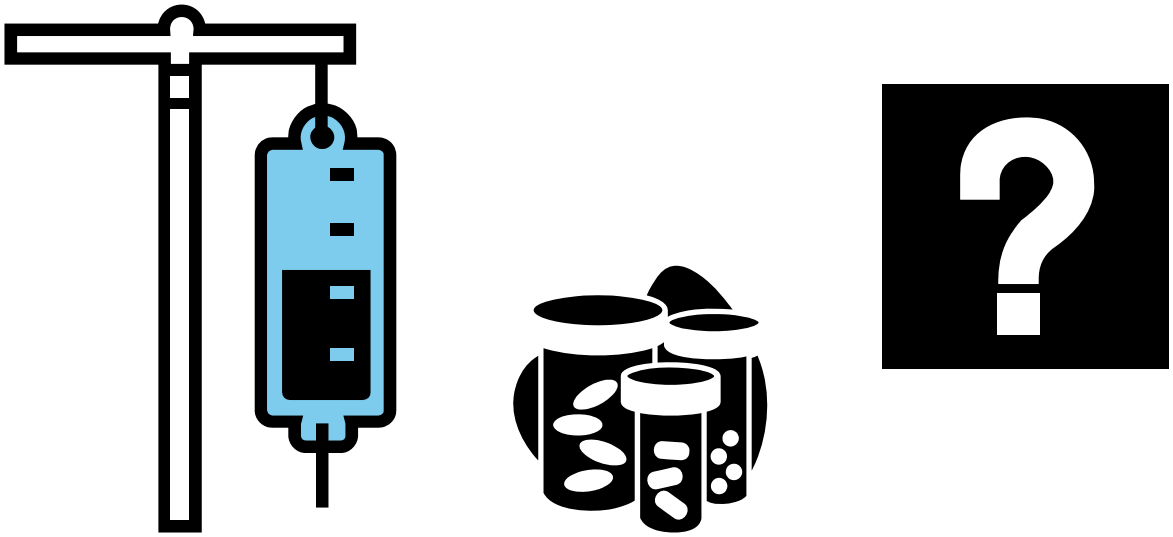
Fever and Empiric Antibiotic Therapy

A guide for medical student and houseofficer



Glenn E. Mathisen MD
Chief—Infectious Disease service
Olive View-UCLA Medical Center
Sylmar, Ca.

Revised: 9/08/16

What you should learn on your ID rotation

Infectious disease and antibiotic use remains one of the most important parts of the internal medicine "curriculum" and a vital part of most physicians' careers. Despite this importance, it seems like there is less and less formal time devoted to infectious diseases in the average residency—rotations are shorter and frequently interrupted by other responsibilities.

This booklet is an attempt to fill in these gaps and provide the "need to know" ID concepts that every physician—regardless of their ultimate career path—need to know. In addition to reinforcing some of the things you learned in medical school, we will try to highlight some of the "practical" knowledge required to manage patients on a day-to-day basis. As a physician, it's "stuff" that you "need to know". By the end of your rotation on the ID service, here are some of the "key" ID concepts that you should try to master…

1. **How to think like an ID clinician:** Infectious disease docs are medical "detectives"—a good history and physical are especially key to narrowing the differential and planning proper therapy. Chapter 1 discusses the initial ID "approach" to the patient with infection, highlighting the importance of disease onset, progression and exposures (travel, food, animals).
2. **Fever evaluation:** Fever evaluation is at the core of ID—review the next 5 chapters (Chapter 2-6) for a practical approach to evaluating the following fever scenarios:
   - **Nosocomial fever:** You are "on call" and a ward patient spikes a fever
   - **ICU fever:** An ICU patient has a persistent fever, unresponsive to antibiotic therapy.
   - **Neutropenic fever:** Fever in the neutropenic patient is potentially deadly and requires a prompt response.
   - **Fever of unknown origin (FUO):** An approach to prolonged, unexplained fever in internal medicine.
   - **Fever in the HIV/AIDS:** How to evaluate persistent fever in the HIV/AIDS patient.
3. **Antibiotic basics:** The host of available antibiotic agents can be bewildering—chapter 7 discusses the major antibiotic families as well as "need to know" data about individual agents.
4. **Choosing empiric antibiotics:** Chapters 8 and 9 provide an overview of the decision making process in choosing empiric antibiotic therapy, giving both a practical "checklist" approach and the rationale behind current empiric antibiotic recommendations.
5. **Antibiotic dosing:** What dose to give and for how long? Chapter 10 introduces the field of antibiotic "pharmacodynamics" that strives to determine the optimal dosing and use of antimicrobial agents.
6. **Practical ID management:** Parenteral vs. oral therapy, the duration of antibiotic therapy and how to tell if your patient is improving—Chapter 11 covers the important day-to-day questions in antibiotic management that are not often addressed in training.
7. **How to use oral antibiotics:** Chapter 12 outlines the principles of oral antimicrobial therapy that you need to know in whatever field of medicine you choose to enter.
8. **How to manage persistent fever:** You've started the patient on antibiotic therapy and they don't seem to be responding—chapter 13 discusses the most common causes of antibiotic "failure" and outlines an approach to getting to the bottom of the problem.
9. **Fever basics:** What is the "normal" temperature and the best way to lower fever? Chapter 14 discusses the "basics" of fever, including the definition of "normal" temperature (Is it really 98.6° F?), the risks/benefits of fever and practical suggestions on how to control fever.
10. **Ten Commandments of ID service:** Moses wasn't an infectious disease specialist but we would like to think he would approve of these ten "commandments" if he was running the ID consultation service.

The Olive View Empiric Antibiotic Manual

Table of contents

Appendix

Chapter 1

Think like an ID Specialist

How does the astute clinician evaluate the patient with an infection? What's the logic behind the infectious disease "approach" to the febrile patient? The physician is like a detective who has arrived at the scene of the crime—our job is to play "Sherlock Holmes" and make a diagnosis based on the information at hand. Of all medical subspecialties, the field of infectious disease especially relies on the skills that make for a good detective. The good clinician uses these skills when approaching an unexplained fever or a puzzling case. I've tried to take this approach and boil it down to a seven-step program that will help with the evaluation of any patient…

The Infectious Disease Casebook—A 7-Step Program

1. **Take the history**
2. **Careful physical examination**
3. **Order the laboratory tests**
4. **Give the patient a diagnosis**
5. **Decide on initial therapy**
6. **Reevaluate the case**
7. **Close the loop**

1. Take the history: As in many medical subspecialities, the patient's clinical history is crucial in solving the case. If individual diseases and pathogens are criminals, they operate with a telltale *modus operandi* that provides clues to their presence. In much the same way, many diseases have characteristic clinical presentations that provide clues to their presence. In any case, pay particular attention to the following details in the patient history:

- **Onset:** Ask about the onset of the disease (acute vs. subacute) and rate of progression. Bacterial illnesses tend to have an abrupt onset—fungal and mycobacterial infections are more often subacute and less likely to be immediately life-threatening.

