

General Approach to Infectious Diseases

2

The pharmacotherapy of infectious diseases confuses many clinicians, but the approach to the patient with an infection is relatively simple and consistent. Understanding this approach is the first step in developing a useful expertise in infectious diseases and antibiotic use.

A note: technically the term *antibiotic* refers only to a subset of antibacterial drugs that are natural products. The terms *anti-infective* and *antimicrobial* encompass antibacterial, antifungal, antiviral, and antiparasitic drugs. However, because *antibiotic* is the more commonly used term, we will use it to refer to antimicrobials in general or antibacterials specifically.

Prophylactic Therapy

The use of antimicrobial chemotherapy—that is, the treatment of microorganisms with chemical agents—falls into one of three general categories: prophylaxis, empiric use, and definitive therapy. *Prophylaxis* is treatment given to prevent an infection that has not yet developed. Use of prophylactic therapy should be limited to patients at high risk of developing an infection, such as those on immunosuppressive therapy, those with cancer, or patients who are having surgery. These patients have weak-

ened natural defenses that render them susceptible to infection. Because the likelihood of infection by some types of organisms in these patients is high and the consequences of infection are dire, we administer antimicrobial drugs to prevent infections from occurring. However, the world is not sterile and breakthrough infections do occur. The key to understanding antimicrobial prophylaxis is to remember that patients who receive it do not have an infection, but they are at risk for one.

Empiric Therapy

Unlike prophylactic therapy, *empiric therapy* is given to patients who have a proven or suspected infection, but the responsible organism(s) has or have not yet been identified. It is the type of therapy most often initiated in both outpatient and inpatient settings. After the clinician assesses the likelihood of an infection based on physical exam, laboratory findings, and other signs and symptoms, he or she will usually collect samples for culture and Gram staining. For most types of cultures, the Gram stain is performed relatively quickly. In the Gram stain, details about the site of presumed infection are revealed, such as the presence of organisms and white blood cells (WBCs), morphology of the organisms present (e.g., Gram-positive cocci in clusters), and the nature of the sample itself, which in some cases indicates if the sample is adequate. The process of culturing the sample begins around the time that the clinician performs the Gram stain. After a day or so, biochemical testing will reveal the identification of the organism, and eventually the organism will be tested for its susceptibility to various antibiotics.

However, this process takes several days, so empiric therapy is generally initiated *before* the clinician knows the exact identification and susceptibilities of the causative organism. Empiric therapy is our best guess of which antimicrobial agent or agents will be most active against the likely cause of infection. Sometimes we are right, and sometimes we are wrong. Keep in mind that empiric therapy should not be directed against every known organism in nature—just those most likely to cause the infection in question. In other words, broad-spectrum antibiotics are not a substitute for rational thought!

Definitive Therapy

After culture and sensitivity results are known, the *definitive therapy* phase of treatment can begin. Unlike empiric therapy, with definitive therapy we know on what organisms to base our treatment and which drugs should work against them. At this phase it is prudent to choose antimicrobial agents that are safe, effective, narrow in spectrum, and cost effective. This helps us avoid unneeded toxicity, treatment failures, and the possible emergence of antimicrobial resistance, and it also helps manage costs. In general, moving from empiric to definitive therapy involves decreasing coverage, because we do not need to target organisms that are not causing infection in our patient. In fact, giving overly broad-spectrum antibiotics can lead to the development of superinfections, infections caused by organisms resistant to the antibiotics in use that occur during therapy.

The clinician who is treating an infected patient should always strive to make the transition to

definitive therapy. Although it seems obvious, this does not always occur. If the patient improves on the first antibiotic, clinicians may be reluctant to transition to more narrow-spectrum therapy. Also, some infections may resolve with empiric therapy before culture results would even be available, as happens with uncomplicated urinary tract infections (UTIs). In other cases, cultures may not be obtained or may be negative in spite of strong signs that the patient has an infection (e.g., clinical symptoms, fever, increased WBC count). In most situations it is important that clinicians continuously consider the need to transition to definitive therapy. Overly broad-spectrum therapy has consequences, and the next infection is likely to be harder to treat. Keep in mind the general pathway for the treatment of infectious diseases shown in **Figure 2-1**.

