHOGENS

Anaerobic, atypical, and intracellular bacteria present distinct diagnostic and therapeutic challenges because of their pathogenicity, metabolic requirements, and cellular structures differ from those of conventional extracellular bacteria. Their clinical importance illustrates how anatomical location, microbial physiology, and intracellular drug penetration influence antimicrobial selection.

Anaerobic Bacteria

Anaerobic bacteria constitute a substantial component of the normal microbiota of the oral cavity, gastrointestinal tract, and female genital tract. Although generally harmless within their usual anatomical environments, they can cause serious infections when mucosal barriers are disrupted, or organisms gain access to normally sterile tissues. Anaerobic infections are frequently polymicrobial and are particularly associated with dental and deep neck infections, aspiration-related pulmonary abscesses, intra-abdominal abscesses, pelvic infections, and selected necrotizing soft-tissue infections.26

B. fragilis, a Gram-negative obligate anaerobe, is an important cause of intra-abdominal infection, particularly following intestinal perforation or other disruption of gastrointestinal integrity. Its polysaccharide capsule contributes to abscess formation, while

beta-lactamase production limits the activity of several commonly used antibiotics. Management frequently requires both antimicrobial therapy and drainage or surgical source control, emphasizing that microbiological susceptibility alone cannot ensure clinical resolution.27

Anaerobic Gram-positive organisms also cause distinctive clinical syndromes. C. perfringens may produce rapidly progressive myonecrosis through toxin-mediated tissue destruction, whereas C. tetani and C. botulinum cause neurological disease through potent exotoxins. These infections demonstrate that bacterial pathogenicity may depend more on toxin production than on the extent of tissue invasion.26

Clostridioides difficile infection is a particularly important consequence of antimicrobial exposure because antibiotic-associated disruption of the intestinal microbiota creates conditions that favor pathogen proliferation. The disruption of the intestinal microbiota permits proliferation of toxigenic strains, which produce toxins A and B and may cause diarrhea, pseudomembranous colitis, toxic megacolon, and life-threatening systemic complications. Each year in the US, there are more than 12,800 associated deaths, and 223,900 cases of C. difficile infection among hospitalized patients.28 Treatment generally involves fidaxomicin or oral vancomycin, depending on clinical circumstances, disease severity, and resource availability.29 Infection by the pathogen C. difficile illustrates the potential consequences of unnecessary antimicrobial exposure and the importance of not overprescribing antibiotics.

Atypical and Intracellular Bacteria

Atypical bacteria differ from conventional bacterial pathogens in their cellular structure, growth characteristics, or intracellular localization. These differences influence both diagnostic testing and antimicrobial susceptibility.

M. pneumoniae lacks a peptidoglycan cell wall and is therefore intrinsically resistant to beta-lactam antibiotics. It causes respiratory infections ranging from mild tracheobronchitis to community-acquired pneumonia, particularly among school-aged children and young adults. Because routine Gram staining and standard bacterial cultures are not reliable methods of identification, molecular testing may be useful when microbiological confirmation is clinically indicated.30

C. trachomatis is an obligate intracellular bacterium responsible for common sexually transmitted infections, including urethritis, cervicitis, and pelvic inflammatory disease, as well as neonatal conjunctivitis and pneumonia. Its intracellular developmental cycle requires antimicrobial agents capable of reaching infected host cells. Doxycycline is generally preferred for uncomplicated chlamydial infection in nonpregnant adolescents and adults, while treatment during pregnancy requires alternative regimens.31

L. pneumophila is an intracellular pathogen that replicates primarily within macrophages and causes Legionnaires' disease, a potentially severe form of pneumonia. Infection is typically acquired through inhalation or aspiration of contaminated water aerosols rather than person-to-person transmission. The infection risk factors include older age, smoking, chronic pulmonary disease, and immunosuppression. Its effective treatment requires agents with intracellular activity, particularly macrolides or respiratory fluoroquinolones.32

Mycobacterium Tuberculosis

M. tuberculosis presents additional biological and therapeutic challenges because its cell envelope contains mycolic acids and other complex lipids that contribute to reduced permeability and resistance to environmental stresses. Unlike conventional bacteria, mycobacteria are identified using acid-fast staining, molecular assays, and specialized culture methods.

Tuberculosis remains a major global infectious disease. The World Health Organization estimated that approximately 10.8 million people developed tuberculosis and 1.25 million died from the disease in 2023.33 Although pulmonary tuberculosis is the most common presentation, infection may involve the lymph nodes, meninges, bones, kidneys, and other extrapulmonary sites. Its treatment requires multiple active drugs administered for an appropriate duration because M. tuberculosis may persist within macrophages and other tissue compartments, while spontaneous resistance can emerge when inadequate regimens are used. Drug-susceptible pulmonary tuberculosis is commonly treated with combinations of isoniazid, rifampin, pyrazinamide, and ethambutol, although eligible patients may receive shorter evidence-based regimens. Drug-resistant tuberculosis requires individualized treatment based on molecular and phenotypic susceptibility results.34

Clinical and Therapeutic Implications

Table 2: Organism characteristics and their therapeutic implications

Microbial feature	Representative example	Clinical implication
Altered penicillin-binding protein	MRSA, PBP2a	Most conventional beta-lactams are ineffective; select an active anti-MRSA agent.
Beta-lactamase production	ESBL-producing Enterobacterales	Resistance mechanism and infection severity influence beta-lactam selection.
Absent conventional cell wall	Mycoplasma pneumoniae	Beta-lactams lack an effective target.
Intracellular replication	Legionella pneumophila	Treatment requires effective intracellular drug exposure.
Biofilm or persistent focus	Device-associated infection	Antibiotics may need to be combined with device management or source control.

These organisms illustrate several principles fundamental to antimicrobial therapy. Anaerobic infections frequently arise from disruption of anatomical barriers and may require source control; toxin-producing bacteria can cause severe disease through mechanisms extending beyond direct tissue invasion; organisms lacking conventional cell walls are intrinsically resistant to cell-wall-active agents; and intracellular pathogens require antimicrobials capable of reaching their sites of replication. Effective antimicrobial therapy therefore depends on the interaction among microbial biology, anatomical location, drug mechanism, tissue penetration, and host factors. Recognizing these relationships allows clinicians to anticipate antimicrobial limitations, select appropriate diagnostic tests, and provide targeted treatment rather than relying exclusively on broad-spectrum empiric coverage (Table 2).

Final treatment depends on site, susceptibility, severity, and host factors.

ANTIMICROBIAL MECHANISMS AND CLINICAL APPLICATIONS

Antimicrobial therapy is most effectively understood by linking drug mechanisms of action to bacterial physiology, antimicrobial spectrum, resistance, pharmacokinetics, and clinical indications. The principal antibacterial targets include cell-wall synthesis, protein synthesis, nucleic-acid synthesis, membrane integrity, and essential metabolic pathways. Although classification by mechanism provides a useful foundation, clinical effectiveness ultimately depends on whether the drug reaches its microbial target at an adequate concentration without causing unacceptable toxicity.35

Beta-Lactam Antibiotics: Inhibition of Cell-Wall Synthesis

Beta-lactams are among the most widely used antibacterial agents because of their established efficacy, generally favorable safety profiles, and activity against numerous clinically important pathogens. They inhibit bacterial cell-wall synthesis by binding penicillin-binding proteins (PBPs), thereby interfering with peptidoglycan cross-linking and compromising cell-wall integrity. Their bactericidal activity is generally time-dependent, with efficacy closely related to the duration that unbound drug concentrations remain above the minimum inhibitory concentration (MIC).36

The beta-lactam family includes penicillins, cephalosporins, carbapenems, and monobactams, each with distinct antimicrobial spectra. Penicillin remains highly effective against susceptible streptococci and selected other organisms, whereas aminopenicillins provide additional activity against certain Gram-negative bacteria and enterococci. Antistaphylococcal penicillins, such as nafcillin and oxacillin, are important for serious methicillin-susceptible S. aureus (MSSA) infections. Beta-lactamase inhibitors expand the activity of selected companion antibiotics by protecting them against susceptible beta-lactamases, although their effectiveness varies according to the specific inhibitor and resistance enzyme.36

Cephalosporins illustrate the importance of understanding individual drug spectra rather than relying exclusively on a knowledge of antibiotic generations. Cefazolin is widely used for MSSA infections and surgical prophylaxis, while ceftriaxone is important in selected cases of community-acquired pneumonia, bacteremia, and bacterial meningitis because of its activity against susceptible pathogens and ability to achieve therapeutic cerebrospinal fluid concentrations under appropriate conditions. Cefepime provides broader Gram-negative coverage, including activity against susceptible Pseudomonas aeruginosa. However, neither ceftriaxone nor cefepime provides reliable activity against MRSA or enterococci.36

Carbapenems, including meropenem and imipenem-cilastatin, possess broad activity against many Gram-positive, Gram-negative, and anaerobic bacteria. They are particularly valuable in serious infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales. Nevertheless, carbapenems do not reliably cover MRSA, and ertapenem lacks clinically useful activity against P. aeruginosa. Thus, their use should therefore be guided by infection severity, resistance risk, and susceptibility findings rather than an assumption that broader coverage necessarily provides superior treatment.20

Glycopeptides: Vancomycin

Vancomycin inhibits Gram-positive bacterial cell-wall synthesis by binding to the D-alanyl-D-alanine termini of peptidoglycan precursors. It remains an important treatment for serious infections caused by MRSA and selected other resistant Gram-positive organisms. Its clinical use illustrates the importance of pharmacokinetics and route of administration. Intravenous vancomycin is required for systemic infections because oral absorption is negligible. Conversely, oral vancomycin achieves high concentrations within the intestinal lumen and is an accepted treatment for C. difficile infection. For serious MRSA infections, contemporary therapeutic monitoring emphasizes the ratio of the area under the concentration-time curve to the MIC (AUC/MIC), with a target AUC/MIC of 400 to 600 for susceptible isolates with an assumed MIC of 1 mg/L, to balance efficacy against nephrotoxicity.37

Protein Synthesis Inhibitors

Protein synthesis inhibitors act primarily at the bacterial 30S or 50S ribosomal subunits. Their therapeutic applications vary according to antimicrobial spectrum, intracellular penetration, resistance, and toxicity.

Macrolides, including azithromycin and clarithromycin, bind the 50S ribosomal subunit and are useful against selected respiratory pathogens and atypical organisms, including Mycoplasma pneumoniae and Legionella pneumophila. Their use must account for local pneumococcal resistance, potential drug interactions, and QT-interval prolongation.

Tetracyclines, particularly doxycycline, inhibit protein synthesis at the 30S subunit and are valuable for several atypical respiratory infections, tick-borne diseases, chlamydial infections, and selected skin and soft-tissue infections. Their broad clinical utility reflects favorable oral bioavailability and tissue distribution.

Aminoglycosides, including gentamicin, tobramycin, and amikacin, also act at the 30S ribosomal subunit but exhibit concentration-dependent bactericidal activity against susceptible aerobic Gram-negative organisms. They are ineffective against obligate anaerobes because bacterial uptake depends on oxygen-dependent transport. Their clinical use is limited by nephrotoxicity and ototoxicity, making appropriate dosing and therapeutic monitoring essential.38

Clindamycin inhibits the 50S ribosomal subunit and has activity against selected Gram-positive and anaerobic organisms. Its ability to suppress bacterial protein synthesis and toxin production can be particularly valuable as adjunctive therapy in severe toxin-mediated infections, including group A streptococcal necrotizing fasciitis. However, its use is constrained by resistance and a substantial association with C. difficile infection.

Linezolid inhibits formation of the bacterial protein synthesis initiation complex and provides activity against resistant Gram-positive organisms, including MRSA and vancomycin-resistant enterococci (VRE). Its excellent oral bioavailability permits oral treatment in selected serious infections. Nevertheless, prolonged therapy may cause myelosuppression, peripheral or optic neuropathy, and clinically significant interactions with serotonergic medications.39

Inhibitors of Nucleic-Acid and Folate Metabolism

Fluoroquinolones, including ciprofloxacin and levofloxacin, inhibit bacterial DNA gyrase and topoisomerase IV, disrupting DNA replication. Their high oral bioavailability and favorable tissue penetration make them useful in selected urinary, respiratory, gastrointestinal, and invasive bacterial infections. However, increasing resistance and potentially serious adverse effects, including tendinopathy, peripheral neuropathy, central nervous system effects, and dysglycemia, limit indiscriminate use.40

Trimethoprim-sulfamethoxazole inhibits sequential steps in bacterial folate synthesis and is effective against susceptible urinary pathogens, selected community-associated MRSA infections, and Pneumocystis jirovecii. Important adverse effects include hypersensitivity reactions, hyperkalemia, and hematological toxicity.

Metronidazole undergoes intracellular reduction in susceptible anaerobic organisms, generating intermediates that damage microbial DNA. It is particularly useful against many obligate anaerobes and selected protozoal pathogens. However, it lacks clinically useful activity against aerobic bacteria and should not be considered a substitute for broader coverage when polymicrobial infection is suspected.

Membrane-Active Antimicrobial Agents

Some antibiotics act primarily by disrupting bacterial membrane integrity. Daptomycin, a cyclic lipopeptide, causes membrane depolarization and rapid bactericidal activity against susceptible Gram-positive organisms, including MRSA and VRE. It is used in selected bloodstream and deep-seated infections but is ineffective for pneumonia because pulmonary surfactant inhibits its activity.15 Polymyxins, including colistin and polymyxin B, disrupt the outer membrane of susceptible Gram-negative bacteria. Although they retain activity against certain highly resistant organisms, their nephrotoxicity and other adverse effects generally favor safer, effective alternatives when available.20

Integrating Mechanism, Spectrum, and Clinical Effectiveness

Understanding antimicrobial mechanisms provides a foundation for predicting activity and resistance, but drug selection requires integration of several additional factors. The organism must possess the relevant target, demonstrate an appropriate susceptibility phenotype, and be exposed to adequate drug concentrations at the infected site. Clinical effectiveness also depends on host physiology, infection severity, drug toxicity, and the adequacy of source control. For example, an antibiotic with excellent urinary concentrations may be appropriate for uncomplicated cystitis but unsuitable for pyelonephritis or bacteremia. Similarly, a drug active against MRSA in bloodstream infection may be ineffective in pneumonia because of pharmacological limitations. These distinctions explain why laboratory susceptibility does not automatically establish clinical suitability.

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) is one of the most significant threats to effective infectious disease management. Its clinical consequences extend beyond reduced antibiotic

susceptibility to include treatment failure, prolonged hospitalization, increased healthcare costs, and mortality. In 2021, bacterial antimicrobial resistance was estimated to be directly responsible for 1.14 million deaths and associated with 4.71 million deaths worldwide.[2] These findings underscore the importance of understanding resistance as both a biological process and a determinant of clinical outcomes (Figure 3).