- **Travel:** Don't forget to ask the patient about travel and leisure time activities. "Adventure travel" has become quite popular—the availability of international jet travel has increased the possibility that a patient with an exotic infectious disease will show up in your waiting room!

- **Occupation:** Questions about occupational exposures are quite important and should be part of your routine patient history. Construction workers are exposed to soil-borne fungal disease, health care personnel run the risk of contracting several viral diseases (hepatitis C, HIV) and farmers are at risk for animal-borne zoonoses such as brucellosis and Q fever.

- **Animal contact:** Always ask about animal contact and pet exposure. Although only a small percentage of the population lives on working farms, the rise in pet ownership has placed individuals at risk for "modern" zoonoses such as toxoplasmosis, cat-scratch disease and salmonellosis.

- **Food:** Unusual food exposures should be part of your routine history. Increased immigration and opportunities for foreign travel have created a demand for exotic and unusual foods. Always ask about raw fish or meat consumption and remember that foreign produce may sometimes bring unusual organisms to our shores.

- **Previous treatment:** Ask the patient about treatments they have already received—be it from a physician or self-treatment with "leftover" antibiotics or alternative medicines. Sometimes, the *lack* of response to an antibiotic permits the exclusion of certain pathogens.

  Such information may provide important epidemiological clues critical in suggesting a diagnosis.

2. Physical examination: A careful and thorough physical examination is crucial to reaching a correct diagnosis. Repeat critical parts of the examination on a daily basis since new or overlooked findings might be especially important. In a patient with staphylococcal bacteremia, the presence of splinter hemorrhages on fingernail examination may confirm the diagnosis of endocarditis. The presence of a palpable spleen in a patient with pneumonia might suggest psittacosis. While such clues rarely permit the diagnosis of a specific pathogen, they aid in localizing the disease and narrowing the differential diagnosis.

3. Laboratory evaluation: Like the crime lab of so many police stories, the laboratory can both support and undermine our initial suspicions. Be wary of expensive, scattershot testing and over-reliance on the laboratory tests—remember that "false positive" tests lead to unnecessary confusion. Be judicious in your testing and only order examinations that will make a clear difference in your management of the case.

Once this initial information is collected, a few additional steps allow for a tentative diagnosis and the initial therapeutic recommendations…

4. Give the patient a diagnosis: Based on the history, physical findings and preliminary laboratory data, localize the organ(s) involved and generate a list of potential pathogens. If at all possible, make a list of the possible diagnoses and rank the likely prospects.

5. Decide on initial therapy: Consider the differential diagnosis—and likely pathogens—when choosing the initial antibiotic therapy. Always ask yourself whether antibiotics are really needed—inappropriate antimicrobial therapy leads to increased bacterial resistance as well as potentially dangerous side effects. The initial choice of antibiotics should be broad enough to cover the most likely pathogens at the primary site of infection. Don't feel, however, that you have to treat *every* organism you've considered—rarely can one construct an antibiotic regimen to cover every conceivable situation.

6. Reevaluate the patient: Perhaps the most critical step is a reevaluation of the case 24-48 hours after start of treatment. Ask the following questions …

- Are any of the cultures positive?
- Has the patient responded to antibiotics?
- Is the patient's fever resolving?
- Can therapy be tailored to a more selective regimen?
- Has the patient developed significant antibiotic side effects or toxicities?

- Is additional history available from families and friends?
- Could this be a non-infectious problem?

…Reevaluate your therapy based on this new information and decide if your initial diagnosis is correct.

7. Close the loop: The importance of a specific diagnosis goes beyond the identification and treatment of an individual case. Like a police chief confronted by a crime wave, whenever possible, we have a responsibility to prevent additional cases. Public health authorities need to investigate the contacts of a tuberculosis patient. That case of salmonellosis may be the index case in a larger outbreak. Do your best to make a specific diagnosis and make sure that you take the necessary steps to prevent it from happening to others!

Putting the 7 step program to work—A Puzzling Case of Pneumonia

Let's use the 7-step method to evaluate a case of pneumonia…

The patient is a 35 year old, previously healthy male who presents with a three day history of fever, shaking chills and chest pain. He has had several episodes of hemoptysis but otherwise has scant sputum production. The patient gives a history of a recent trip (4 days prior to the onset of the illness) to San Diego but denies any unusual food or animal exposures.

Step1 - Clinical history: How did the patient's condition present? The relatively abrupt onset—(less than 48 hours) suggests a bacterial (or viral) process versus the more subacute presentation of a typical fungal or mycobacterial illness. The history of high fever and multiple shaking chills also strongly supports the possibility of an underlying bacterial infection or viral infection such as influenza. Although pulmonary embolism can cause fever, it's not generally accompanied by true rigors and temperature is usually (but not always!) less than 38.7° C [102° F].

On examination he has a fever (40°C), a blood pressure of 100/70 and a pulse rate of 90 beats per minute. Chest examination shows rales in the right upper lobe and the chest radiograph confirms the presence of pneumonia with right upper lobe consolidation.

ID Principle: In the infectious disease world, "history" is key—question the patient about the timing of the "onset", progression (abrupt; gradual) and key features of the illness. While there is considerable overlap, many infectious conditions have a characteristic onset, physical findings and key features. For example, typhoid fever tends to have a standard incubation period (1-4 weeks), a typical onset (usually gradual) with specific signs (headache; abdominal pain; relative bradycardia). While it may be difficult to "call" the pathogen when you first see the patient, the history certainly helps to limit diagnostic possibilities and guide laboratory testing.

Step 2 - Physical examination: In this case, the physical examination and chest radiograph led to a diagnosis of right upper lobe pneumonia. Although this may well be a typical case of pneumococcal pneumonia, certain features (e.g. the pulse-temperature dissociation with high temperature and relatively low pulse) also suggests the possibility of an "atypical" pneumonia such as Legionnaire's disease, psittacosis *(Chlamydia psittaci)* or Q fever (*Coxiella burnettii*).

ID Principle: Although the physical examination may not permit an immediate diagnosis, it allows you to localize the site of the infection and may provide clues helping the clinician to narrow the differential. In this case, although the presence of pneumonia was "non-specific", the relative bradycardia—and later non-response to a β-lactam—was a tipoff to the possibility of an "atypical" pneumonia such as Legionnaire's Disease.