Examples of Therapy

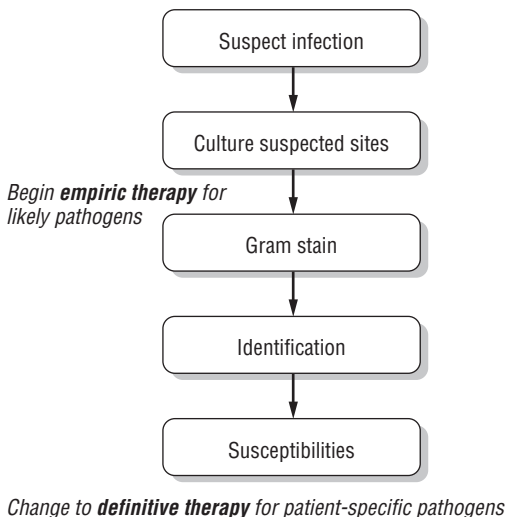
Here are a few examples of each type of therapy:

Prophylaxis

- Trimethoprim/sulfamethoxazole (TMP/SMX) to prevent *Pneumocystis jirovecii* (formerly *carinii*) pneumonia in a patient on cyclosporine and prednisone after a liver transplant
- Azithromycin to prevent *Mycobacterium avium intracellulare* (MAI or MAC) in an advanced HIV patient
- Cefazolin given before surgery to prevent a staphylococcal skin infection of the surgical site

Empiric Therapy

- Levofloxacin initiated for a patient with presumed community-acquired pneumonia

**Figure 2-1**

General Approach to Infectious Diseases

- Ceftriaxone given for the treatment of suspected pyelonephritis
- Voriconazole initiated for a neutropenic bone marrow transplant patient with shortness of breath and a radiograph suggestive of pulmonary aspergillosis
- Vancomycin, tobramycin, and meropenem for a patient with probable hospital-acquired pneumonia in the intensive care unit

Definitive Therapy

- Transitioning from piperacillin/tazobactam to ampicillin in a patient with a wound infection caused by *Enterococcus faecalis*, which is susceptible to both drugs

- Discontinuing ceftriaxone and initiating ciprofloxacin for a patient with a UTI caused by *Klebsiella pneumoniae* that is resistant to ceftriaxone but susceptible to ciprofloxacin
- Stopping caspofungin and initiating fluconazole for a patient with *Candida* in a blood isolate when the species is identified as *Candida albicans* (which is reliably susceptible to fluconazole)
- Narrowing therapy from vancomycin, ciprofloxacin, and imipenem/cilastatin to vancomycin alone for a patient with hospital-acquired pneumonia whose deep respiratory culture grew only methicillin-resistant *Staphylococcus aureus* (MRSA) that is susceptible to vancomycin

Case Study

Here is an example of treating a patient with an infection by the above pathway:

TR is a 63-year-old man with a history of diabetes, hypertension, and coronary artery disease who comes to the hospital complaining of pain, redness, and swelling around a wound on his foot. Close inspection reveals that he has an infected diabetic foot ulcer. He is admitted to the hospital (Day 1). The clinician performs surgical debridement that evening and sends cultures from the wound during surgery as well as blood cultures. The clinician initiates *empiric therapy* with vancomycin and piperacillin/tazobactam.

On Day 2, Gram stain results from the wound are available. There are many WBCs with many Gram-positive cocci but no Gram-negative rods (GNRs), so the clinician discontinues piperacillin/tazobactam. Blood cultures do not grow any organisms.

The following day (Day 3), culture results from the wound reveal many *Staphylococcus aureus*. Because vancomycin is usually effective against this organism, its use is continued.

On Day 4, susceptibility results from the wound culture return. The *S. aureus* is found to be susceptible to methicillin, oxacillin, cefazolin, piperacillin/tazobactam, clindamycin, TMP/SMX, and vancomycin. It is resistant to penicillin, ampicillin, tetracycline, and levofloxacin. Because the isolate from TR's wound is methicillin-sensitive *Staphylococcus aureus* (MSSA), the clinician discontinues vancomycin and initiates *definitive therapy* with oxacillin.

Note how in TR's case we began empiric therapy with a broad-spectrum regimen of vancomycin and piperacillin/tazobactam to cover the Gram-positive and Gram-negative aerobes and anaerobes that tend to cause diabetic foot infections but narrowed that therapy gradually as Gram stain and culture data returned. Eventually we were able to choose a highly effective, narrow-spectrum, inexpensive, and safe choice of definitive therapy that was driven by microbiology results. Both vancomycin and piperacillin/tazobactam were active against TR's *Staphylococcus aureus* as well, but both are broader in spectrum than oxacillin and represent less-ideal therapy choices.