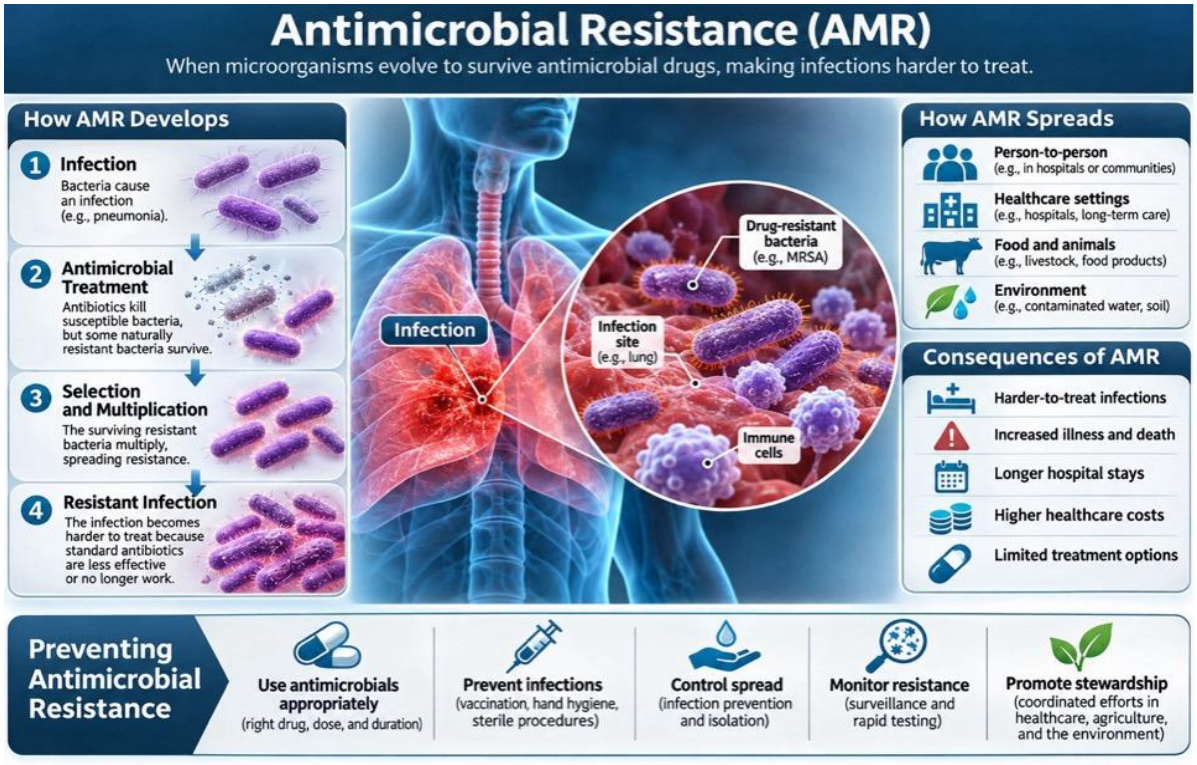


Figure 3

Molecular Mechanisms of Resistance

Bacteria can develop resistance through several fundamental mechanisms: enzymatic inactivation of antimicrobial agents, modification or protection of drug targets, reduced membrane permeability, active drug efflux, and metabolic bypass. The resistance may arise through spontaneous chromosomal mutations or acquisition of resistance genes through horizontal gene transfer, including conjugation, transformation, and transduction. Mobile genetic elements, particularly plasmids and transposons, facilitate dissemination of resistance determinants within and between bacterial species. 41 The mechanisms and genetic basus of antimicrobial resistance is shown in Figure 4). The clinically important antibiotic resistance mechnaisms are showin in Table 3.

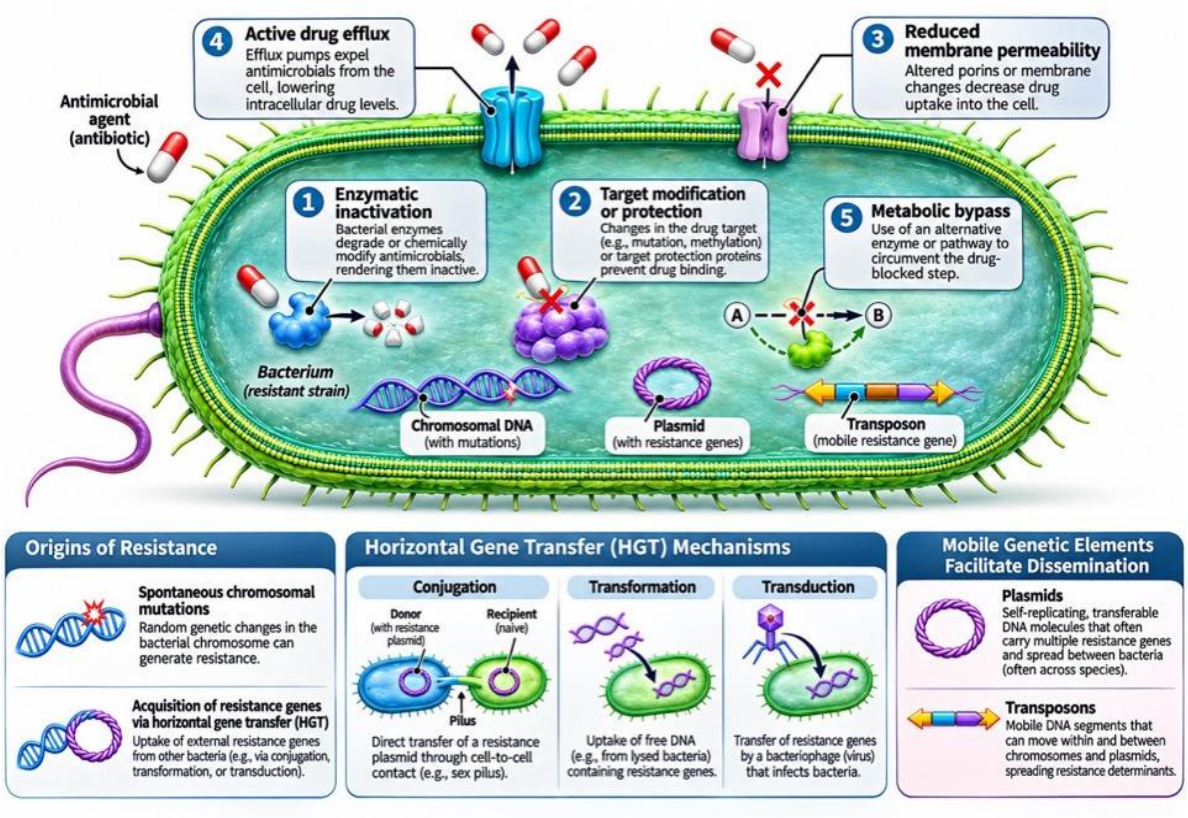


Figure 4: Mechanisms and genetic basis of bacterial antimicrobial resistance

Table 3: Clinically important resistance phenotypes

Antibiotic Resistance	Mechanism
Methicillin-resistant Staphylococcus aureus (MRSA):	Resistance is primarily mediated by the mecA gene, which encodes the altered penicillin-binding protein PBP2a, reducing susceptibility to most conventional beta-lactam antibiotics.
Vancomycin-resistant enterococci (VRE):	Resistance commonly results from modification of peptidoglycan precursors, particularly replacement of D-alanyl-D-alanine with D-alanyl-D-lactate, markedly reducing vancomycin binding.
Extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales:	Enzymatic hydrolysis compromises many penicillins, third-generation cephalosporins, and aztreonam, creating important limitations in treating invasive infections.
AmpC-producing Enterobacterales	Constitutive or inducible beta-lactamase expression can confer resistance to several cephalosporins, including resistance that may emerge during treatment in selected organisms.
Carbapenem-resistant Enterobacterales (CRE)	Resistance may involve carbapenemases such as KPC, NDM, or OXA-48-like enzymes, or combinations of other beta-lactamases with reduced membrane permeability. 20

Multidrug Resistance and Clinical Consequences

Gram-negative organisms, particularly K. pneumoniae, E. coli, P. aeruginosa, and A. baumannii, may accumulate multiple resistance mechanisms, resulting in multidrug-resistant (MDR), extensively drug-resistant (XDR), or, rarely, pandrug-resistant (PDR) phenotypes. These categories describe progressively restricted antimicrobial susceptibility

and are particularly relevant to healthcare-associated infections.42 Resistance becomes clinically consequential when available antimicrobial agents cannot achieve adequate activity at the infected site or when treatment requires drugs with greater toxicity, less favorable pharmacokinetics, or limited clinical evidence. However, resistance does not invariably predict treatment failure, just as laboratory susceptibility does not guarantee success. Clinical outcomes also depend on infection severity, host immune function, antimicrobial exposure, and adequate source control.

Antimicrobial Selection Pressure and Transmission

Antimicrobial resistance is also an ecological and epidemiological process. Antibiotic exposure suppresses susceptible bacterial populations while favoring organisms carrying resistance determinants. Repeated or unnecessary antimicrobial use can amplify this selection pressure, particularly in healthcare environments where resistant organisms may spread through patient contact, contaminated equipment, invasive devices, and environmental reservoirs. Resistance genes may also circulate among humans, animals, and environmental microbial communities, reinforcing the importance of a One Health approach to antimicrobial resistance prevention.43 Importantly, appropriate antimicrobial use can still select for resistance; the objective of stewardship is therefore to avoid unnecessary exposure while ensuring timely and effective treatment when antibiotics are clinically indicated.

Clinical Implications and Antimicrobial Stewardship

Understanding resistance mechanisms is essential for interpreting antimicrobial susceptibility reports and selecting effective treatment. For example, identification of an ESBL-producing organism may favor carbapenem therapy for serious invasive infection, whereas detection of a specific carbapenemase can guide selection of an active newer agent. In contrast, broad-spectrum treatment without a defined clinical indication may increase resistance pressure without improving patient outcomes.20

Antimicrobial stewardship seeks to optimize these decisions through appropriate diagnostic testing, evidence-based empiric therapy, timely review of microbiological results, de-escalation when appropriate, and selection of the shortest effective treatment duration. Infection prevention, vaccination, surveillance, and control of healthcare-associated transmission complement these prescribing strategies.[1]

Antimicrobial resistance must therefore be understood as the interaction of microbial genetics, antimicrobial exposure, host factors, and pathogen transmission. Integrating these principles into clinical decision-making enables physicians to anticipate resistance, interpret susceptibility findings appropriately, and preserve antimicrobial effectiveness while providing optimal patient care.

MICROBIOLOGICAL DIAGNOSIS AND TEST INTERPRETATION

An accurate microbiological diagnosis requires the appropriate selection, collection, and interpretation of laboratory tests within the context of the patient's clinical presentation. Diagnostic methods include direct microscopy, microbial culture, antigen detection,

serological testing, and molecular assays, each offering distinct advantages and limitations. The clinical value of testing depends not only on analytical performance but also on whether the result meaningfully establishes the diagnosis, identifies a causative pathogen, or guides antimicrobial treatment.9

Selection of Microbiological Tests

Microbiological investigations should be guided by the suspected infectious syndrome, anatomical source, disease severity, host characteristics, and probability of specific pathogens. Routine testing is not necessary for every infection, particularly when the diagnosis is clinically established and microbiological identification is unlikely to change management. Conversely, microbiological confirmation is especially important in severe, invasive, recurrent, or treatment-refractory infections and when antimicrobial resistance is a concern.

Conventional culture remains fundamental because it permits organism isolation, identification, and, when appropriate, phenotypic antimicrobial susceptibility testing. Blood cultures are essential in evaluating suspected bacteremia and infective endocarditis, while cerebrospinal fluid examination is central to diagnosing bacterial meningitis. Urine cultures are particularly valuable in pyelonephritis, complicated urinary tract infections, and selected high-risk patients. Respiratory cultures may help identify pathogens in severe pneumonia, although their interpretation is complicated by upper-airway colonization and specimen contamination.44

Direct microscopy, including Gram staining, provides rapid preliminary information about bacterial morphology and inflammatory responses. Antigen-based tests can identify selected pathogens without requiring viable organisms, whereas molecular methods detect microbial nucleic acids and may identify organisms that are difficult or slow to culture. The choice among these methods should reflect diagnostic accuracy, turnaround time, availability, and the likelihood that the result will influence clinical decisions.10

Specimen Quality and Collection

The reliability of microbiological testing depends substantially on specimen quality. Samples should be collected from the suspected site of infection using techniques that minimize contamination by normal microbiota. Whenever possible, specimens obtained directly from infected tissue, aspirated fluid, or normally sterile anatomical compartments provide stronger diagnostic evidence than superficial swabs or samples exposed to colonizing organisms.

For example, blood culture contamination by skin commensals may lead to unnecessary antimicrobial treatment, additional investigations, and prolonged hospitalization. In contrast, recovery of Staphylococcus aureus from blood cultures generally warrants evaluation for clinically significant bacteremia. Similarly, growth of bacteria from a superficial wound swab may reflect colonization rather than the pathogen responsible for a deep tissue infection.8,14

Appropriate specimen volume, collection technique, transport conditions, and timing also influence diagnostic yield. Blood culture sensitivity is strongly affected by the

volume of blood collected, while delays in processing or inappropriate transport may reduce recovery of fastidious organisms. For suspected anaerobic infections, specimens should be collected and transported under conditions that preserve organism viability.45

When clinically feasible, microbiological specimens should be obtained before antimicrobial administration because prior treatment can reduce culture sensitivity. However, diagnostic sampling must not delay urgently indicated antimicrobial therapy, particularly in patients with septic shock, suspected bacterial meningitis, or rapidly progressive invasive infection. In such circumstances, blood cultures and other appropriate specimens should be collected promptly if this can be accomplished without meaningfully delaying treatment.46

Interpretation of Positive and Negative Results

A fundamental principle of microbiological diagnosis is that detection of a microorganism does not necessarily establish that it is causing disease. Positive results may represent true infection, asymptomatic colonization, specimen contamination, or detection of residual microbial material following treatment. Interpretation requires consideration of the anatomical site, specimen quality, organism identity, microbial burden when relevant, host factors, and compatibility with the clinical syndrome. For example, a positive urine culture in a patient without urinary symptoms may represent asymptomatic bacteriuria rather than symptomatic infection. Except in selected circumstances, particularly pregnancy and before certain invasive urological procedures, antimicrobial treatment of asymptomatic bacteriuria is generally not recommended.5

Similarly, isolation of coagulase-negative staphylococci from a single blood culture may represent contamination, although the same organisms can cause genuine bloodstream infections in patients with intravascular catheters, prosthetic valves, or other implanted devices. Interpretation therefore depends on the number and pattern of positive cultures, clinical findings, and the presence of relevant risk factors.8 Negative microbiological results must also be interpreted cautiously. A negative culture does not exclude infection, particularly when specimens were obtained after antimicrobial exposure, the organism requires specialized culture conditions, or the infectious process is localized to a poorly sampled anatomical compartment. Diagnostic sensitivity varies among tests and pathogens, making clinical judgment essential when laboratory findings and clinical presentation are discordant.

Molecular Diagnostics and Rapid Pathogen Identification

Molecular diagnostic techniques, including polymerase chain reaction (PCR), multiplex nucleic acid amplification panels, and other rapid identification methods, have substantially expanded the ability to detect infectious pathogens. These approaches can shorten the interval between specimen collection and organism identification, particularly in bloodstream infections, meningitis, respiratory infections, and infections caused by fastidious or difficult-to-culture organisms.47

Some molecular assays also identify selected antimicrobial resistance determinants, such as mecA in MRSA or genes encoding particular carbapenemases. Early recognition of

these markers can support timely modification of empiric therapy and facilitate infection prevention measures. However, molecular detection has important limitations. Identification of microbial DNA or RNA does not necessarily indicate viable organisms or active infection, and a detected resistance gene may not fully predict the organism's susceptibility phenotype. Conversely, the absence of a particular resistance determinant does not exclude resistance mediated by mechanisms outside the assay's detection panel. Molecular results must therefore be interpreted alongside the clinical presentation, conventional microbiology, and susceptibility testing when available.47

Diagnostic Stewardship and Clinical Decision-Making

Diagnostic stewardship seeks to improve the appropriateness of microbiological testing and the interpretation of laboratory results. Its purpose is not simply to reduce testing but to ensure that the right test is performed for the right patient, using the right specimen, at the appropriate time, and that results are translated into clinically meaningful decisions.9 Unnecessary testing can produce incidental findings that lead to inappropriate antimicrobial treatment, while inadequate testing may delay identification of serious infections or resistant pathogens. Effective diagnostic stewardship therefore requires balancing the benefits of early pathogen detection against the risks of overdiagnosis, false-positive findings, and unnecessary treatment.

ANTIMICROBIAL SUSCEPTIBILITY AND PHARMACOKINETICS

Antimicrobial susceptibility testing provides essential information for selecting effective treatment, but its clinical interpretation requires an understanding of bacterial susceptibility, antimicrobial pharmacokinetics and pharmacodynamics (PK/PD), infection site, and patient-specific factors. Although laboratory testing identifies agents with potential activity against an organism, clinical success depends on achieving sufficient antimicrobial exposure at the site of infection while minimizing toxicity. These relationships are particularly important in severe infections, infections involving difficult-to-penetrate anatomical compartments, and infections caused by resistant pathogens.