Laboratory data shows a leukocyte count of 20,000 (90% polys) and sputum gram stain demonstrates polymorphonuclear leukocytes with rare gram-negative rods.

Step 3 - Laboratory testing: Laboratory findings were non-specific but the elevated leukocyte count suggests a serious bacterial infection. The sputum examination is non-diagnostic; however, the presence of rare gram-negative bacteria on sputum Gram stain—rather than gram positive cocci—makes pneumococcal pneumonia less likely.

Step 4 - Give the patient a diagnosis: The history, physical examination and chest radiograph findings support the diagnosis of community acquired pneumonia—the next step is to narrow down the list of potential pathogens. While many bacteria and viruses can cause pneumonia, the list of the most common organisms is relatively brief—depending upon the study, *Streptococcus pneumoniae* and "atypical" pathogens (*Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae*) account for approximately 50-70% of cases. Other pathogens such as *Hemophilus influenzae* (5-10%), *Staphylococcus aureus* (5%), gram-negative organisms (<10%) and anaerobes (10%) are less common but account for another 10-20% of identified cases. Clinical diagnosis still remains somewhat imperfect—even in careful clinical studies, between 30 and 50% of cases remain "undiagnosed".

Step 5 – Decide on therapy: Based on the likely diagnosis, choose an antibiotic regimen which will cover the most likely pathogens. For community acquired pneumonia, the American Thoracic Society recommends empiric therapy (see below) based on disease severity and underlying risk factors.

Table 1: Community-acquired pneumonia (Hospitalized patient)

Mild-moderate illness
3rd generation cephalosporin (IV) + macrolide (PO) or tetracycline (PO)
Severe illness (ICU patient)*
3rd generation cephalosporin + macrolide (IV)
or
Respiratory quinolone (IV)
* Add IV vancomycin or linezolide in patient with MRSA risk factors

The patient was thought to have pneumococcal pneumonia and was started on an intravenous 3rd generation cephalosporin (ceftriaxone) per standard CAP protocol. In this case, "atypical" coverage (macrolide or tetracycline) was not added since the clinicians thought these pathogens were less likely. Over the next 48 hours the patient remained febrile and continued to be symptomatic despite the initial therapy. The negative cultures—and continued fever—forced the patient's physicians to reconsider the case.

ID Principle: Guidelines are there for a purpose—if you choose to ignore them, make sure you have a pretty good reason. In this case, inclusion of a macrolide might have led to an earlier clinical response; however, it still requires the clinician to consider the pathogen and order correct laboratory tests.

Step 6 – Reevaluate the case: The lack of response to ceftriaxone would be surprising in an otherwise "healthy" patient with an uncomplicated pneumococcal pneumonia—most of these patients have a prompt response to antibiotics within 48 hours. Such a finding suggests the possibility of another pathogen, or a pneumonia "mimic" such as a vasculitis or pulmonary embolism.

The poor response to therapy—and the negative blood cultures—forced a reassessment of the case and a consideration of other possibilities. Additional laboratory tests were ordered and antibiotic coverage was broadened with the addition of intravenous azithromycin (500 mg IV q24 hrs) for coverage of "atypical" pulmonary pathogens.

During the following 48 hours the patient's clinical status improved dramatically—his fever abated and he felt well for the first time in almost a week. Because of his rapid improvement, he was discharged home and given a 2-week course of oral azithromycin. Later in the week, the laboratory reported that the Legionella urine antigen and blood serology (IFA) were positive for Legionnaire's disease.

Further questioning revealed that the patient had spent several hours in a hot tub during his trip to San Diego. The hotel management told him that the pool had recently been overgrown with algae and required chlorine treatment. *Legionella* grows readily in natural water sources (lakes, swamps, mud) and may contaminate potable water supplies, plumbing, humidifiers, cooling towers and hot tubs.

Although *Legionella* is often sensitive to β-lactams antimicrobials in vitro, these drugs are a poor choice for therapy since they provide little intracellular penetration. In our case, public health authorities were contacted and initiated an investigation of the suspect motel, but were unable to find additional cases in the hotel guests.

ID Principle: Historical clues are important in all cases; however, they are especially vital when the diagnosis is uncertain and the patient fails to respond to empiric therapy. In such cases, take the time to reevaluate the patient and pay attention to unusual exposures and travel.

Step 7: Close the loop: In addition to ensuring that the patient receives proper treatment, it's important to consider public health issues—a single case of Legionaire's disease may be the sentinel case of an outbreak and needs to be reported to local public health authorities. In this case, public health authorities were unable to perform a detailed review, but a limited investigation suggested the lack of additional cases.

ID Casefile: The guinea pig and the coughing conventioneers

Legionnaire's disease was first identified after a dramatic outbreak of respiratory disease that followed the 1976 American Legion convention in Philadelphia, Pennsylvania. Over 200 people—many of whom stayed at the convention headquarters at the Bellevue-Stratford Hotel—developed a respiratory disease characterized by fever, cough and pneumonia; over 34 people died of from complications of the illness. As part of the investigative efforts, a CDC rickettsia specialist--Joseph McDade—exposed guinea pigs to human tissue from some of the victims and was able to cultivate a possible pathogen in antibiotic free hen's eggs. Serological studies suggested that this organism was likely the cause of the initial outbreak and McDade subsequently developed a special media (CYE-Charcoal yeast extract) that permitted growth of the organism from clinical specimens. Investigators named the organism *Legionella pneumophila* in honor of the original victims of the outbreak and a recognition of its ability to cause pneumonia (*pneumophila*—"lung loving"). *Legionella pneumophila* is responsible for most clinical cases; however, in the past 30 years, researchers have identified over 40 additional *Legionella* species, many of which can cause disease in humans. One of these species—*Legionella micdadei*—bears the name of the determined laboratory detective who first isolated the bacteria and help solve the mystery of the "coughing conventioneers".

Think like an ID specialist—what you need to know…

- Patient history is key in the subspecialty of infectious disease—question the patient about the specific "onset" of the disease (When did the illness *really* start?), the key symptoms and the progression of the condition (acute vs subacute vs chronic?).
- Additional history (travel, animal exposure, food ingestions) is especially important if cultures are negative and you are unsure of the initial diagnosis.
- While rarely providing a definitive, bacteriological diagnosis, a careful physical examination can offer clues to help separate out the likely pathogens.
- Try to localize the "site" (major organ involved) in any patient with fever and suspected infection—this will define the likely pathogens and help you choose appropriate empiric therapy.
- Reevaluate the case after 24-48 hours—pay special attention to culture results, response to therapy and any additional findings.
- If you have a putative pathogen, try to "narrow" therapy to a more selective antibiotic regimen.
- In patients with "contagious" pathogens (e.g. influenza; tuberculosis, meningococcus), make sure you "close the loop" and report the case to public health—you may be able to prevent or identify additional cases.