Antimicrobial Susceptibility Testing and Minimum Inhibitory Concentrations

Antimicrobial susceptibility testing evaluates the activity of antimicrobial agents against an isolated microorganism under standardized laboratory conditions. The minimum inhibitory concentration (MIC) is defined as the lowest concentration of an antimicrobial agent that prevents visible bacterial growth in a standardized in vitro assay. MICs provide quantitative information about antimicrobial activity but do not independently establish whether a drug will be clinically effective.48

MIC results are interpreted using organism-specific and antimicrobial-specific clinical breakpoints established by organizations such as the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). These breakpoints integrate MIC distributions, resistance mechanisms, pharmacokinetic and pharmacodynamic data, dosing regimens, and available clinical

outcomes. The organisms are consequently classified into susceptibility categories that help predict whether treatment is likely to succeed under specified exposure conditions.48

A susceptible result generally indicates that the organism is likely to respond when the antimicrobial is administered using an appropriate regimen. A resistant result indicates a greater likelihood of treatment failure despite clinically achievable exposure. Intermediate or increased-exposure categories require particular attention because their interpretation depends on the breakpoint system and may involve higher doses, modified administration schedules, or favorable drug concentrations at specific anatomical sites. Importantly, MIC values cannot be directly compared across unrelated antimicrobial agents to determine which antibiotic is clinically superior. An MIC of 0.5 mg/L for one drug does not necessarily indicate greater effectiveness than an MIC of 2 mg/L for another. Each value must be interpreted relative to the drug's established breakpoint, achievable exposure, and pharmacodynamic characteristics.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics describes how the body absorbs, distributes, metabolizes, and eliminates an antimicrobial agent. Pharmacodynamics describes the relationship between antimicrobial exposure and its effects on microorganisms. Together, these principles explain why antibiotic selection involves more than determining whether an organism is susceptible in vitro.49

Three principal pharmacodynamic indices are used to characterize antimicrobial activity:

- Free Time above the MIC (fT>MIC): The percentage of a dosing interval during which unbound antimicrobial concentrations remain above the MIC. This is the principal efficacy determinant for most beta-lactam antibiotics.
- Peak concentration relative to the MIC (Cmax/MIC): The relationship between maximum drug concentration and the MIC. This is particularly important for aminoglycosides, which exhibit concentration-dependent bacterial killing.
- Total antimicrobial exposure relative to the MIC (AUC/MIC): The ratio of the area under the drug concentration-time curve to the MIC. This is important for agents such as vancomycin and fluoroquinolones (Table 4).49

Table 4: Pharmacodynamic targets and practical dosing considerations

PK/PD index	Representative drugs	Clinical implication
Free time above MIC (fT>MIC)	Most beta-lactams	Optimize time above the MIC; prolonged infusion may be appropriate in selected patients.
Peak/MIC (Cmax/MIC)	Aminoglycosides	Achieve an adequate peak while limiting toxic exposure.
Exposure/MIC (AUC/MIC)	Vancomycin, fluoroquinolones	Balance total exposure, efficacy, and toxicity; monitor when indicated.

MIC, minimum inhibitory concentration; AUC, area under the concentration-time curve. Targets vary by drug, pathogen, and clinical setting.

These relationships have direct implications for antimicrobial dosing. Because beta-lactam efficacy generally depends on maintaining free drug concentrations above the MIC, prolonged or continuous infusions may improve pharmacodynamic target attainment in selected critically ill patients. Aminoglycosides, in contrast, benefit from achieving sufficiently high peak concentrations while allowing concentrations to decline between doses, supporting extended-interval dosing in appropriate patients. Vancomycin dosing for serious MRSA infections increasingly relies on AUC-guided monitoring to optimize exposure while reducing nephrotoxicity.37

Pharmacodynamic targets are not identical across drugs, pathogens, infection sites, or patient populations. Consequently, dosing strategies must reflect the specific antimicrobial and clinical circumstances rather than applying a single exposure target to all antibiotic classes.

Anatomical Distribution and Tissue Penetration

Antimicrobial treatment may fail in vivo, if adequate drug concentrations cannot be achieved at the infected anatomical site, even when an organism is susceptible to an antibiotic in vitro. This is because, the in vivo tissue distribution is influenced by molecular size, lipid solubility, protein binding, local blood flow, membrane permeability, and the presence of inflammation. This consideration is particularly important in infections involving the central nervous system, bone, cardiac vegetations, abscesses, and implanted medical devices. In bacterial meningitis, antimicrobial agents must achieve effective concentrations in cerebrospinal fluid despite the restrictive properties of the blood-brain barrier. Drug penetration varies considerably among antibiotics and may change with meningeal inflammation. Consequently, the antimicrobial drugs suitable for bloodstream or pulmonary infections may be inadequate for central nervous system infection, even when laboratory susceptibility is demonstrated.50

Osteomyelitis and prosthetic-device infections present different challenges. This is because effective therapy requires adequate exposure within infected bone or surrounding tissues, while bacterial biofilms on implanted materials can reduce antimicrobial effectiveness and promote persistent infection. Similarly, abscesses may contain poorly perfused tissue, necrotic material, and high bacterial burdens that impair antimicrobial activity. These infections may require drainage, debridement, or removal of infected material in addition to appropriate antibiotics.

Urinary tract infections provide another important example of anatomical pharmacology. This is because Nitrofurantoin achieves high concentrations in urine but inadequate renal parenchymal and systemic concentrations, making it useful for susceptible uncomplicated cystitis but inappropriate for pyelonephritis or bacteremia. This distinction demonstrates why urinary susceptibility does not necessarily establish suitability for an invasive infection.20

Patient-Specific Pharmacokinetic Variability

Antimicrobial drug effectiveness also depends on individual patient characteristics. Renal and hepatic dysfunction can alter drug clearance, while obesity, critical illness,

hypoalbuminemia, pregnancy, and substantial fluid shifts may change the volume of distribution or unbound drug concentrations. In critically ill patients, increased capillary permeability and aggressive fluid resuscitation may expand the volume of distribution of hydrophilic antibiotics. Conversely, augmented renal clearance can increase antimicrobial elimination, potentially producing subtherapeutic concentrations despite conventional dosing. Patients with impaired renal function may experience drug accumulation and toxicity unless dosing is appropriately adjusted.51

These considerations are particularly important for agents with narrow therapeutic margins, including aminoglycosides and vancomycin. Therapeutic drug monitoring, when indicated, allows dosing to be individualized according to measured exposure, renal function, treatment response, and toxicity risk.

Integrating Susceptibility Results with Clinical Decision-Making

Antimicrobial susceptibility testing should be interpreted as one component of a broader clinical assessment. An appropriate treatment decision requires consideration of the identified pathogen, resistance phenotype, MIC interpretation, achievable pharmacodynamic exposure, anatomical site, illness severity, host physiology, and need for source control. For example, an organism may be categorized as susceptible to an antibiotic that cannot achieve adequate concentrations in cerebrospinal fluid, rendering that agent unsuitable for meningitis. Conversely, certain antimicrobials may be effective for localized urinary infection because of exceptionally high urinary concentrations despite limited systemic exposure. Infections involving abscesses, necrotic tissue, or prosthetic materials may also persist despite apparently appropriate antimicrobial therapy unless the infected focus is adequately addressed.

SOURCE CONTROL

Source control is a fundamental component of effective infection management and refers to the physical elimination, drainage, or containment of an infectious focus and correction of the anatomical abnormalities that sustain infection. Although antimicrobial therapy is essential for treating many bacterial infections, antibiotics alone may be insufficient when infected material, necrotic tissue, obstructed anatomical structures, or colonized medical devices remain in place. Successful management therefore requires an integrated approach that addresses both the causative microorganism and the underlying source of infection.52

Principles and Clinical Applications

Source-control interventions include drainage of abscesses, surgical debridement of infected or necrotic tissue, removal of infected intravascular catheters or prosthetic materials when indicated, and decompression of obstructed urinary or biliary systems. The appropriate intervention depends on the anatomical site, extent of infection, physiological stability of the patient, and feasibility of procedural or surgical management (Figure 5).

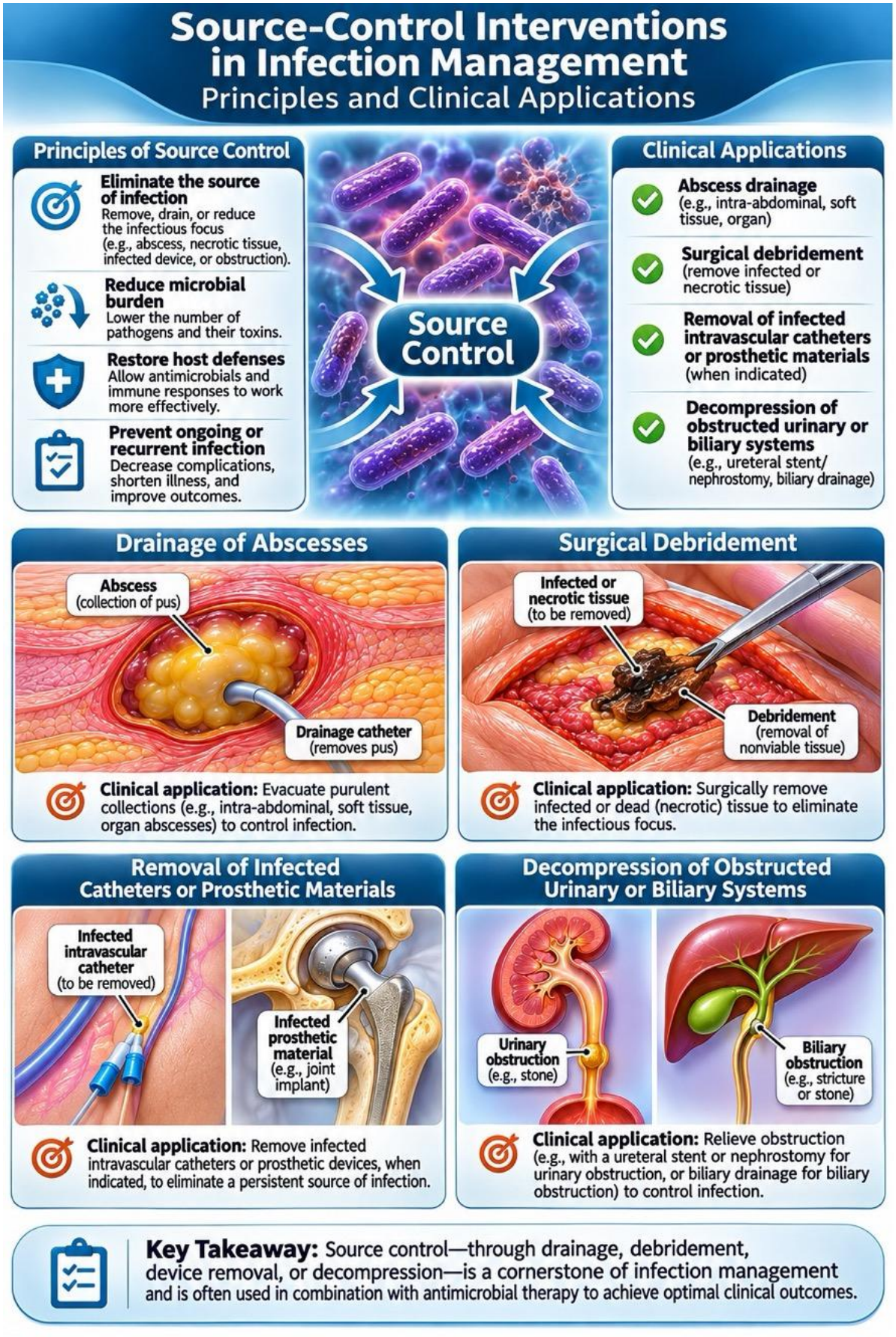

Source-Control Interventions in Infection Management
Principles and Clinical Applications
Principles of Source Control
Eliminate the source of infection
Remove, drain, or reduce the infectious focus (e.g., abscess, necrotic tissue, infected device, or obstruction).
Reduce microbial burden
Lower the number of pathogens and their toxins.
Restore host defenses
Allow antimicrobials and immune responses to work more effectively.
Prevent ongoing or recurrent infection
Decrease complications, shorten illness, and improve outcomes.
Source Control
Clinical Applications
Abscess drainage (e.g., intra-abdominal, soft tissue, organ)
Surgical debridement (remove infected or necrotic tissue)
Removal of infected intravascular catheters or prosthetic materials (when indicated)
Decompression of obstructed urinary or biliary systems (e.g., ureteral stent/ nephrostomy, biliary drainage)
Drainage of Abscesses
Abscess (collection of pus)
Drainage catheter (removes pus)
Clinical application: Evacuate purulent collections (e.g., intra-abdominal, soft tissue, organ abscesses) to control infection.
Surgical Debridement
Infected or necrotic tissue (to be removed)
Debridement (removal of nonviable tissue)
Clinical application: Surgically remove infected or dead (necrotic) tissue to eliminate the infectious focus.
Removal of Infected Catheters or Prosthetic Materials
Infected intravascular catheter (to be removed)
Infected prosthetic material (e.g., joint implant)
Clinical application: Remove infected intravascular catheters or prosthetic devices, when indicated, to eliminate a persistent source of infection.
Decompression of Obstructed Urinary or Biliary Systems
Urinary obstruction (e.g., stone)
Biliary obstruction (e.g., stricture or stone)
Clinical application: Relieve obstruction (e.g., with a ureteral stent or nephrostomy for urinary obstruction, or biliary drainage for biliary obstruction) to control infection.
Key Takeaway: Source control—through drainage, debridement, device removal, or decompression—is a cornerstone of infection management and is often used in combination with antimicrobial therapy to achieve optimal clinical outcomes.

Figure 5

Several clinical scenarios illustrate the importance of these interventions:

- Intra-abdominal infection: Perforated appendicitis, complicated diverticulitis, and intra-abdominal abscesses may require drainage, resection, or repair of the underlying pathological process. Antibiotics cannot reliably eliminate infection when ongoing gastrointestinal contamination or an undrained collection persists.
- Obstructed urinary tract infection: Pyelonephritis complicated by an obstructing ureteral calculus and infected collecting system requires urgent decompression, typically through ureteral stenting or percutaneous nephrostomy, in addition to antimicrobial therapy.
- Necrotizing soft-tissue infection: Rapid surgical exploration and debridement are essential because progressive tissue necrosis, vascular compromise, and toxin-mediated injury cannot be adequately controlled with antibiotics alone.
- Intravascular catheter-associated infection: Removal of an infected catheter may be necessary, particularly in infections involving Staphylococcus aureus, certain fungi, or persistent bloodstream infection.
- Prosthetic-device infection: Infected orthopedic implants, cardiac devices, and other prosthetic materials may require debridement, removal, or replacement, depending on the pathogen, duration of infection, device stability, and available treatment strategies.53

These examples demonstrate that source control is not a uniform procedure but a clinical principle requiring anatomical localization and timely intervention.

Why Antimicrobial Therapy May Be Insufficient

The biological and pharmacological limitations of antimicrobial treatment, demonstrate the need for source control. For example, abscess cavities and necrotic tissues may have impaired blood supply, limiting antibiotic delivery and host immune-cell access. High bacterial burdens, altered local pH, and reduced microbial metabolic activity may further diminish antimicrobial effectiveness.

Biofilm-associated infections present additional challenges. Bacteria embedded within extracellular matrices on catheters, prosthetic joints, or other implanted materials may exhibit substantial tolerance to antimicrobial exposure despite apparent susceptibility under conventional laboratory conditions. These infections may persist or recur unless the infected material is removed or an appropriate device-retention strategy is implemented.54 Consequently, an organism reported as susceptible to an antimicrobial agent may remain clinically difficult to eradicate when the underlying infectious focus is not adequately controlled. This distinction reinforces the principle that laboratory susceptibility does not guarantee treatment success.

Timing and Clinical Reassessment

The timing of source control is particularly important in severe infection and sepsis. Once an anatomical focus requiring intervention is identified, source control should be pursued as soon as medically and logistically feasible, with urgency determined by the clinical

condition and nature of the infection. The Surviving Sepsis Campaign emphasizes rapid identification of anatomical sources requiring intervention and timely implementation of appropriate source-control measures.46

Persistent bacteremia, ongoing fever, hemodynamic instability, or clinical deterioration despite apparently appropriate antimicrobial therapy should prompt reassessment for an undrained abscess, infected device, obstructed system, metastatic infection, or other uncontrolled focus. Although antimicrobial resistance and inadequate drug exposure must also be considered, automatic escalation to broader-spectrum therapy without reassessing the source may delay the intervention necessary for recovery. Repeat imaging, targeted microbiological sampling, and consultation with surgical, interventional radiology, or other procedural specialists may be appropriate when the clinical course suggests inadequate source control.

Source Control in Complicated Intra-Abdominal Infection

Complicated intra-abdominal infections provide a particularly important example of the relationship between antimicrobial therapy and anatomical intervention. These infections extend beyond the organ of origin into the peritoneal space and may involve localized or diffuse peritonitis, abscess formation, or ongoing contamination from gastrointestinal perforation. Management of these infections, requires prompt assessment of the anatomical source, appropriate antimicrobial coverage for likely enteric pathogens, and drainage or surgical intervention when indicated. Intra-abdominal cultures obtained during source-control procedures can be particularly valuable in healthcare-associated infections, critically ill patients, and infections involving suspected resistant organisms.55 Importantly, successful source control may also permit shorter courses of antimicrobial therapy. In a randomized trial involving 518 patients with complicated intra-abdominal infection and adequate source control, a fixed antimicrobial course of approximately four days produced outcomes similar to a longer course continued until resolution of physiological abnormalities, which had a median duration of eight days.56 These findings demonstrate that effective anatomical intervention can reduce the need for prolonged antibiotic exposure without compromising clinical outcomes in appropriately selected patients.

Integrating Source Control with Antimicrobial Stewardship

Source control and antimicrobial stewardship are complementary rather than competing principles. An appropriate antimicrobial treatment limits bacterial proliferation and systemic dissemination, while source control removes the anatomical conditions that sustain infection. Together, these interventions improve the likelihood of recovery and may reduce unnecessary broad-spectrum or prolonged antimicrobial exposure. The adequacy of source control should therefore be reassessed when determining treatment duration, interpreting persistent microbiological findings, and evaluating apparent antimicrobial failure.

EMPIRIC ANTIMICROBIAL THERAPY

Empiric antimicrobial therapy refers to the initiation of treatment before the definitive identification of the causative pathogen or availability of antimicrobial susceptibility

results. It is a fundamental component of infectious disease management, particularly when delayed treatment may result in rapid clinical deterioration, organ dysfunction, or death. Effective empiric therapy requires balancing the need for timely coverage of likely pathogens against the risks of unnecessary antimicrobial exposure, toxicity, and selection for resistance. The objective is not to prescribe the broadest available regimen but to select treatment that is sufficiently comprehensive for the patient's clinical presentation and risk profile while remaining appropriate to the suspected infectious syndrome.[46]

Clinical Assessment and Selection of Empiric Therapy

Empiric antimicrobial selection begins with recognition of the infectious syndrome and identification of the probable anatomical source. This initial assessment establishes the most likely pathogens and determines the antimicrobial spectrum required before microbiological confirmation. Several factors should guide treatment selection, including illness severity, host immune status, community or healthcare exposure, prior microbiological findings, recent antimicrobial use, local resistance patterns, drug allergies, renal and hepatic function, and the likelihood of resistant organisms. The presence of implanted devices, recent hospitalization, invasive procedures, or structural abnormalities may further influence pathogen probability (Figure 6).

Previous culture and susceptibility results are particularly valuable because they may identify resistant organisms that remain clinically relevant during subsequent infections. Similarly, recent exposure to broad-spectrum antibiotics may increase the probability of resistant Gram-negative pathogens or other organisms selected by antimicrobial pressure. However, individual risk factors should be interpreted within the clinical context rather than used as automatic indications for broad-spectrum treatment.57

The anatomical site also determines whether an antimicrobial can achieve adequate therapeutic concentrations. For example, an agent suitable for uncomplicated urinary infection may be inappropriate for bacteremia or meningitis despite activity against the suspected organism. Thus, empiric therapy must integrate microbiological probability with antimicrobial pharmacokinetics, pharmacodynamics, and tissue penetration.

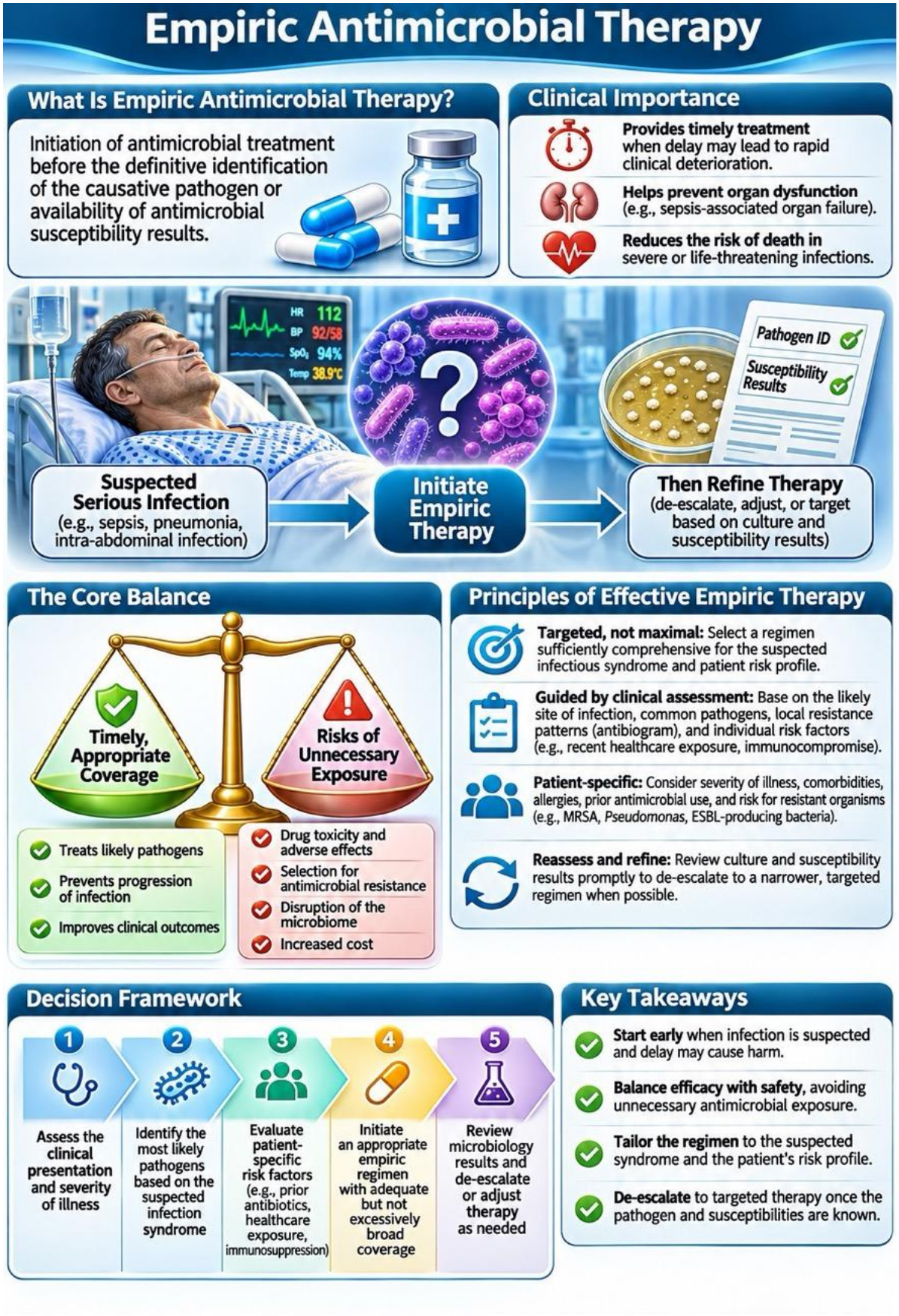

Empiric Antimicrobial Therapy
What Is Empiric Antimicrobial Therapy?
Initiation of antimicrobial treatment before the definitive identification of the causative pathogen or availability of antimicrobial susceptibility results.
Clinical Importance
Provides timely treatment when delay may lead to rapid clinical deterioration.
Helps prevent organ dysfunction (e.g., sepsis-associated organ failure).
Reduces the risk of death in severe or life-threatening infections.
HR 112
BP 92/58
SpO2 94%
Temp 38.9°C
Pathogen ID
Susceptibility Results
Suspected Serious Infection (e.g., sepsis, pneumonia, intra-abdominal infection)
Initiate Empiric Therapy
Then Refine Therapy (de-escalate, adjust, or target based on culture and susceptibility results)
The Core Balance
Timely, Appropriate Coverage
Risks of Unnecessary Exposure
Treats likely pathogens
Prevents progression of infection
Improves clinical outcomes
Drug toxicity and adverse effects
Selection for antimicrobial resistance
Disruption of the microbiome
Increased cost
Principles of Effective Empiric Therapy
Targeted, not maximal: Select a regimen sufficiently comprehensive for the suspected infectious syndrome and patient risk profile.
Guided by clinical assessment: Base on the likely site of infection, common pathogens, local resistance patterns (antibiogram), and individual risk factors (e.g., recent healthcare exposure, immunocompromise).
Patient-specific: Consider severity of illness, comorbidities, allergies, prior antimicrobial use, and risk for resistant organisms (e.g., MRSA, Pseudomonas, ESBL-producing bacteria).
Reassess and refine: Review culture and susceptibility results promptly to de-escalate to a narrower, targeted regimen when possible.
Decision Framework
1 Assess the clinical presentation and severity of illness
2 Identify the most likely pathogens based on the suspected infection syndrome
3 Evaluate patient-specific risk factors (e.g., prior antibiotics, healthcare exposure, immunosuppression)
4 Initiate an appropriate empiric regimen with adequate but not excessively broad coverage
5 Review microbiology results and de-escalate or adjust therapy as needed
Key Takeaways
Start early when infection is suspected and delay may cause harm.
Balance efficacy with safety, avoiding unnecessary antimicrobial exposure.
Tailor the regimen to the suspected syndrome and the patient's risk profile.
De-escalate to targeted therapy once the pathogen and susceptibilities are known.

Figure 6

Syndrome-Specific Empiric Therapy

The use of appropriate empiric regimen varies substantially among infectious syndromes because pathogen distribution, resistance risk, and anatomical considerations differ.

Community-acquired pneumonia

Empiric treatment generally targets Streptococcus pneumoniae and other common respiratory pathogens, with consideration of atypical organisms such as Mycoplasma pneumoniae and Legionella pneumophila. Regimen selection depends on disease severity, comorbidities, and treatment setting. Routine empiric coverage for MRSA or Pseudomonas aeruginosa is not recommended unless validated risk factors or relevant prior microbiological findings support its use.4

Hospital-acquired and ventilator-associated pneumonia

These infections require greater consideration of resistant Gram-negative organisms, including P. aeruginosa, and MRSA in selected patients. Empiric coverage should reflect local susceptibility patterns, prior intravenous antibiotic exposure, illness severity, and institutional resistance prevalence. Broader initial therapy may be justified in patients at substantial risk of resistant infection, but treatment should be reassessed when microbiological results become available (Figure 7).6

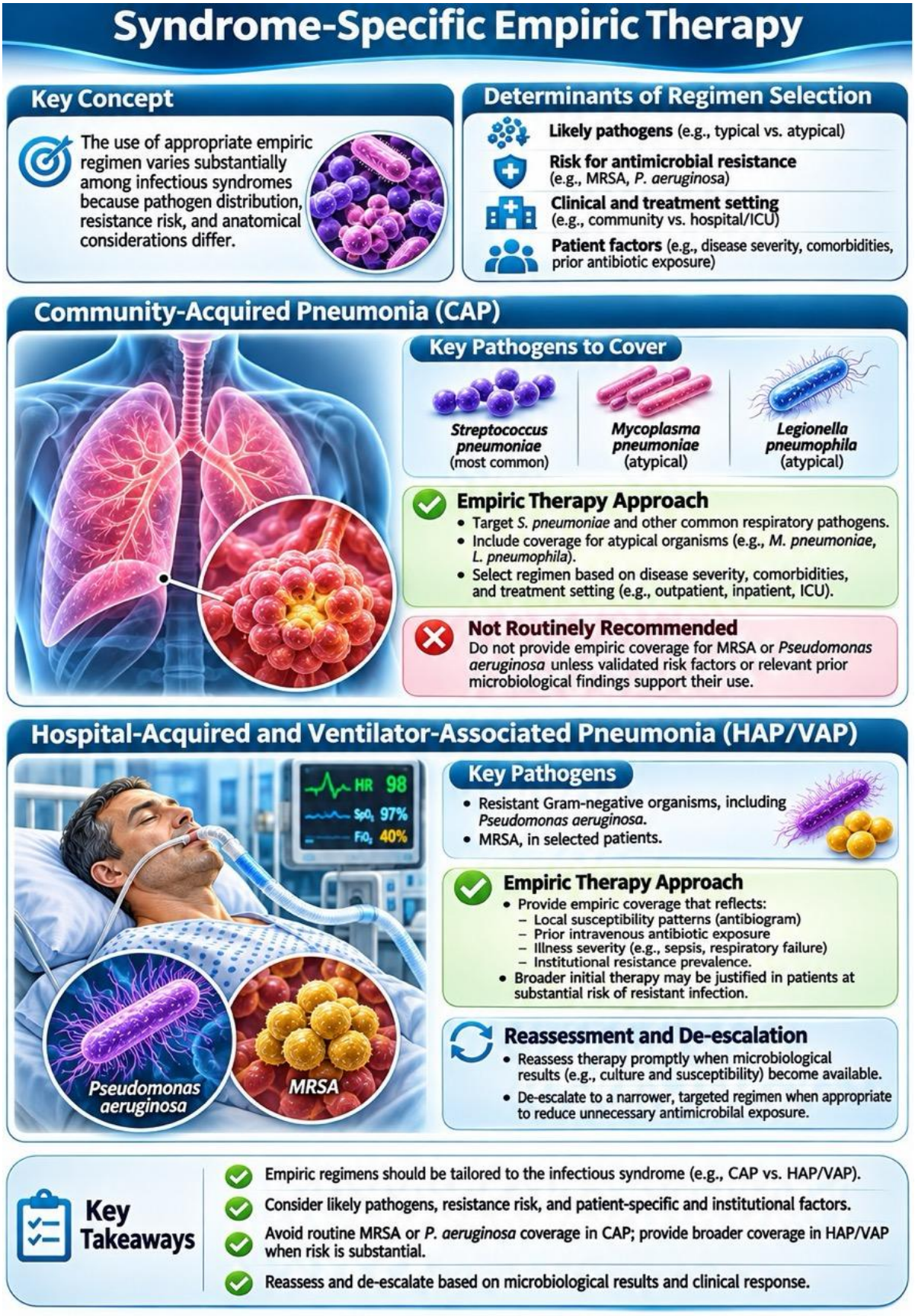

Syndrome-Specific Empiric Therapy
Key Concept
The use of appropriate empiric regimen varies substantially among infectious syndromes because pathogen distribution, resistance risk, and anatomical considerations differ.
Determinants of Regimen Selection
Likely pathogens (e.g., typical vs. atypical)
Risk for antimicrobial resistance (e.g., MRSA, P. aeruginosa)
Clinical and treatment setting (e.g., community vs. hospital/ICU)
Patient factors (e.g., disease severity, comorbidities, prior antibiotic exposure)
Community-Acquired Pneumonia (CAP)
Key Pathogens to Cover
Streptococcus pneumoniae (most common)
Mycoplasma pneumoniae (atypical)
Legionella pneumophila (atypical)
Empiric Therapy Approach
Target S. pneumoniae and other common respiratory pathogens.
Include coverage for atypical organisms (e.g., M. pneumoniae, L. pneumophila).
Select regimen based on disease severity, comorbidities, and treatment setting (e.g., outpatient, inpatient, ICU).
Not Routinely Recommended
Do not provide empiric coverage for MRSA or Pseudomonas aeruginosa unless validated risk factors or relevant prior microbiological findings support their use.
Hospital-Acquired and Ventilator-Associated Pneumonia (HAP/VAP)
HR 98
SpO2 97%
FiO2 40%
Pseudomonas aeruginosa
MRSA
Key Pathogens
Resistant Gram-negative organisms, including Pseudomonas aeruginosa.
MRSA, in selected patients.
Empiric Therapy Approach
Provide empiric coverage that reflects:
Local susceptibility patterns (antibiogram)
Prior intravenous antibiotic exposure
Illness severity (e.g., sepsis, respiratory failure)
Institutional resistance prevalence.
Broader initial therapy may be justified in patients at substantial risk of resistant infection.
Reassessment and De-escalation
Reassess therapy promptly when microbiological results (e.g., culture and susceptibility) become available.
De-escalate to a narrower, targeted regimen when appropriate to reduce unnecessary antimicrobilal exposure.
Key Takeaways
Empiric regimens should be tailored to the infectious syndrome (e.g., CAP vs. HAP/VAP).
Consider likely pathogens, resistance risk, and patient-specific and institutional factors.
Avoid routine MRSA or P. aeruginosa coverage in CAP; provide broader coverage in HAP/VAP when risk is substantial.
Reassess and de-escalate based on microbiological results and clinical response.