Chapter 2

"Saturday night fever"… nosocomial fever in the hospitalized patient

It's your first night on call and you've just been paged about a patient who earlier in the evening "spiked" a fever. What are the likely causes? What percentage will respond to antibiotics? This chapter is designed to help the houseofficer with the "fever on call" problem—what to do when a previously afebrile patient, suddenly spikes a fever. When confronted by this situation, keep in mind the following points and questions…

1. What is the definition of nosocomial fever ?

Many patients that we see have a fever when admitted to the hospital—the fever is due to the underlying condition that brought them to medical attention. A "***nosocomial***" fever refers to a new-onset fever occurring in patients *following* hospital admission; although the fever may be related to the patient's primary disease, more often than not it is related to a new, hospital-acquired problem.

"Nosocomial fever"—Know the definition

By definition—and purposes of study—a "nosocomial" fever implies the following:

- ✓ **Temperature** ≥ 38 °C (100.4 °F)
- ✓ **Timing:** Occurs ≥ 48 hours after admission; patient afebrile at least 3 days prior to admission
- ✓ **Location:** Patient on in-hospital, general medicine service

Although we frequently use the temperature of 38ºC (100.4ºF) as a cutoff for "fever", the actual definition of fever in any one individual depends upon their baseline temperature. Patients with underlying chronic medical conditions (renal failure, CHF, liver disease) often run a lower temperature than the "normal" individual—a temperature of 37.5 ºC in a dialysis patient might represent a "fever" in an individual who typically runs "normal" temperatures in the 36°C range.

ID Tip

When called to see a hospitalized patient with some new complaint or problem, review vital signs (including temperature) for the preceding 48-72 hours to establish a patient "baseline"—a "borderline" temperature of 37.9 °C might be an indication of a true fever in someone who normally runs temperatures closer to 36°C.

2. What are the sources of in-hospital fever on a general medicine service?

A study of 100 patients (see following Table 1) on an in-hospital, general medicine ward outlined the epidemiology of new-onset nosocomial fever (defined as an oral temperature greater than 38ºC *at least* 48 hours after admission). In this case, the authors tried to exclude fevers present *prior* to admission and focused on fevers that developed *after* hospitalization.

Table 1: Etiology of Nosocomial Fever in 100 Patients

Etiology	*# of Pts*	*Etiology*	*# of Pts.*
Infection	**56**	**Non-infectious**	**25**
Urinary tract	18	Procedure-related†	5
Pneumonia	12	Drug fever	5
Bloodstream	10	Pancreatitis	3
Vascular infection (phlebitis)	4	Hematoma	2
Upper respiratory infection	4	Sickle cell crisis	2
AIDS/PCP (*Pneumocystis*)	2	Pulmonary embolism	2
Other infections*	6	Malignancy	2
		Other non-infectious conditions**	3
		No Apparent Source	**19**
		Total	**100**

* Includes 3 abdominal infections, 1 tracheobronchitis, 1 soft tissue infection, 1 aseptic meningitis
† Includes 3 transfusions, 1 bronchoscopy, 1 therapeutic arterial embolization
**Other non-infectious conditions (1 each): Neuroleptic malignant syndrome; Subarachnoid hemorrhage; Connective tissue disease; Acute gouty arthritis

Table adapted from Arbo MJ et al. Am J Med 1993:95:505-512

This study outlined several important features about this syndrome:

- ✓ **Infection** accounted for over 50% of patients with nosocomial fever. Of these cases, bacterial infection— including urinary tract infection, pneumonia and "blood stream" infection (bacteremia; line sepsis)—was responsible for over 75% of infectious causes.
- ✓ **Non-infectious causes** accounted for 25% of cases—the most common sources being post-procedure fever (5 patients), drug fever (5 patients) and then, a host of miscellaneous causes including pancreatitis, pulmonary embolism and underlying malignancy.
- ✓ **No source:** Despite careful evaluation, almost a quarter of patients had no obvious source—in these patients, the fever resolved rapidly and there appeared to be no long-term adverse consequences.

A key message from this study is that close to half of patients with "nosocomial fever" have uncertain or non-infectious causes. When patients do have a documented infection, the majority of these are bacterial infections (urinary tract infection; pneumonia; line infection) that should respond to antibiotic therapy.

3. What features of nosocomial fever predict bacterial infection?

Is it possible to predict which patients are most likely to have a bacterial infection that will benefit from antibiotic therapy? Certainly, presence of a clear source on exam (e.g. pneumonia; pyuria; obvious line infection) raises the odds of a bacterial infection and lowers the threshold for antimicrobial therapy.

The above study identified several additional factors that increased the likelihood that a "nosocomial" fever would be due to bacterial infection…

- ➢ **Diabetes mellitus:** Diabetics are at greater risk for in-hospital bacterial infection.
- ➢ **T_{max} > 38.7ºC (102ºF):** The higher the temperature, the more likely a bacterial process.
- ➢ **Length of hospitalization** *prior* to fever onset of greater than 10 days. If the patient is afebrile for most of the hospitalization—and suddenly develops a new, unexplained fever—this could be a clue to the possibility of an underlying bacterial infection.
- ➢ **Leukocyte count** > 10,000 cells/mm^3 with > 75% neutrophils. When evaluating a new onset fever, the higher the leukocyte count, the more likely the possibility of bacterial infection.

If any of these factors are present—especially in combination—be suspicious for bacterial infection and have a lower threshold for antibiotic therapy.

4. Non-infectious fever—infectious disease "mimics"

While we associated fever with infection, non-infectious conditions may be a significant cause of in-hospital, nosocomial fever (up to 25% of cases in the previously referenced study). As you evaluate febrile patients, keep in mind the following conditions:

- **Procedure-associated fever:** A fever spike is not uncommon following blood transfusions and "surgical" procedures such as endoscopy and catheterization. In most of these cases, the fever is relatively brief (< 24 hours) and has an otherwise "negative" evaluation. Since transient bacteremia may follow these procedures, empiric antibiotic therapy may be appropriate (pending cultures) if the patient appears particularly toxic.
- **Drug fever:** Approximately 10% of all new, in-hospital fevers are due to drug reactions. Patients with drug fever often appear relatively non-toxic despite the presence of fever. Other clues (not always seen) that suggest the possibility of drug fever include rash (17%), relative bradycardia (<10%), pruritus (5%) and eosinophilia (15%)[1]. Drugs classes most commonly associated with drug fever include the following:

  - **Antibiotics:** B-lactam antibiotics (penicillins, cephalosporins), sulfonamides, amphotericin B
  - **Cardiovascular drugs:** quinidine, procainamide, hydralazine, amiodarone
  - **Antineoplastic drugs:** bleomycin, daunorubicin, cytarabine, monoclonal antibody preparations
  - **Central nervous system agents:** diphenylhydantoin, carbamazepine, anti-psychotic agents

  Although drug fever is usually seen following administration of a new agent, drug fever may emerge despite years of previously successful therapy.