Figure 7

Bacterial meningitis

Suspected acute bacterial meningitis requires urgent administration of bactericidal agents capable of achieving effective cerebrospinal fluid concentrations. In adults, empiric therapy commonly includes a third-generation cephalosporin and vancomycin, with ampicillin added when coverage for Listeria monocytogenes is indicated, such as in older adults, pregnant patients, or individuals with relevant immunocompromising conditions. The precise regimen depends on age, immune status, epidemiological factors, and whether infection is community-acquired or healthcare-associated. Antimicrobial treatment must not be delayed when lumbar puncture or neuroimaging cannot be performed promptly.12

Complicated urinary tract infection

Empiric therapy should account for illness severity, urinary obstruction, recent instrumentation, prior resistant isolates, and the possibility of bacteremia. Patients with severe systemic infection may require intravenous therapy with activity against resistant Enterobacterales, while clinically stable patients may be candidates for narrower regimens based on individual risk factors. Obstruction or an infected collecting system requires prompt anatomical evaluation and drainage when indicated.

Intra-abdominal infection

Empiric therapy generally requires activity against relevant enteric Gram-negative organisms and, in many circumstances, anaerobic bacteria. The necessary spectrum depends on whether infection is community-acquired or healthcare-associated, the anatomical source, illness severity, and resistance risk. Antimicrobial treatment must be accompanied by timely evaluation for drainage or surgical source control.55

Necrotizing soft-tissue infection

Suspected necrotizing infection warrants immediate broad-spectrum antimicrobial treatment and urgent surgical assessment. Initial regimens commonly provide coverage for streptococci, S. aureus including MRSA, Gram-negative organisms, and anaerobes until the causative pathogens are established. When group A streptococcal necrotizing fasciitis is confirmed, penicillin combined with clindamycin is recommended because clindamycin suppresses bacterial protein synthesis and toxin production.58

Timing of Antimicrobial Administration

The urgency of empiric antimicrobial therapy depends on both the probability of bacterial infection and the consequences of delayed treatment. In septic shock and other life-threatening infections, prompt administration of appropriately active antimicrobials is essential. The Surviving Sepsis Campaign recommends immediate antimicrobial treatment, ideally within one hour of recognition, for patients with septic shock or a high likelihood of sepsis. In patients with possible sepsis but without shock, a rapid assessment of infectious and noninfectious causes is appropriate, with antimicrobial timing guided by the resulting clinical probability and severity.46

This distinction is important because indiscriminate antibiotic administration to every patient with systemic inflammatory findings may expose individuals without bacterial infection to unnecessary treatment. Fever, leukocytosis, tachycardia, and elevated inflammatory markers are not specific for infection and may accompany noninfectious conditions. Accordingly, the urgency of treatment should reflect the balance between the risks of delay and the probability that antimicrobial therapy will provide benefit. When feasible, blood cultures and other relevant specimens should be collected before the first antimicrobial dose. However, diagnostic investigations must not meaningfully delay treatment in patients with septic shock, suspected bacterial meningitis, or other rapidly progressive infections.

Balancing Adequate Coverage and Antimicrobial Stewardship

The principal challenge of empiric therapy is achieving adequate initial coverage without unnecessary expansion of antimicrobial spectrum. Inadequate treatment of severe bacterial infection may contribute to clinical deterioration, whereas unnecessarily broad therapy increases the risks of adverse drug reactions, Clostridioides difficile infection, microbiome disruption, and selection for resistant organisms.

Broad-spectrum treatment may be appropriate initially when the probability or consequences of resistant infection are substantial. However, the need for broad coverage should be reassessed as clinical findings, microbiological results, and susceptibility data become available. Empiric treatment should therefore be regarded as a provisional, evidence-informed decision rather than a fixed regimen. Clinical reassessment should consider whether infection remains the most likely diagnosis, whether the suspected source has been identified, whether source control is required, and whether the initial antimicrobial spectrum remains justified.

DEFINITIVE THERAPY AND DE-ESCALATION

Definitive antimicrobial therapy represents the transition from probability-based empiric treatment to a more individualized regimen informed by microbiological identification, antimicrobial susceptibility results, clinical response, and the established anatomical source of infection. As diagnostic uncertainty decreases, antimicrobial treatment should be reassessed to ensure that the selected agent provides reliable activity against the causative pathogen while minimizing unnecessary spectrum, toxicity, and selection pressure for resistance. This process is a central component of antimicrobial stewardship and requires consideration of drug selection, dose, route, duration, and the adequacy of source control.3

Transition From Empiric to Definitive Therapy

Empiric antimicrobial regimens are selected to cover likely pathogens before definitive microbiological information becomes available. Once culture results, molecular identification, and susceptibility testing clarify the diagnosis, the initial regimen should be reviewed and modified when appropriate. Definitive treatment should preferentially employ an effective agent with the narrowest appropriate spectrum, provided that it achieves adequate exposure at the infected site and has an acceptable safety profile. For example,

identification of “methicillin-susceptible S. aureus” (MSSA) in a patient initially receiving vancomycin generally supports transition to an antistaphylococcal beta-lactam, such as cefazolin or nafcillin, because these agents are preferred for serious MSSA infections.[14]

Similarly, identification of a susceptible Gram-negative pathogen may permit replacement of broad-spectrum empiric therapy with a narrower agent. However, susceptibility results must be interpreted in relation to the organism's resistance mechanisms, infection site, and clinical severity. For example, serious invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales may still warrant carbapenem treatment despite apparent in vitro susceptibility to certain alternative agents.20 Definitive therapy therefore requires more than selecting an antibiotic labeled susceptible on a laboratory report. The clinician must determine whether the antimicrobial is appropriate for the organism, anatomical site, anticipated bacterial burden, host physiology, and severity of infection.

Antimicrobial De-escalation

Antimicrobial de-escalation refers to modification of an empiric regimen to reduce unnecessary antimicrobial exposure as diagnostic information becomes available. It may involve narrowing the antimicrobial spectrum, discontinuing redundant agents, reducing the number of antibiotics administered, or stopping antimicrobial treatment entirely when bacterial infection becomes unlikely.

For example, empiric vancomycin may be discontinued when a suspected infection is confirmed to involve a pathogen that does not require MRSA coverage. Likewise, antipseudomonal therapy may be narrowed when microbiological findings and clinical assessment no longer support the need for such coverage.

De-escalation is particularly important because broad-spectrum antimicrobial exposure can disrupt the normal microbiota, promote colonization by resistant organisms, increase the risk of Clostridioides difficile infection, and contribute to drug-related toxicity. However, de-escalation should not be equated with indiscriminate narrowing. Appropriate treatment must continue to account for unresolved diagnostic uncertainty, polymicrobial infection, inadequate source control, and the possibility that available specimens do not fully represent the causative pathogens.

A systematic antimicrobial reassessment, often performed approximately 48 to 72 hours after treatment initiation, provides an opportunity to review culture results, clinical improvement, infection source, and the continuing need for each prescribed agent. This practice is commonly incorporated into antimicrobial stewardship programs.3

Transition from Intravenous to Oral Therapy

Intravenous antimicrobial administration is frequently necessary during the initial management of severe infection, hemodynamic instability, impaired gastrointestinal absorption, or infections requiring reliable systemic drug exposure. However, prolonged intravenous treatment is not inherently superior when an effective oral regimen can achieve adequate concentrations at the infected site.

Transition to oral therapy may be appropriate when the patient demonstrates clinical stability, can absorb oral medications, has a pathogen susceptible to an appropriate oral agent, and no longer requires intravenous administration for other clinical reasons. Oral bioavailability, pharmacodynamic exposure, infection site, and adherence must also be considered. Several antimicrobial agents, including fluoroquinolones, linezolid, doxycycline, and trimethoprim-sulfamethoxazole, have favorable oral bioavailability, although their suitability depends on the organism and clinical syndrome. Oral beta-lactams may also be appropriate in selected infections when dosing and exposure are adequate.

Evidence increasingly supports oral treatment strategies for carefully selected patients with infections historically managed using prolonged intravenous therapy. In a randomized trial involving 1,054 adults with bone and joint infections, oral antibiotic therapy was noninferior to intravenous therapy during the first six weeks of treatment with respect to treatment failure at one year.59 Similarly, a randomized trial involving 400 clinically stable patients with left-sided infective endocarditis demonstrated that partial oral therapy was noninferior to continued intravenous treatment in appropriately selected patients.60 These findings do not establish that oral therapy is suitable for every invasive infection. Rather, they demonstrate that the route of administration should be determined by antimicrobial exposure, clinical stability, infection characteristics, and available evidence rather than the assumption that intravenous treatment is universally more effective.

Optimizing Treatment Duration

The duration of definitive antimicrobial therapy should reflect the infectious syndrome, causative organism, anatomical site, adequacy of source control, host immune status, and clinical response. Historically, prolonged treatment courses were frequently prescribed despite limited evidence supporting their necessity. Contemporary clinical trials increasingly demonstrate that shorter courses can achieve outcomes comparable to longer regimens in appropriately selected patients.

For example, in a randomized trial involving 604 patients with uncomplicated Gram-negative bacteremia who were clinically stable by day 7, seven days of antibiotic treatment was noninferior to 14 days for a composite outcome that included mortality, relapse, and other clinically important complications.61

Similarly, the STOP-IT trial demonstrated that approximately four days of antimicrobial therapy following adequate source control produced outcomes comparable to a longer treatment course in selected patients with complicated intra-abdominal infection.56 These findings reinforce the importance of tailoring treatment duration to the underlying disease process rather than extending therapy solely because an infection was initially severe. Nevertheless, shorter treatment courses are not appropriate for every infection. Infective endocarditis, certain cases of osteomyelitis, central nervous system infections, persistent bacteremia, and infections involving inadequately controlled sources may require prolonged or highly individualized treatment. The presence of prosthetic material, substantial immunosuppression, or complications may further influence duration. The objective is therefore to prescribe the shortest evidence-supported course that provides reliable clinical cure, not simply the shortest possible course.

Clinical Reassessment and Treatment Failure

Definitive therapy requires continued evaluation of treatment response. Persistent fever, bacteremia, organ dysfunction, or clinical deterioration should prompt reassessment of the diagnosis, antimicrobial susceptibility, drug exposure, and adequacy of source control.

An apparent antimicrobial failure may result from an undrained abscess, infected device, anatomical obstruction, inadequate tissue penetration, subtherapeutic dosing, an unrecognized resistant pathogen, or an incorrect initial diagnosis. Consequently, escalation to broader-spectrum treatment should not be the automatic response to persistent symptoms.

Repeat microbiological testing, imaging, therapeutic drug monitoring, or specialist consultation may be appropriate depending on the clinical circumstances. The purpose of reassessment is to identify the reason for an inadequate response and correct the underlying problem rather than merely increase antimicrobial exposure.

Integrating Definitive Therapy with Antimicrobial Stewardship

Definitive therapy is the stage at which microbiological evidence, antimicrobial pharmacology, and clinical response are integrated into an optimized treatment plan. Appropriate management requires confirming the need for continued antibiotics, selecting the most suitable active agent, determining whether oral treatment is feasible, and establishing an evidence-based duration.

These decisions should be revisited when new microbiological information becomes available or the patient's condition changes. Narrowing therapy, discontinuing unnecessary antibiotics, and avoiding unnecessarily prolonged treatment can reduce adverse effects and antimicrobial selection pressure while preserving clinical effectiveness.

ANTIMICROBIAL TOXICITY AND INDIVIDUALIZED TREATMENT

Antimicrobial selection requires balancing microbiological efficacy with patient-specific safety considerations. Although an antibiotic may demonstrate excellent activity against a pathogen, its clinical suitability also depends on renal and hepatic function, age, comorbidities, concomitant medications, pregnancy status, allergy history, and the anticipated duration of treatment. Adverse effects may be dose-dependent, related to cumulative exposure, or attributable to individual susceptibility. Consequently, rational antimicrobial prescribing requires an understanding of both the therapeutic benefits and potential harms of each agent (Figure 8).

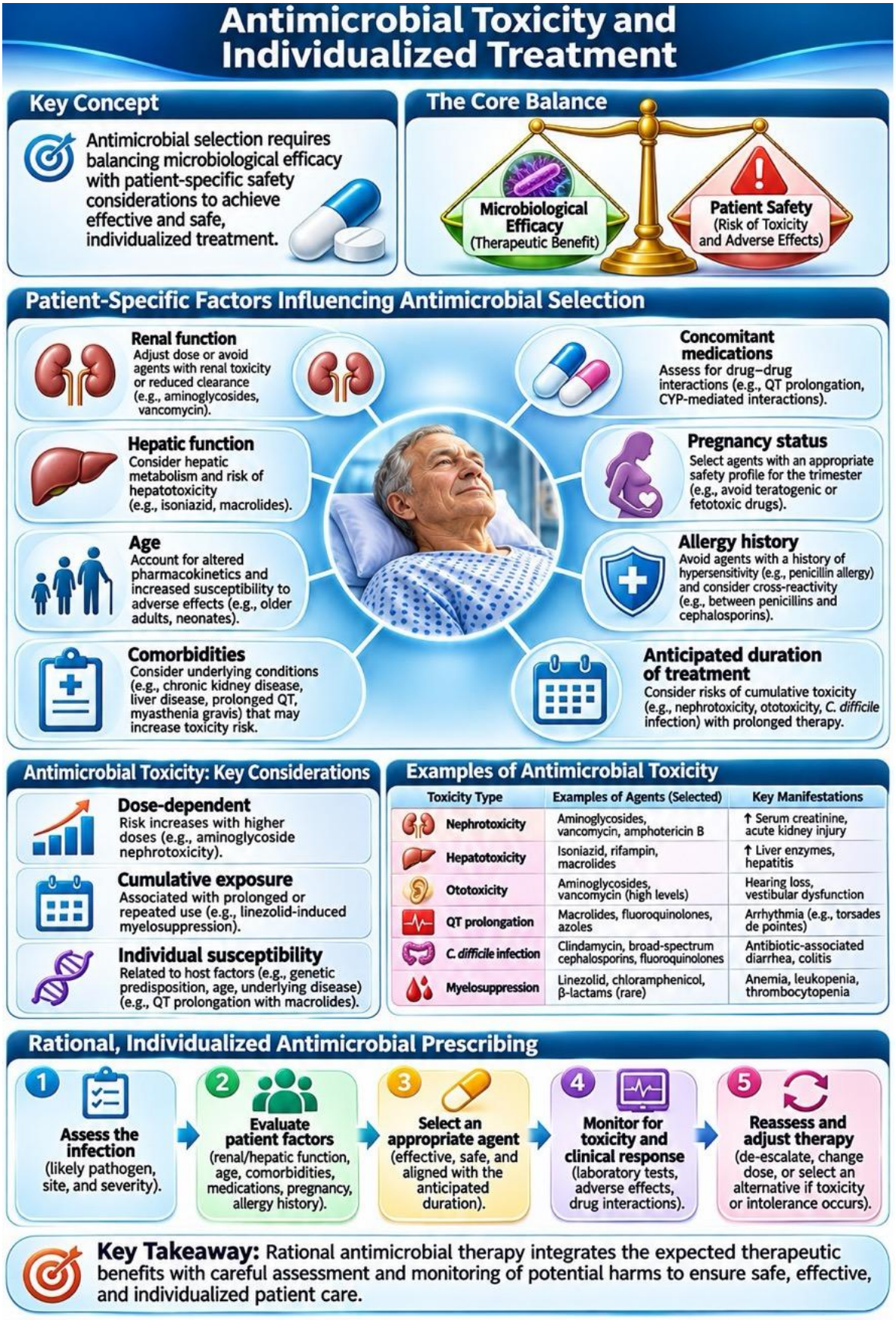

Antimicrobial Toxicity and Individualized Treatment
Key Concept
Antimicrobial selection requires balancing microbiological efficacy with patient-specific safety considerations to achieve effective and safe, individualized treatment.
The Core Balance
Microbiological Efficacy (Therapeutic Benefit)
Patient Safety (Risk of Toxicity and Adverse Effects)
Patient-Specific Factors Influencing Antimicrobial Selection
Renal function
Adjust dose or avoid agents with renal toxicity or reduced clearance (e.g., aminoglycosides, vancomycin).
Hepatic function
Consider hepatic metabolism and risk of hepatotoxicity (e.g., isoniazid, macrolides).
Age
Account for altered pharmacokinetics and increased susceptibility to adverse effects (e.g., older adults, neonates).
Comorbidities
Consider underlying conditions (e.g., chronic kidney disease, liver disease, prolonged QT, myasthenia gravis) that may increase toxicity risk.
Concomitant medications
Assess for drug–drug interactions (e.g., QT prolongation, CYP-mediated interactions).
Pregnancy status
Select agents with an appropriate safety profile for the trimester (e.g., avoid teratogenic or fetotoxic drugs).
Allergy history
Avoid agents with a history of hypersensitivity (e.g., penicillin allergy) and consider cross-reactivity (e.g., between penicillins and cephalosporins).
Anticipated duration of treatment
Consider risks of cumulative toxicity (e.g., nephrotoxicity, ototoxicity, C. difficile infection) with prolonged therapy.
Antimicrobial Toxicity: Key Considerations
Dose-dependent
Risk increases with higher doses (e.g., aminoglycoside nephrotoxicity).
Cumulative exposure
Associated with prolonged or repeated use (e.g., linezolid-induced myelosuppression).
Individual susceptibility
Related to host factors (e.g., genetic predisposition, age, underlying disease) (e.g., QT prolongation with macrolides).
Examples of Antimicrobial Toxicity
Toxicity Type | Examples of Agents (Selected) | Key Manifestations
Nephrotoxicity | Aminoglycosides, vancomycin, amphotericin B | ↑ Serum creatinine, acute kidney injury
Hepatotoxicity | Isoniazid, rifampin, macrolides | ↑ Liver enzymes, hepatitis
Ototoxicity | Aminoglycosides, vancomycin (high levels) | Hearing loss, vestibular dysfunction
QT prolongation | Macrolides, fluoroquinolones, azoles | Arrhythmia (e.g., torsades de pointes)
C. difficile infection | Clindamycin, broad-spectrum cephalosporins, fluoroquinolones | Antibiotic-associated diarrhea, colitis
Myelosuppression | Linezolid, chloramphenicol, β-lactams (rare) | Anemia, leukopenia, thrombocytopenia
Rational, Individualized Antimicrobial Prescribing
1 Assess the infection (likely pathogen, site, and severity).
2 Evaluate patient factors (renal/hepatic function, age, comorbidities, medications, pregnancy, allergy history).
3 Select an appropriate agent (effective, safe, and aligned with the anticipated duration).
4 Monitor for toxicity and clinical response (laboratory tests, adverse effects, drug interactions).
5 Reassess and adjust therapy (de-escalate, change dose, or select an alternative if toxicity or intolerance occurs).
Key Takeaway: Rational antimicrobial therapy integrates the expected therapeutic benefits with careful assessment and monitoring of potential harms to ensure safe, effective, and individualized patient care.

Figure 8

Nephrotoxicity and Ototoxicity

Vancomycin and aminoglycosides are important examples of antibiotics for which drug exposure and renal function substantially influence toxicity risk.

Vancomycin-associated nephrotoxicity is particularly concerning in patients with preexisting kidney dysfunction, prolonged treatment, excessive systemic exposure, or concurrent administration of other nephrotoxic medications. Contemporary recommendations favor area under the concentration-time curve (AUC)-guided monitoring for serious MRSA infections, targeting an AUC/MIC ratio of 400 to 600 when the MIC is assumed to be 1 mg/L. This strategy aims to preserve antimicrobial efficacy while reducing unnecessary nephrotoxic exposure.37

Aminoglycosides, including gentamicin, tobramycin, and amikacin, can cause acute kidney injury and irreversible cochlear or vestibular toxicity. Their risk is influenced by cumulative exposure, treatment duration, renal clearance, and concomitant nephrotoxic agents. Because aminoglycosides exhibit concentration-dependent bacterial killing, appropriately selected extended-interval dosing strategies can optimize antibacterial activity while limiting excessive drug accumulation. Therapeutic drug monitoring and individualized dose adjustment are especially important during prolonged treatment or in patients with unstable renal function.38 These examples demonstrate that antimicrobial toxicity is closely linked to pharmacokinetic exposure and may be reduced through appropriate dosing, monitoring, and avoidance of unnecessary treatment.

Cardiac and Neurological Adverse Effects

Macrolides and certain fluoroquinolones can prolong the QT interval, increasing the risk of potentially serious ventricular arrhythmias, including torsades de pointes. This concern is particularly relevant in patients with congenital or acquired QT prolongation, electrolyte abnormalities, structural cardiac disease, or concurrent use of other QT-prolonging medications. Macrolides may also produce clinically significant drug interactions, particularly through inhibition of hepatic cytochrome P450 enzymes by agents such as clarithromycin and erythromycin.

Fluoroquinolones have additional safety limitations, including tendinitis and tendon rupture, peripheral neuropathy, central nervous system adverse effects, and disturbances in glucose regulation. Tendon injury is of particular concern in older adults, patients receiving systemic corticosteroids, and individuals with relevant predisposing conditions. The regulatory safety warnings have emphasized the importance of reserving fluoroquinolones for appropriate indications when their expected benefits outweigh these risks.40 Beta-lactam antibiotics are generally well tolerated but may cause neurological toxicity, particularly when excessive drug exposure occurs in patients with impaired renal clearance. Cefepime-associated neurotoxicity is a clinically important example and may manifest as encephalopathy, myoclonus, seizures, or nonconvulsive status epilepticus. Recognition of these adverse effects is essential because neurological deterioration during antibiotic treatment may otherwise be incorrectly attributed to progression of the underlying infection.62

Hematological, Metabolic, and Neurological Toxicity

Trimethoprim-sulfamethoxazole is associated with several clinically important adverse effects, including hypersensitivity reactions, hyperkalemia, renal-related laboratory abnormalities, and hematological toxicity. Trimethoprim can impair renal potassium excretion, increasing the risk of hyperkalemia, particularly in patients with kidney dysfunction or those receiving angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or potassium-sparing diuretics. The drug may also cause cytopenias and, rarely, severe cutaneous adverse reactions.63

Linezolid provides valuable activity against resistant Gram-positive organisms, including MRSA and vancomycin-resistant enterococci, but prolonged treatment increases the risk of myelosuppression, particularly thrombocytopenia, as well as peripheral and optic neuropathy. Linezolid also possesses monoamine oxidase-inhibiting activity and may interact with serotonergic medications, potentially contributing to serotonin toxicity. Complete blood count monitoring and reassessment of neurological symptoms are particularly important during extended treatment courses.39

Metronidazole is generally well tolerated during appropriately selected short courses, but prolonged or high cumulative exposure may be associated with peripheral neuropathy and, less commonly, central nervous system toxicity. These effects further illustrate why antimicrobial duration is an important component of medication safety.

Beta-Lactam Hypersensitivity and Allergy Assessment

Beta-lactam hypersensitivity is a common concern in antimicrobial prescribing. Reactions range from mild cutaneous manifestations to immediate IgE-mediated anaphylaxis and severe delayed hypersensitivity syndromes. However, a documented penicillin allergy does not necessarily indicate persistent or clinically significant hypersensitivity. Approximately 10% of patients in the United States report a penicillin allergy, yet fewer than 1% of the population is truly allergic when evaluated.64 Inaccurate allergy labels may lead clinicians to avoid preferred beta-lactams and prescribe broader-spectrum, less effective, or more toxic alternatives.

A structured allergy assessment should distinguish immediate reactions from delayed manifestations and clarify the timing, severity, clinical features, and treatment of the reported event. When appropriate, risk stratification, direct oral challenge, or formal allergy evaluation may permit safe use of preferred antibiotics. Nevertheless, patients with histories suggestive of severe delayed hypersensitivity reactions require particular caution and specialist assessment. Accurate allergy evaluation is therefore both a patient-safety intervention and an important component of antimicrobial stewardship.

Individualized Dosing and Special Populations

Antimicrobial toxicity is influenced not only by the selected drug but also by the patient's ability to distribute, metabolize, and eliminate it.

Renal dysfunction may increase exposure to renally eliminated antibiotics, requiring dose adjustment or modification of the dosing interval. Conversely, augmented renal

clearance in some critically ill patients can produce subtherapeutic concentrations despite conventional dosing. Hepatic impairment may alter the metabolism of selected agents, while obesity, pregnancy, critical illness, and substantial fluid shifts may change antimicrobial distribution and exposure.51

Older adults may be particularly vulnerable to adverse effects because of altered renal function, polypharmacy, and increased susceptibility to neurological or cardiovascular complications. Patients receiving multiple medications require careful assessment for pharmacokinetic and pharmacodynamic interactions, particularly when antimicrobials affect cardiac conduction, renal potassium handling, hepatic metabolism, or serotonergic pathways. Individualized treatment may therefore require therapeutic drug monitoring, laboratory surveillance, dose adjustment, selection of an alternative agent, or modification of treatment duration.

Balancing Efficacy, Toxicity, and Antimicrobial Stewardship

The safest antimicrobial is not necessarily the least potent or narrowest-spectrum agent. Rather, the optimal regimen is one that provides reliable activity against the causative pathogen, achieves adequate exposure at the infected site, and minimizes preventable harm. For example, an antistaphylococcal beta-lactam is generally preferred over vancomycin for serious MSSA infection because it provides effective targeted therapy while avoiding unnecessary glycopeptide exposure. Similarly, a highly bioavailable oral antimicrobial may permit discontinuation of intravenous treatment when clinical circumstances allow, reducing catheter-related complications without sacrificing efficacy.

Treatment duration is another important determinant of safety. Unnecessarily prolonged therapy increases cumulative exposure and may contribute to adverse drug reactions, microbiome disruption, Clostridioides difficile infection, and selection for resistant organisms. Regular reassessment of antimicrobial necessity, dose, route, and duration is therefore essential throughout treatment.

Individualized antimicrobial therapy requires selecting the agent and regimen that provide the greatest likelihood of clinical cure with the lowest acceptable risk for the specific patient. Integrating microbiological susceptibility, pharmacokinetic exposure, comorbidities, drug interactions, allergy history, and toxicity monitoring transforms antimicrobial prescribing from a standardized approach into a patient-centered therapeutic decision.

SEPSIS: INTEGRATION OF CLINICAL MICROBIOLOGY AND TREATMENT

Sepsis represents one of the most clinically important applications of integrated microbiological and therapeutic reasoning. It is a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection. Under the Sepsis-3 consensus definition, sepsis is operationalized as an acute increase of at least two points in the Sequential Organ Failure Assessment (SOFA) score attributable to infection. Septic shock represents a more severe subset characterized by profound circulatory and metabolic abnormalities, with a substantially increased risk of mortality.65 The global burden of sepsis underscores its clinical importance, because an estimated 48.9 million cases of sepsis and 11.0 million sepsis-related deaths occurred worldwide in 2017,

accounting for approximately 19.7% of all global deaths.66 These findings demonstrate why prompt recognition and coordinated treatment are essential components of modern medical practice.

Recognition and Initial Clinical Assessment

Sepsis should be suspected when a patient with known or possible infection develops acute organ dysfunction, including altered mental status, respiratory failure, hypotension, oliguria, thrombocytopenia, or other evidence of impaired organ function. Although fever, tachycardia, tachypnea, and leukocytosis may accompany infection, these findings are neither sufficiently sensitive nor specific to establish sepsis independently.

Initial evaluation requires simultaneous assessment of physiological instability, the probability of infection, and the likely anatomical source. Common sources include the lungs, urinary tract, abdominal cavity, skin and soft tissues, and intravascular devices. Patient-specific factors, including age, immunosuppression, recent hospitalization, prior antimicrobial exposure, and underlying organ dysfunction, influence both pathogen probability and the risk of resistant infection.

Serum lactate measurement may assist in assessing tissue hypoperfusion and illness severity, although elevated lactate is not specific for sepsis and should be interpreted in its clinical context. Early recognition of organ dysfunction is essential because delayed treatment may permit progression to circulatory failure and multiorgan dysfunction.46

Early Resuscitation and Hemodynamic Support

Initial sepsis management requires prompt physiological stabilization alongside diagnostic evaluation and antimicrobial treatment. Patients with sepsis-induced hypoperfusion or septic shock generally require intravenous crystalloid resuscitation, with subsequent fluid administration guided by hemodynamic response, tissue perfusion, and the risk of fluid overload.

The Surviving Sepsis Campaign recommends administering at least 30 mL/kg of intravenous crystalloid within the first three hours for patients with sepsis-induced hypoperfusion or septic shock, while emphasizing the need for continued individualized reassessment. Balanced crystalloids are generally preferred over normal saline for initial resuscitation.46 When hypotension persists despite appropriate fluid administration, vasopressor therapy is indicated. Norepinephrine is the preferred first-line vasopressor, with an initial mean arterial pressure target of approximately 65 mm Hg for most adults with septic shock. Additional hemodynamic support should be individualized according to perfusion, cardiovascular function, and clinical response.46 These interventions are essential because antimicrobial activity alone cannot reverse established circulatory dysfunction without adequate support of tissue perfusion and organ function.

Microbiological Diagnosis and Empiric Antimicrobial Therapy

Sepsis management requires rapid identification of the probable infectious source and timely initiation of appropriately active antimicrobial therapy. Blood cultures and other

relevant microbiological specimens should be collected before antimicrobial administration whenever feasible, provided that sampling does not meaningfully delay treatment.

In patients with septic shock or a high likelihood of sepsis, antimicrobial therapy should begin immediately, ideally within one hour of recognition. Initial regimens should provide sufficient coverage for the most likely pathogens, taking into account the suspected anatomical source, illness severity, prior microbiological findings, recent antibiotic exposure, and local resistance patterns.46

The necessary spectrum varies substantially by clinical syndrome. For example, community-acquired pneumonia may warrant coverage for common respiratory pathogens, whereas healthcare-associated intra-abdominal infection or complicated urinary infection may require consideration of resistant Gram-negative organisms. Empiric MRSA or antipseudomonal coverage should be based on relevant clinical and epidemiological risk factors rather than applied indiscriminately to all patients with sepsis.

The urgency of treatment must also be balanced against diagnostic uncertainty. In patients without shock whose presentation is compatible with either infectious or noninfectious disease, rapid clinical evaluation may help determine whether immediate antimicrobial treatment is warranted. Nevertheless, diagnostic uncertainty should not delay therapy when the probability and consequences of severe bacterial infection are high.

Source Control and Anatomical Management

Identification and control of the infectious source are central to sepsis management. Potential interventions include drainage of abscesses, removal of infected intravascular catheters, debridement of necrotic tissue, and decompression of obstructed urinary or biliary systems. The Surviving Sepsis Campaign recommends rapidly identifying anatomical sources that require intervention and implementing appropriate source control as soon as medically and logistically feasible.46 This principle is particularly important in abdominal sepsis, necrotizing soft-tissue infection, obstructive pyelonephritis, and device-associated bloodstream infection. The failure to achieve adequate source control may sustain bacteremia, inflammatory activation, and organ dysfunction despite administration of antibiotics to which the causative organism is susceptible. Consequently, persistent hemodynamic instability or clinical deterioration should prompt reassessment of the anatomical source rather than automatic escalation of antimicrobial coverage.

Antimicrobial Pharmacokinetics in Critical Illness

Sepsis can substantially alter antimicrobial pharmacokinetics and pharmacodynamics. Increased capillary permeability, fluid resuscitation, altered tissue perfusion, hypoalbuminemia, and organ dysfunction may change drug distribution and clearance. These alterations are particularly important for hydrophilic antibiotics, including beta-lactams, vancomycin, and aminoglycosides. In some critically ill patients, augmented renal clearance may result in subtherapeutic antimicrobial concentrations despite conventional dosing. Conversely, acute kidney injury may reduce drug elimination and increase toxicity risk.51 The appropriate treatment therefore requires not only selection of an active antimicrobial agent but also administration of a regimen capable of achieving the relevant

pharmacodynamic target. Prolonged beta-lactam infusions and therapeutic drug monitoring may be useful in selected patients, particularly when infection is severe, pharmacokinetic variability is substantial, or resistant pathogens have elevated MICs. These considerations demonstrate that microbiological susceptibility alone cannot guarantee effective treatment in patients with sepsis.

Reassessment, De-escalation, and Treatment Optimization

Sepsis management is a dynamic process requiring repeated integration of clinical findings, laboratory results, microbiological identification, and physiological response. As culture and susceptibility results become available, empiric therapy should be reassessed and narrowed when appropriate. Unnecessary agents should be discontinued, and antimicrobial treatment should be stopped if subsequent evaluation establishes that bacterial infection is unlikely. The duration of therapy should reflect the identified pathogen, infection site, clinical response, and adequacy of source control rather than the initial severity of illness alone.