- **Intraabdominal conditions:** Various intra-abdominal conditions may be associated with nosocomial fever including pancreatitis, intestinal infarction, acalculous cholecystitis and retroperitoneal bleeding (following anticoagulation). In patients who have received antibiotics, don't overlook pseudomembranous enterocolitis (an infectious cause)—ask about diarrhea and check a white blood count (an elevated leukocyte count is a hallmark of PMC and a clue to its presence).
- **Drug withdrawal:** Alcohol withdrawal may be delayed and emerge during hospitalization—look for patient confusion and question the patient (and family) carefully about a history of significant drug or alcohol ingestion.
- **Clots and infarcts:** Conditions such as myocardial infarction, deep venous thrombosis and pulmonary embolism are commonly accompanied by a low grade fever. Pulmonary embolism presenting with cough, dyspnea and pneumonitis may mimic pulmonary infection—in the PIOPED study of pulmonary embolism, at least a quarter of patients were febrile.
- **Underlying neoplasm:** Fever maybe associated with underlying neoplasm—especially hematological malignancies (e.g. lymphoma) and sometimes with metastatic adenocarcinoma.

Beware! Don't underestimate the importance of non-infectious fever—prolonged (and inappropriate) antibiotic therapy in these cases can have clear adverse consequences including increasing bacterial resistance and drug toxicity.

5. Which patients require antibiotic therapy?

Once you are confronted with a new, nosocomial fever, you have to make a decision as to the need for empiric antibiotic therapy. The decision isn't always an easy one—not all patients require immediate antibiotic therapy and some individuals can be safely "observed" pending results of cultures and radiographs. Nevertheless, once you have evaluated the patient, consider starting antibiotic therapy in the following situations:

- **Identified source:** Patients with a readily apparent infection on examination (e.g. pneumonia, UTI, infected catheter) generally should be started on antibiotic treatment.
- **Sepsis syndrome:** Patients with new onset of high fever (38.5º C or 102º F), rigors (shaking chills) and/or signs of "sepsis" (hypotension, confusion, tachycardia) have a higher risk of bacterial infection.
- **Laboratory clues:** Laboratory data suggesting "sepsis" including leukocyte count > 10,000 cells/mm^3 (with "left" shift of > 75% polymorphonuclear leukoyctes), new-onset respiratory alkalosis (suggests early sepsis) or unexplained metabolic acidosis. Obtain a **serum lactate** level—elevated lactate levels may be a sign of occult sepsis.
- **Neutropenic patients:** Individuals with neutropenia (Absolute neutrophil count < 500 cells/mm^3) have a high mortality associated with bacteremia, especially if there are significant delays in treatment. For this reason, patients with a neutropenic fever should almost always receive immediate, empiric antibiotic treatment after the initial evaluation and cultures.

ID Tip

Decisions about "when to treat" can be difficult ones; but in general boil down to the following: ***the higher the fever and the sicker the patient…the greater the need for empiric antibiotic therapy***. Have an especially low threshold for neutropenic patients and those with "complicated" underlying medical conditions (e.g. severe CHF, renal or liver failure)—these individuals have less "reserve" and are less likely to tolerate delays in therapy.

ID Checklist: *What is the appropriate evaluation for a patient with a nosocomial fever?*

Most patients don't require extensive testing to identify the cause of a fever—a brief physical examination and a few choice laboratory tests will identify a potential source in most cases.

- **Make sure the temperature is accurate:** See if this is a "new" fever—or an intermittent fever that has been present since admission. If there is any question about the accuracy, obtain a rectal temperature and compare it with a corresponding oral reading (you may be surprised to find that the "real", core temperature is much higher, a potential sign of more serious disease).

- **Perform a physical examination:** A brief, "targeted" physical exam will go a long way towards determining the likely source of an infection, if one is present. Pay special attention to the following areas:

  - ✓ ***HEENT:*** In patients with an NG tube, look for signs of sinusitis (nasal discharge, sinus tenderness). Nosocomial meningitis is rare and usually seen in post-neurosurgery patients—consider a lumbar puncture in those with headache, confusion and meningismus.
  - ✓ ***Lungs:*** Examine the lungs carefully and obtain a chest radiograph if those with suspected aspiration (this is particularly a problem in patients with NG tubes or individuals with altered mental status). Remember that pulmonary emboli can cause fever and question the patient about chest pain, dyspsnea and hemoptysis.
  - ✓ **IV sites:** Catheter infections and phlebitis are common sources of in-hospital fever. Examine all lines carefully and remove any venous catheter in place for longer than 72 hours—90% of such lines are infected even if they appear "normal". In those with central catheters, obtain at least one set of blood cultures from the line in addition to a set from a peripheral site.
  - ✓ **Abdomen:** In addition to the usual causes of intraabdominal infection, keep in mind the following causes of "nosocomial" fever in the hospitalized patient…
    - **Acalculous cholecystitis**…? RUQ pain…√ liver tests and RUQ ultrasound
    - **Pseudomembranous colitis**…? Antibiotics + new onset diarrhea …√ Stool *C. difficile* toxin
    - **Intestinal ischemia/infarction**…New onset abdominal pain in those with CHF or atrial fibrillation.
    - **Retroperitoneal hematoma**…New onset abdominal, back or flank pain during anticoagulation
  - ✓ **Genitourinary:** Urinary tract infection secondary to an indwelling foley catheter is one of the most common nosocomial infection— look for signs of **epididymo-orchitis** (purulent urethral discharge, epididymal enlargement/tenderness) and check a urine culture and urinalysis on all patients with unexplained fever.
  - ✓ **Roll the patient over:** Check for a decubitus ulcer and while you are at it, examine the rectum to make sure there is no evidence of a perirectal abscess.

- **Review the medication record:** While any drug may potentially cause fever, look especially for the "common" ones including antibiotics (B-lactam agents; sulfa drugs), seizure medications and cardiac drugs (procainamide; quinidine).