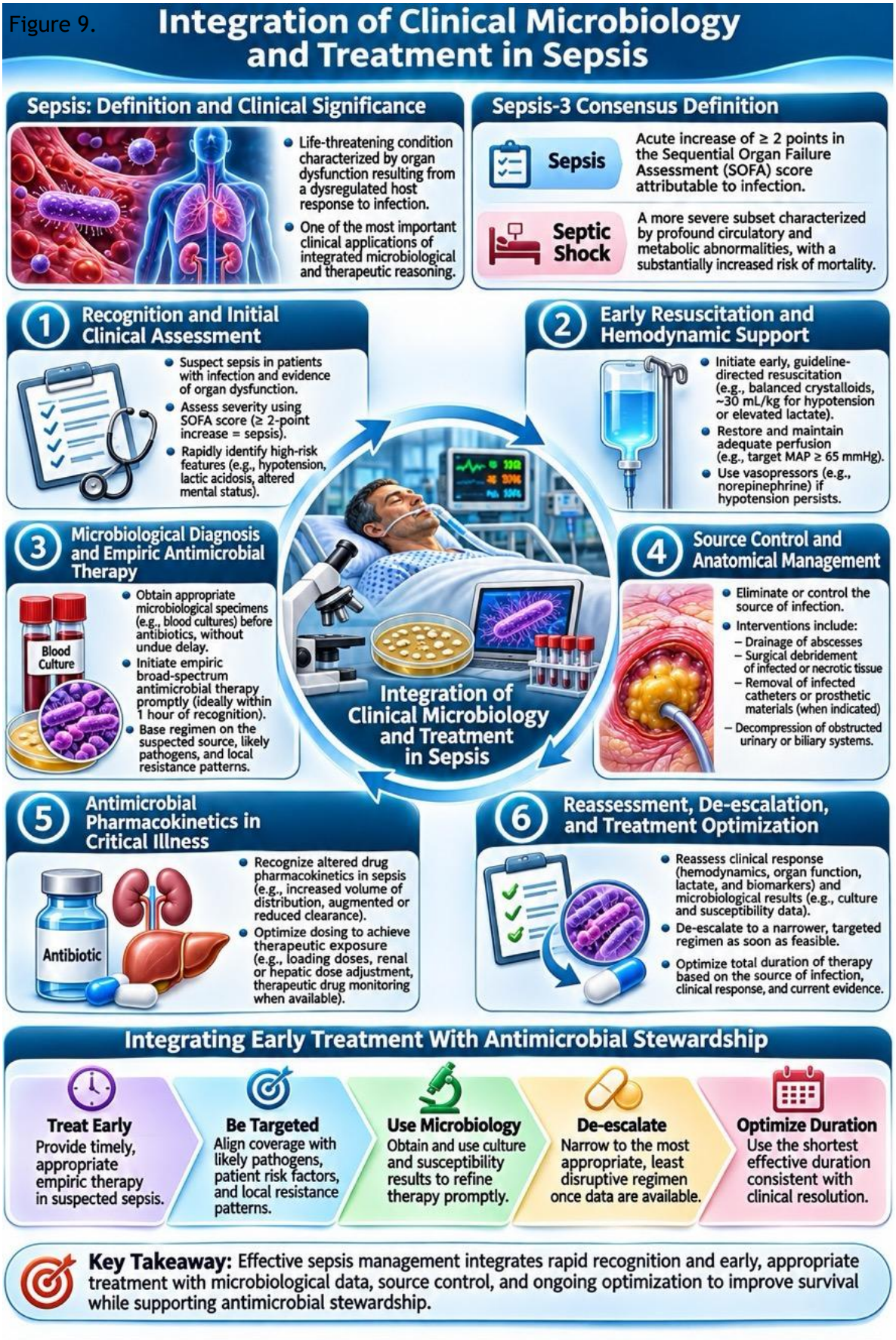
Persistent fever, bacteremia, hypotension, or organ dysfunction despite treatment should prompt systematic evaluation for inadequate antimicrobial activity, insufficient drug exposure, resistant pathogens, uncontrolled infection, or an alternative diagnosis. Repeat imaging, microbiological testing, and consultation with relevant specialists may be necessary. Importantly, not every patient with suspected sepsis has a bacterial infection. This is because viral, fungal, and noninfectious inflammatory conditions may produce similar clinical manifestations. The continued diagnostic reassessment is therefore essential to prevent unnecessary or prolonged antibacterial treatment.

Integrating Early Treatment with Antimicrobial Stewardship

Sepsis illustrates the apparent tension between immediate broad-spectrum treatment and responsible antimicrobial prescribing. In life-threatening infection, delayed administration of active therapy may have serious consequences. However, prolonged unnecessary antimicrobial exposure increases toxicity, microbiome disruption, C. difficile infection, and selection for resistant organisms.

These priorities are not contradictory. Effective management involves providing timely, sufficiently broad empiric therapy when clinically indicated, followed by systematic reassessment and refinement as diagnostic certainty increases. Antimicrobial stewardship is therefore an integral component of sepsis care rather than a competing objective (Figure 9).

Figure 9.


Integration of Clinical Microbiology and Treatment in Sepsis
Sepsis: Definition and Clinical Significance
Life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection.
One of the most important clinical applications of integrated microbiological and therapeutic reasoning.
Sepsis-3 Consensus Definition
Sepsis
Acute increase of ≥ 2 points in the Sequential Organ Failure Assessment (SOFA) score attributable to infection.
Septic Shock
A more severe subset characterized by profound circulatory and metabolic abnormalities, with a substantially increased risk of mortality.
1 Recognition and Initial Clinical Assessment
Suspect sepsis in patients with infection and evidence of organ dysfunction.
Assess severity using SOFA score (≥ 2-point increase = sepsis).
Rapidly identify high-risk features (e.g., hypotension, lactic acidosis, altered mental status).
2 Early Resuscitation and Hemodynamic Support
Initiate early, guideline-directed resuscitation (e.g., balanced crystalloids, ~30 mL/kg for hypotension or elevated lactate).
Restore and maintain adequate perfusion (e.g., target MAP ≥ 65 mmHg).
Use vasopressors (e.g., norepinephrine) if hypotension persists.
Integration of Clinical Microbiology and Treatment in Sepsis
3 Microbiological Diagnosis and Empiric Antimicrobial Therapy
Blood Culture
Obtain appropriate microbiological specimens (e.g., blood cultures) before antibiotics, without undue delay.
Initiate empiric broad-spectrum antimicrobial therapy promptly (ideally within 1 hour of recognition).
Base regimen on the suspected source, likely pathogens, and local resistance patterns.
4 Source Control and Anatomical Management
Eliminate or control the source of infection.
Interventions include:
– Drainage of abscesses
– Surgical debridement of infected or necrotic tissue
– Removal of infected catheters or prosthetic materials (when indicated)
– Decompression of obstructed urinary or biliary systems.
5 Antimicrobial Pharmacokinetics in Critical Illness
Antibiotic
Recognize altered drug pharmacokinetics in sepsis (e.g., increased volume of distribution, augmented or reduced clearance).
Optimize dosing to achieve therapeutic exposure (e.g., loading doses, renal or hepatic dose adjustment, therapeutic drug monitoring when available).
6 Reassessment, De-escalation, and Treatment Optimization
Reassess clinical response (hemodynamics, organ function, lactate, and biomarkers) and microbiological results (e.g., culture and susceptibility data).
De-escalate to a narrower, targeted regimen as soon as feasible.
Optimize total duration of therapy based on the source of infection, clinical response, and current evidence.
Integrating Early Treatment With Antimicrobial Stewardship
Treat Early
Provide timely, appropriate empiric therapy in suspected sepsis.
Be Targeted
Align coverage with likely pathogens, patient risk factors, and local resistance patterns.
Use Microbiology
Obtain and use culture and susceptibility results to refine therapy promptly.
De-escalate
Narrow to the most appropriate, least disruptive regimen once data are available.
Optimize Duration
Use the shortest effective duration consistent with clinical resolution.
Key Takeaway: Effective sepsis management integrates rapid recognition and early, appropriate treatment with microbiological data, source control, and ongoing optimization to improve survival while supporting antimicrobial stewardship.

ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship aims to improve outcomes while reducing unnecessary exposure, drug toxicity, microbiome disruption, and selection for resistant organisms. It begins with a diagnostic question: does the patient have an infection for which an antimicrobial is indicated? A positive microbiological test is not synonymous with infection. For example, asymptomatic bacteriuria generally should not be treated except in defined circumstances, notably pregnancy and before selected invasive urological procedures.5,9

When treatment is indicated, stewardship supports prompt, appropriately active therapy in serious infection, not delay or indiscriminate restriction. Initial coverage should reflect the syndrome, illness severity, host factors, previous isolates, and local susceptibility data. Once results become available, clinicians should review the diagnosis and narrow or stop unnecessary agents. A structured reassessment at approximately 48 to 72 hours can identify opportunities for de-escalation, intravenous-to-oral conversion, dosing adjustment, and an evidence-supported treatment duration.3

Antimicrobial optimization also requires attention to pharmacokinetic and pharmacodynamic exposure, renal and hepatic function, drug interactions, and therapeutic monitoring when indicated. The evidence supporting shorter courses after adequate source control and oral therapy in carefully selected bone, joint, and endocardial infections illustrates why route and duration should follow clinical evidence rather than routine practice.56,59,60,61

Antimicrobial stewardship integrates diagnostic accuracy, appropriate antimicrobial selection, and continuous treatment reassessment to optimize clinical outcomes while minimizing unnecessary antimicrobial exposure and resistance. Local antibiograms, prospective audit and feedback, prescribing guidelines, rapid diagnostics linked to clinical interpretation, vaccination, infection prevention, and surveillance can reduce avoidable exposure and transmission.3,67 As illustrated in Figure 10, effective stewardship begins by distinguishing true infection from colonization or incidental microbiological findings, followed by individualized treatment decisions, monitoring of clinical response, and timely modification or discontinuation of therapy when appropriate. Asymptomatic bacteriuria exemplifies this principle because positive urine cultures alone generally do not justify antimicrobial treatment, except in specific circumstances, including pregnancy and before selected invasive urological procedures. This approach promotes patient safety, preserves antimicrobial effectiveness, and reduces the emergence of resistant organisms.

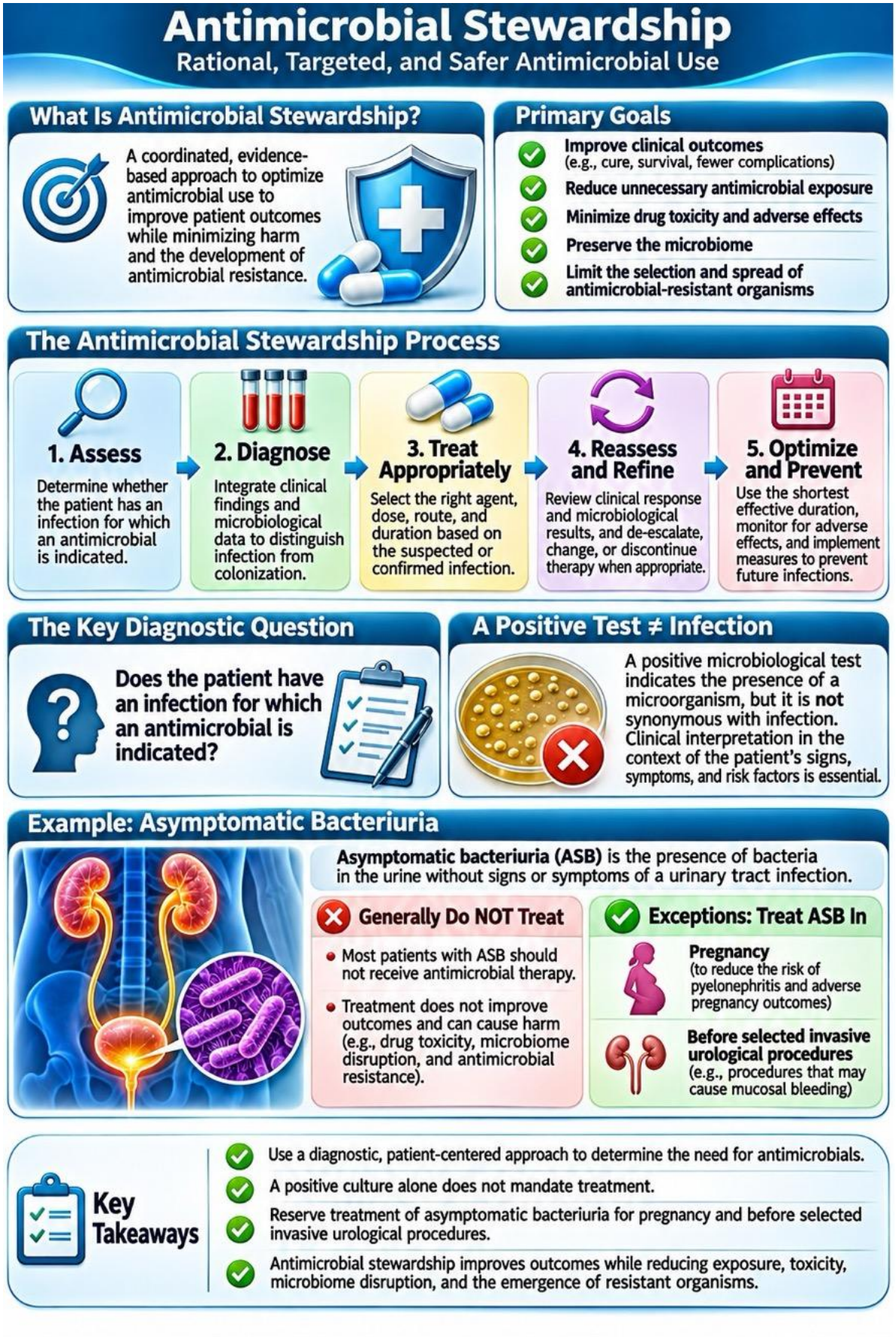

Antimicrobial Stewardship
Rational, Targeted, and Safer Antimicrobial Use
What Is Antimicrobial Stewardship?
A coordinated, evidence-based approach to optimize antimicrobial use to improve patient outcomes while minimizing harm and the development of antimicrobial resistance.
Primary Goals
Improve clinical outcomes (e.g., cure, survival, fewer complications)
Reduce unnecessary antimicrobial exposure
Minimize drug toxicity and adverse effects
Preserve the microbiome
Limit the selection and spread of antimicrobial-resistant organisms
The Antimicrobial Stewardship Process
1. Assess
Determine whether the patient has an infection for which an antimicrobial is indicated.
2. Diagnose
Integrate clinical findings and microbiological data to distinguish infection from colonization.
3. Treat Appropriately
Select the right agent, dose, route, and duration based on the suspected or confirmed infection.
4. Reassess and Refine
Review clinical response and microbiological results, and de-escalate, change, or discontinue therapy when appropriate.
5. Optimize and Prevent
Use the shortest effective duration, monitor for adverse effects, and implement measures to prevent future infections.
The Key Diagnostic Question
Does the patient have an infection for which an antimicrobial is indicated?
A Positive Test ≠ Infection
A positive microbiological test indicates the presence of a microorganism, but it is not synonymous with infection. Clinical interpretation in the context of the patient's signs, symptoms, and risk factors is essential.
Example: Asymptomatic Bacteriuria
Asymptomatic bacteriuria (ASB) is the presence of bacteria in the urine without signs or symptoms of a urinary tract infection.
Generally Do NOT Treat
Most patients with ASB should not receive antimicrobial therapy.
Treatment does not improve outcomes and can cause harm (e.g., drug toxicity, microbiome disruption, and antimicrobial resistance).
Exceptions: Treat ASB In
Pregnancy (to reduce the risk of pyelonephritis and adverse pregnancy outcomes)
Before selected invasive urological procedures (e.g., procedures that may cause mucosal bleeding)
Key Takeaways
Use a diagnostic, patient-centered approach to determine the need for antimicrobials.
A positive culture alone does not mandate treatment.
Reserve treatment of asymptomatic bacteriuria for pregnancy and before selected invasive urological procedures.
Antimicrobial stewardship improves outcomes while reducing exposure, toxicity, microbiome disruption, and the emergence of resistant organisms.

Figure 10

AN INTEGRATED CLINICAL REASONING FRAMEWORK TO LEARN ABOUT CLINICAL MICROBIOLOGY

The most transferable way to learn clinical microbiology is to organize knowledge around the decisions required at the bedside. The following sequence links foundational microbiology to practical management without reducing complex presentations to isolated organism–drug associations.

Establish the Syndrome and Anatomical Source

Determine whether the presentation is compatible with infection and identify the most likely site, such as lung, urinary tract, bloodstream, central nervous system, abdomen, or skin and soft tissue. The anatomical compartment narrows the differential and determines which specimens and treatments are relevant.