- **Order baseline tests:** While not all are always necessary, a few simple tests will help to identify a source and sort out the sicker patients (requiring antibiotic therapy) from those who can be observed:
  - ✓ **Blood count (CBC):** Look for leukocytosis, "left shift" and presence of eosinophilia.
  - ✓ **Urinalysis/Urine culture:** Especially important in those with Foley catheter or recent instrumentation.
  - ✓ **Blood cultures x 2:** In those with an indwelling central line, try to obtain one set from the line itself.
  - ✓ **Chest radiograph:** Important in patients with possible aspiration or pulmonary symptoms.

- ✓ **Lactic acid level:** Check a routine chemistry panel and lactic acid level—this will help identify occult sepsis and might tip you towards empiric antibiotic treatment.

- **Consider the possibility of ID "mimics":** As outlined previously, approximately 50% of in-hospital, nosocomial fevers are due to non-infectious causes. Be especially wary of drug fever, recent transfusions, and invasive procedures performed within the past 24 hours. Pulmonary embolism causes fever in up to 33% of patients—check an O_2 saturation, d-Dimer level and/or CT angiogram in suspect cases. Don't forget the patient's underlying illness—intermittent fever may be seen with neoplastic or rheumatological disease.

- **Decide on empiric antibiotic therapy:** As stated earlier, order empiric antibiotic therapy (depending upon the suspected source) in patients with suspected sepsis (fever > 102 F; hypotension; rigors), neutropenic patients and those with an identified source of infection. Not all patients require empiric antibiotics (in non-toxic, "stable" patients, the appropriate maneuver may be to culture the patient and "observe"); however, have a low threshold for antibiotic treatment in toxic-appearing patients with significant underlying disease.

In-hospital, "nosocomial" fever—what you need to know…

- Nosocomial fever refers to a new-onset fever of greater than or equal to 38ºC (100.4ºF) presenting 48 hours or more following admission to the hospital general medicine ward. The requirement for "48 hours" helps to exclude fever due to preexisting conditions that were present *prior* to hospitalization.
- The spectrum of conditions responsible for "nosocomial fever" is different from community-acquired causes of fever and includes conditions such as nosocomial infection, drug toxicity and fever related to transfusions and invasive hospital procedures (e.g. endoscopy, surgery).
- A rapid, "targeted" physical examination and history frequently uncovers a potential infectious source of fever in a patient with nosocomial fever. Pay special attention to IV sites (line sepsis), lungs (? Aspiration pneumonia), abdomen (? colitis, biliary tract disease) and urinary tract (? presence of Foley catheter).
- Infectious etiologies such as urinary tract infection, aspiration pneumonia and line sepsis account for approximately 50% of "nosocomial" fevers; of these, close to 75% may be due to an underlying bacterial infection that will respond to antibiotics.
- "Non-infectious" etiologies are seen in approximately 25% of patients with nosocomial fever and include such entities as drug fever, post-procedure fever, deep venous thrombosis and pulmonary embolism.
- In up to 25% of cases, patients may have a single fever "spike" where an etiology cannot be determined—if cultures are "negative", most of these patients tend to do well without subsequent adverse effects.
- Almost any agent can cause drug fever; however, common drugs associated with "nosocomial" fever include antibiotics (β-lactam agents; sulfa drugs), seizure medications, cardiovascular drugs and chemotherapeutic agents.
- Intraabdominal conditions associated with nosocomial fever include retroperitoneal hematoma (in patients receiving anticoagulation), acalculous cholecystitis (especially in ICU patients) and pseudomembranous colitis.
- Factors that help predict bacterial infection include 1). Presence of diabetes mellitus, 2). A temperature > 38.7ºC (102ºF) and 3). a peripheral leukocyte count greater than 10,000 cells/mm^3 (with greater than 75% neutrophils).
- In addition to a careful physical examination, obtain a simple laboratory screen including a complete blood count (? Presence of leukocytosis), urinalysis (with urine culture), blood cultures (x 2) and a basic chemistry panel (? metabolic acidosis). Many experts recommend a serum lactate level—elevated lactic acid levels suggest the possibility of occult sepsis and lowers the threshold for empiric antibiotic therapy.
- In a patient with nosocomial fever, start empiric antibiotics in those with an identified infection site, patients with neutropenic fever, and—where a site is not obvious—in those with signs of sepsis (fever ≥ 38.7°; hypotension; "toxic" appearance).

[1] Mackowiak PA, LeMaistre CF, Drug Fever: A Critical Appraisal of Conventional Concepts. Ann Int Med 1987;106:728-33.

Chapter 3

The 8 "W"s of ICU and Post-operative fever

You are working in the intensive care unit and called to see a patient with a fever of 38.5°C. Fever in the ICU is a common problem—over half of all ICU admissions experience fever sometime during their stay, with the cause being related to a host of infectious—and non-infectious—etiologies. Beginning with the "epidemiology" of ICU fever, the following chapter offers a time tested system (The 8 "W"s of ICU/Postop fever) to help guide evaluation and make sure you ferret out the underlying cause.

The epidemiology of ICU fever

Despite the wealth of ICU patients, there are few epidemiological studies of fever in the ICU population. One of the earliest (Circiumaru B et al. Intensive Care Med (1999) 25: 668-673.) examined 100 consecutive admissions (both surgical and medical cases) to a "general" intensive care unit (ICU). Most of the surgical patients were post-operative surgical cases (e.g. GI surgery: 45 cases; cardiopulmonary surgery: 7 cases). Despite the limits of such a study, the authors made several important observations about ICU fever:

- ✓ **Fever in the ICU is common:** Of the 100 patients, over 70 individuals experienced fever during the course of their ICU admission—most of these cases had fever on admission or within 24 hours of entry to the unit.
- ✓ **Infectious etiologies:** Of the patient who developed infection, the three most common sites were lower respiratory tract (15 cases), blood (9) and abdomen (5). "Persistent" fever (lasting > 5 days) was usually due to infection and had a higher mortality than non-infectious fever.
- ✓ **Microbiology:** The single commonest bacterial isolate (*Staphylococcus epidermidis*) was usually found as part of a mixed bacterial flora but, in some cases, may represent a skin "contaminant". .Other frequently isolated species (see Table 1) were *Enterobacteriaceae, E. faecalis* and *Staphylococcus aureus*. Fungi (usually *Candida albicans*) were surprisingly common in this study and likely reflect superinfection following antibacterial drugs.