Estimate Pathogen Probability and Clinical Urgency

Age, immune status, prior antibiotic exposure, healthcare contact, devices, travel, structural abnormalities, and previous cultures modify the likelihood of specific organisms and resistance. At the same time, assess whether shock, meningitis, or rapidly progressive infection requires immediate treatment and resuscitation (Figure 1).4,6,46

Obtain Meaningful Diagnostic Evidence

Choose cultures, microscopy, or molecular tests according to the suspected source and whether the results will change management. Collect specimens before antibiotics when feasible, but do not delay urgently indicated treatment. Interpret positive findings as possible infection, colonization, or contamination, not automatic proof of causation.9

Select Initial Therapy for the Likely Pathogens and Infected Site

Consider the necessary spectrum, local resistance, previous microbiology, allergies, organ function, and drug penetration. For example, nitrofurantoin may be appropriate for susceptible uncomplicated cystitis but not pyelonephritis or bacteremia; daptomycin can treat selected invasive Gram-positive infections but not pneumonia.15,20

Refine Treatment using Organism Identification and Susceptibility

Distinguish MSSA from MRSA, recognize ESBL and carbapenemase phenotypes, and interpret minimum inhibitory concentrations against drug-specific breakpoints rather than comparing raw values across antibiotics. Confirm that the selected regimen can achieve effective exposure in the affected compartment.14,20,48

Address the Infectious Focus and Reassess

Drain abscesses, relieve infected obstruction, debride necrotic tissue, or manage infected devices when indicated. Persistent symptoms should prompt review of source control, diagnosis, drug exposure, and resistance rather than automatic broadening of antibiotics. When clinical findings permit, narrow treatment, use an effective oral agent, and prescribe the shortest evidence-supported course.52,56,61

These steps are iterative, not rigidly sequential. A critically ill patient may require simultaneous resuscitation, specimen collection, empiric therapy, and urgent source control. The educational objective is to understand why a pathogen is plausible, what a test establishes, whether an antimicrobial can work at the infected site, and how new evidence should change management.

The integration of clinical microbiology into antimicrobial decision-making provides a systematic framework for the diagnosis and management of infectious diseases. As illustrated in the figure, this process begins with recognition of the clinical syndrome and identification of the suspected infection site, followed by appropriate specimen collection and preliminary microbiological evaluation, including Gram staining and bacterial morphology. These findings, together with the anatomical source of infection, likely pathogens, disease severity, patient-specific risk factors, and local resistance patterns, guide the selection of empiric antimicrobial therapy. Subsequent culture identification and antimicrobial susceptibility testing permit reassessment and refinement of treatment, including de-escalation to narrower-spectrum agents when appropriate. Additional considerations, including antimicrobial pharmacokinetics, tissue penetration, drug toxicity, potential interactions, and the need for source control, further inform therapeutic decisions. Collectively, this integrated approach supports timely and effective treatment while promoting antimicrobial stewardship, minimizing unnecessary antimicrobial exposure, and reducing the emergence of antimicrobial resistance (Figure 11).

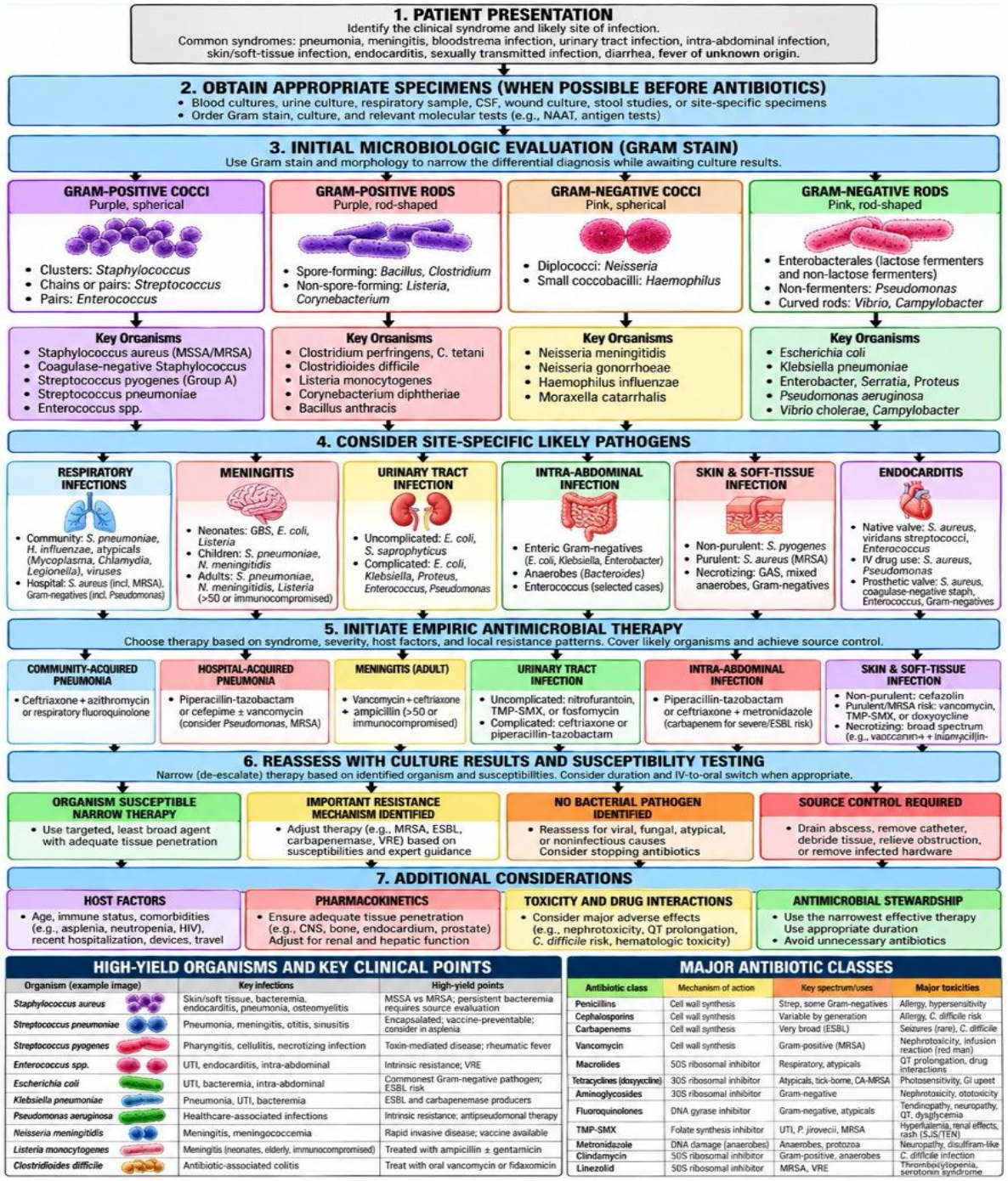


Figure 11: Clinical microbiology and antibiotics decision tree.

CONCLUSION

Clinical microbiology is most valuable when its foundational concepts guide decisions for individual patients. Anatomical localization and host characteristics shape pathogen probability; microscopy, culture, and molecular tests refine but do not replace clinical judgment; and susceptibility results inform treatment only when interpreted alongside drug exposure, resistance mechanisms, toxicity, and the infected anatomical site. Effective management therefore combines timely treatment when delay is dangerous with accurate diagnosis, adequate source control, and repeated reassessment. As uncertainty decreases,

therapy should become more precise through appropriate de-escalation, route selection, and evidence-based duration. Antimicrobial stewardship is intrinsic to this process because unnecessary exposure can harm patients and increase resistance without improving care.

The enduring lesson is to reason from syndrome and source to likely pathogen, meaningful diagnostic evidence, effective therapy, and clinical response. This integrated approach makes complex infectious disease problems more comprehensible while supporting safer and more responsible antimicrobial prescribing.

Disclosure

The authors did not report any disclosures.

REFERENCES

GBD 2019 Antimicrobial Resistance Collaborators. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022;400(10369):2221-2248. doi:10.1016/S0140-6736(22)02185-7.

GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. Lancet. 2024;404(10459):1199-1226. doi:10.1016/S0140-6736(24)01867-1.

Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis.2016;62(10). doi:10.1093/cid/ciw118.

Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7). doi:10.1164/rccm.201908-1581ST.

Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis. 2019;68(10). doi:10.1093/cid/ciy1121.

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). doi:10.1093/cid/ciw353.

Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269-284. doi:10.1038/nrmicro3432.

Hall KK, Lyman JA. Updated review of blood culture contamination. Clin Microbiol Rev. 2006;19(4):788-802. doi:10.1128/CMR.00062-05.

Morgan DJ, Malani P, Diekema DJ. Diagnostic stewardship: leveraging the laboratory to improve antimicrobial use. JAMA. 2017;318(7):607-608. doi:10.1001/jama.2017.8531.

Tille PM, ed. Bailey & Scott's Diagnostic Microbiology. 15th ed. Elsevier; 2022.

Silhavy TJ, Kahne D, Walker S. The bacterial cell envelope. Cold Spring Harb Perspect Biol. 2010;2(5). doi:10.1101/cshperspect.a000414.

Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39(9):1267-1284. doi:10.1086/425368.

Marino A, Maniaci A, Lentini M, et al. The Global Burden of Multidrug-Resistant Bacteria. Epidemiologia (Basel). 2025;6(2):21. doi:10.3390/epidemiologia6020021.

Holland TL, Arnold C, Fowler VG Jr. Clinical management of Staphylococcus aureus bacteremia: a review. JAMA. 2014;312(13):1330-1341. doi:10.1001/jama.2014.9743.

Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52(3). doi:10.1093/cid/ciq146.

Stevens DL, Bryant AE. Severe group A streptococcal infections. In: Ferretti JJ, Stevens DL, Fischetti VA, eds. Streptococcus pyogenes: Basic Biology to Clinical Manifestations. University of Oklahoma Health Sciences Center; 2016.

Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59(RR-10):1-36.

Weiser JN, Ferreira DM, Paton JC. Streptococcus pneumoniae: transmission, colonization and invasion. Nat Rev Microbiol. 2018;16(6):355-367. doi:10.1038/s41579-018-0001-8.

Arias CA, Murray BE. The rise of the Enterococcus: beyond vancomycin resistance. Nat Rev Microbiol. 2012;10(4):266-278. doi:10.1038/nrmicro2761.

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant Gram-negative infections. Clin Infect Dis. Published online August 7, 2024. doi:10.1093/cid/ciae403.

Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol. 2019;11:1756287219832172. Published 2019 May 2. doi:10.1177/1756287219832172.

Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5). doi:10.1093/cid/ciq257.

Russo TA, Marr CM. Hypervirulent Klebsiella pneumoniae. Clin Microbiol Rev. 2019;32(3). doi:10.1128/CMR.00001-19.

Armbruster CE, Mobley HLT. Merging mythology and morphology: the multifaceted lifestyle of Proteus mirabilis. Nat Rev Microbiol. 2012;10(11):743-754. doi:10.1038/nrmicro2890.

Martin-Loeches I, Torres A, Roquilly A. Hospital-acquired pneumonia: Past, present, and perspectives. J Crit Care. 2026;91:155306. doi:10.1016/j.jcrc.2025.155306.

Brook I. Spectrum and treatment of anaerobic infections. J Infect Chemother. 2016;22(1):1-13. doi:10.1016/j.jiac.2015.10.010.

Wexler HM. Bacteroides: the good, the bad, and the nitty-gritty. Clin Microbiol Rev. 2007;20(4):593-621. doi:10.1128/CMR.00008-07.

Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019. US Department of Health and Human Services; 2019. doi:10.15620/cdc:82532.

Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of Clostridioides difficile infection in adults. Clin Infect Dis. 2021;73(5). doi:10.1093/cid/ciab549.

Waites KB, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. Clin Microbiol Rev. 2004;17(4):697-728. doi:10.1128/CMR.17.4.697-728.2004.

Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1.

Phin N, Parry-Ford F, Harrison T, et al. Epidemiology and clinical management of Legionnaires' disease. Lancet Infect Dis. 2014;14(10):1011-1021. doi:10.1016/S1473-3099(14)70713-3.

World Health Organization. Global Tuberculosis Report 2024. World Health Organization; 2024.

Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63(7). doi:10.1093/cid/ciw376.

Kohanski MA, Dwyer DJ, Collins JJ. How antibiotics kill bacteria: from targets to networks. Nat Rev Microbiol. 2010;8(6):423-435. doi:10.1038/nrmicro2333.

Bush K, Bradford PA. ß-Lactams and ß-lactamase inhibitors: an overview. Cold Spring Harb Perspect Med. 2016;6(8). doi:10.1101/cshperspect.a025247.

Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020;77(11):835-864. doi:10.1093/ajhp/zxaa036.

Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: an overview. Cold Spring Harb Perspect Med. 2016;6(6). doi:10.1101/cshperspect.a027029.

Hashemian SMR, Farhadi T, Ganjparvar M. Linezolid: a review of its properties, function, and use in critical care. Drug Des Devel Ther. 2018;12:1759-1767. doi:10.2147/DDDT.S164515.

US Food and Drug Administration. FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. Published July 26, 2016. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-warnings-oral-and injectable-fluoroquinolone-antibiotics-due-disabling-side-effects.

Munita JM, Arias CA. Mechanisms of antibiotic resistance. Microbiol Spectr. 2016;4(2). doi:10.1128/microbiolspec.VMBF-0016-2015.

Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-281. doi:10.1111/j.1469-0691.2011.03570.x.

McEwen SA, Collignon PJ. Antimicrobial resistance: a One Health perspective. Microbiol Spectr. 2018;6(2). doi:10.1128/microbiolspec.ARBA-0009-2017.

Miller JM, Binnicker MJ, Campbell S, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018;67(6). doi:10.1093/cid/ciy381.

Lamy B, Dargère S, Arendrup MC, Parienti JJ, Tattevin P. How to optimize the use of blood cultures for the diagnosis of bloodstream infections? A state-of-the-art. Front Microbiol. 2016;7:697. doi:10.3389/fmicb.2016.00697.

Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-1247. doi:10.1007/s00134-021-06506-y.

Ramanan P, Bryson AL, Binnicker MJ, Pritt BS, Patel R. Syndromic panel-based testing in clinical microbiology. Clin Microbiol Rev. 2018;31(1). doi:10.1128/CMR.00024-17.

Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.

Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998;26(1):1-10. doi:10.1086/516284.

Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev. 2010;23(4):858-883. doi:10.1128/CMR.00007-10.

Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14(6):498-509. doi:10.1016/S1473-3099(14)70036-2.

Marshall JC, al Naqbi A. Principles of source control in the management of sepsis. Crit Care Clin. 2009;25(4):753-768. doi:10.1016/j.ccc.2009.08.001.

Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1-45. doi:10.1086/599376.

Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet. 2001;358(9276):135-138. doi:10.1016/S0140-6736(01)05321-1.

Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(2):133-164. doi:10.1086/649554.

Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372(21):1996-2005. doi:10.1056/NEJMoa1411162.

MacFadden DR, Coburn B, Shah N, et al. Utility of prior cultures in predicting antibiotic resistance of bloodstream infections due to Gram-negative pathogens: a multicentre observational cohort study. Clin Microbiol Infect. 2018;24(5):493-499. doi:10.1016/j.cmi.2017.07.032.

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2). doi:10.1093/cid/ciu296.

Li HK, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. N Engl J Med. 2019;380(5):425-436. doi:10.1056/NEJMoa1710926.

Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med. 2019;380(5):415-424. doi:10.1056/NEJMoa1808312.

Yahav D, Franceschini E, Koppel F, et al. Seven versus 14 days of antibiotic therapy for uncomplicated Gram-negative bacteremia: a noninferiority randomized controlled trial. Clin Infect Dis. 2019;69(7):1091-1098. doi:10.1093/cid/ciy1054.

Payne LE, Gagnon DJ, Riker RR, et al. Cefepime-induced neurotoxicity: a systematic review. Crit Care. 2017;21(1):276. doi:10.1186/s13054-017-1856-1.

Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. CMAJ. 2011;183(16):1851-1858. doi:10.1503/cmaj.111152.

Centers for Disease Control and Prevention. Clinical features of penicillin allergy. Updated August 25, 2025. https://www.cdc.gov/antibiotic-use/hcp/clinical-signs/index.html.

Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287.

Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200-211. doi:10.1016/S0140-6736(19)32989-7.

Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. Clin Infect Dis. 2017;64(1):15-23. doi:10.1093/cid/ciw649.