Table 1: A prospective study of fever in the ICU—Infectious etiology

Gram-negative bacteria	#	Gram-positive bacteria	#	Fungi	#
Enterobacteriaceae	10	Coagulase-negative staphylococci	15	*Candida albicans*	7
Klebsiella aerogenes	2	*Enterococcus faecalis*	10	Yeast, not *C. albicans*	1
Pseudomonas aeruginosa	2	*Staphylococcus aureus* (MSSA)	6	*Aspergillus fumigatus*	1
Serratia marcescens	1	Methicillin-resistant S. aureus (MRSA)	4		
Branhanella catarrhalis	1				
Anaerobes	1				
Source: Circiumaru B et al. A prospective study of feverin the intensive care unit Intensive Care Med (1999) 25: 668-673.					

- ✓ **Multifactorial:** In approximately 10% of patients, fever was "multifactorial" and could not be attributed solely to one condition or cause..
- ✓ **Post-operative fever usually benign:** Of the 70 cases of fever, postoperative fever was the most common cause of fever and accounted for 34 cases; most cases of postoperative fever appeared relatively benign and disappeared within 48 hours of onset.

The "102° Rule"—a clue to the causes of ICU fever

The infectious disease specialist Burke Cunha has popularized the "102 Rule"—a simple rule that helps the ICU clinician sort out the likely (Infectious vs. non-infectious) causes of ICU fever. Based on experience and clinical observation, Cunha suggests the following rules regarding ICU fever (see table):

- **Temperature less than 102°F (<38.9°C)** usually represents "non-infectious" syndromes such as venous thrombosis, pulmonary embolism, myocardial infarction or pulmonaryatelectasis. While careful observation is warranted, most of these cases don't require immediate empiric antibiotic therapy unless a "new" infection is immediately apparent.

- **Temperature ≥ 102°F to 104°F (≥ 38.9-40°C)** is generally due to infectious etiologies and requires cultures, and possibly antibiotic therapy. In the ICU setting, common infections include catheter-associated bacteremia, ventilator pneumonia and intraabdominal abscess (secondary to intestinal perforation). Several "non-infectious" entities may cause fever in this range including drug fever, acute adrenal insufficiency, and transient fever related to blood product administration or following an i+nvasive procedure.

- **Temperature ≥ 104°F (≥ 40°C):** Paradoxically, extreme pyrexia is often due to non-infectious conditions such as drug fever including serotonin and neuroleptic malignant syndrome, endocrine causes (Thyroid storm; acute adrenal insufficiency), malignant hyperthermia (secondary to anaesthetic reaction) and primary central nervous system conditions (stroke; encephalitis).

Table 1: The 102 "Rule" and ICU fever

< 102°F (< 38.9°C)	≥ 102°F to 104°F (≥ 38.9-40°C)	≥ 104°F (≥ 40°C)
Acute myocardial infarction **Pulmonary embolism** **GI bleed** **Acute pancreatitis** **Hematomas** **Phlebitis** **Pleural effusion** **Uncomplicated wound infection** **Atelectasis/dehydration** **Antibiotic-associated diarrhea (*C. difficile*)** **Acalculous cholecystitis**	**Infectious diseases** **Catheter associated bacteremia** **Nosocomial/ventilator pneumonia** **Complicated pyelonephritis** **Nosocomial sinusitis** **Intraabdominal abscess (perforation)** **Non-infectious diseases** **Drug fever** **Acute adrenal insufficiency** **Blood product transfusion** **Post-procedure**	**Neuroleptic malignant syndrome** **Malignant hyperthermia** **Thyroid storm** **Acute adrenal insufficiency** **CNS lesions (stroke, encephalitis)** **Heat stroke** **Source: Cunha B.**

When using the "102 rule", keep in mind the following important caveats…

- ✓ **Accurate temperatures:** Proper employment of the rule depends on accurate temperature measurement. In the critically ill patient, oral (and axillary) temperatures notoriously unreliable. When using the rule make sure you have obtained an accurate "core" temperature or temperature recorded from indwelling pulmonary catheter.
- ✓ **Not infections only!** Although we often think of infection with fever, over 50% of ICU fevers are due to non-infectious conditions.
- ✓ **Rules are made to be broken:** The rule is a guideline that requires thoughtful interpretation in each case—there is some degree of overlap despite the implied rigidity of the categories.

Remember: ***No rule is perfect—the smart clinician plays the odds and employs the "102" rule as a guide in their evaluation of fever.***

The 8 "W"s of ICU and post-operative fever

Most cases of ICU/post-operative fever fall into one of several categories. As a resident, we were taught the 4 "W"s of ICU post-operative fever—in the "modern" era, we've retained the approach but expanded the list to "8". When confronted by fever in the ICU, use this mnemonic as a handy way to remember the most common causes:

1. Wind (Respiratory tract)

Not surprisingly, respiratory tract problems are especially common in ICU and postoperative patients. Keep in mind the following when the patient first spikes a fever:

- **Sinusitis:** This is especially a problem with nasogastric or nasotracheal tubes—check for purulent nasal discharge and obtain a sinus CT scan to look for sinusitis on the side of the intubation.
- **Pneumonia:** Obtain a chest radiograph and look for a new infiltrate; consider a bacterial "superinfection" in patients with a preexisting pneumonia and increased sputum production.
- **Atelectasis:** This may cause post-operative fevers though the temperature is generally less than 102ºF (38.3ºC)—look for platelike atelectasis on chest and initiate a vigorous program of pulmonary toilet.
- **Parapneumonic effusion/empyema:** In a patient with pneumonia, an underlying empyema can cause persistent fever—obtain a chest CT scan (or ultrasound) and consider tapping any pleural effusion.

2. Water (Genitourinary and intravenous line infections)

This category addresses infections (and complications) associated with interventions such as Foley catheters and intravenous lines.

- **Urinary tract infection**: A large percentage of patients (>70%) are infected following placement of a Foley catheter—send a urine to the laboratory (for U/A) and examine the patient (males) for evidence of epididymo-orchitis and prostatitis (rectal examination).
- **Infected IV lines:** Again, most peripheral catheters are infected within several days of placement (Don't be fooled if the catheter "looks good"—studies demonstrate >90% catheter colonization after 72 hours). Examine the entry site for erythema, tenderness and purulent drainage. If in doubt, "pull it out".
- **Sterile thrombophlebitis** is the next step after catheter infection—look for tenderness along the course of the catheterized vein. Persistent bacteremia despite removal of an infected catheter suggests underlying endocarditis or a septic thrombophlebitis.
- **Central line thrombosis** and pulmonary emboli; obtain a TEE if there is strong suspicion of superior vena cavae thrombosis following central line placement.
- **Right sided endocarditis** due to infected central venous catheter. In addition to bacteremia and murmur, the new appearance of wedge-shaped pulmonary infiltrates may be a clue to this entity.

3. Wound (Surgical and postoperative wound infection)

Of course, wound infection is always a consideration in the post-operative case. In the febrile patient, keep in mind the following possibilities…

- **Post-operative wound infection**: This is especially a problem in trauma patients or those undergoing procedures with a high likelihood of wound contamination (e.g. gastrointestinal surgery). Examine the wound as well as discharge from any drainage catheters. Keep in mind the wound infection may be "internal"—an intraabdominal abscess following a partial colectomy would fall in this category.
- **Infection at site of tracheostomy, gastrostomy, rectal tube:** Examine all ostomies and tubes for evidence of infection at the site of tube placement.
- **Decubitus ulcers:** Don't overlook the possibility of a new decubitus ulcer—roll the patient over and examine all pressure points including the heels and occiput.

4. Walking (Venous clots and hypercoaguable states)

Don't forget some of these non-infectious conditions associated with the lower extremity…

- **Deep venous thrombosis and pulmonary emboli:** According to the PIOPED study, approximately a third of patients with pulmonary embolism have associated fever. Carefully examine the lower extremities for evidence of deep venous thrombosis (calf tenderness; unexplained swelling; distended veins) and question the patient about unexplained shortness of breath or chest pain.
- **Gout:** A low grade fever is common with acute attacks of gout—questions the patient about previous episodes and erythema/tenderness in the great toe (podagra) and knees.

5. Waist (Intraabdominal source)

A number of occult intraabdominal conditions (some non-infectious) may emerge in the post-operative or ICU patient. In a patient with abdominal pain or diarrhea, keep in mind the following…

- **Acalculous or calculous (with cholelithiasis) cholecystitis**: Acalculous cholecystitis is a well-recognized complication of prolonged ICU hospitalization—look for RUQ tenderness, abnormal liver tests and evidence of a compromised gall bladder on ultrasound (distended gall bladder; thickened wall; pericholic fluid). If in doubt, obtain a nuclear medicine scan (e.g. HIDA scan) to demonstrate normal gall bladder function.
- **Alcoholic hepatitis** is a common cause of persistent fever in the hospitalized alcoholic. These patients typically have elevated liver tests (AST>ALT) as well as leukocytosis (sometimes up to 100K!) that mimics underlying infection. Look for a history of heavy alcohol use (this is sometimes occult) and obtain liver tests.
- **Pancreatitis:** This may be medication or stone-induced—order pancreatic enzymes (e.g. lipase; amylase) and obtain an abdominal CT scan if uncertain of the diagnosis.
- **Ischemic colitis:** Although uncommon as a cause of prolonged fever, consider the possibility of ischemic colitis in the patient with underlying cardiac disease (CHF, CAD, atrial fibrillation) with new onset of abdominal pain and bloody diarrhea; aggressive overdiuresis or new onset arrhythmia may be a clue to this entity.
- **Pseudomembranous colitis:** In addition to diarrhea and fever, an unexplained leukocytosis is often a clue to underlying PMC. Review the chart looking for a history of recent antibiotic use—although almost all antibiotics have been associated with the condition, it is especially common following use of ampicillin, clindamycin, cephalosporins
- **Occult intraabdominal abscess:** In post-operative patients following abdominal surgery, consider the possibility of an intraabdominal infection such as a subphrenic or subhepatic abscess. Fever and persistent leukocytosis (often 6-10 days following surgery) are clues to this entity.
- **Perirectal abscess/prostatitis:** These conditions are especially common in patients with a rectal tube or indwelling foley catheter.

6. Wright stain (Hematologic problems)

Sometimes overlooked, consider the possibility of a transfusion reaction—or blood-borne pathogen—in ICU/postop patients with new onset fever and chills.

- **Transfusion reaction** (ABO incompatibility or leukoagglutinin rxn): Review the record to see if the patient has received a blood or platelet transfusion within the past 24 hours.
- **Drug-induced hemolysis**: Drugs associated with hemolysis include sulfa drugs (G-6PD deficiency) and B-lactam agents (Coombs+ hemolytic anemia following prolonged therapy). Order a hemolysis panel (e.g. LDH, bilirubin, haptoglobin) and examine the peripheral smear for evidence of hemolytic anemia (e.g. spherocytes).
- **Transfusion associated infection:** Although the current blood supply is heavily screened and pretty safe, consider the possibility of blood-borne pathogens in those who have received transfusions. In addition to some of the "classic" pathogens (e.g. malaria, HIV) viruses such as West Nile virus and CMV are sometimes associated with transfusion or organ transplantation.

7. Wonder "drugs" (Drug-associated fever)

In hospitalized patients, drug fever is one of the most common causes of new-onset, unexplained fever. Patients frequently "look good" despite fevers in the 39-40°C range; other clinical clues (often not seen) include a relative bradycardia (hi temperature; normal pulse), eosinophilia and rash. The most common drugs associated with drug fever are the following:

- **Antibiotics:** Most common are B-lactam agents and sulfa drugs; amphotericin B
- **H2 blockers:** Cimetadine
- **Anticonvulsants:** Diphenylhydantoin
- **Chemotherapy:** Bleomycin, Ara-C
- **Thiazide diuretics and sulfa derivatives** (oral hypoglycemics, furosemide)
- **Heparin:** Fever may be the presenting symptom of heparin-induced thrombocytopenia (HIT) syndrome
- **Drug withdrawal:** Delirium tremens and drug withdrawal may first appear following surgery or ICU admission.

8. Wonder "bugs" (Bacterial and fungal superinfection)

In patients already receiving broad-spectrum antibiotics, the emergence of resistant pathogens (bacterial or fungal superinfection) is always a possibility. Check the most recent cultures (or reculture the patient), keeping in mind the following pathogens:

- **MRSA:** Methicillin resistant *Staph aureus*: Resistant to oxacillin…Rx c vancomycin
- **VRE:** Vancomycin resistant enterococci: Rx c linezolid or daptomycin
- **MDR GNR:** Multidrug resistant gram negative bacilli: Usually *Pseudomonas* or *Acinetobacter*..may require "combination" antibiotic therapy or colistin
- **ESBL GNR:** Extended spectrum B-lactamase gram negative bacilli…usually *E. coli* or *Klebsiella species*. Usually resistant to 3rd generation cephalosporins…best Rx is with carbapenems
- **Candida species:** Look for persistent fever despite antibiotics and + cultures for *Candida* (sputum, urine or blood [50%]). Signs include retinal fungal "balls" (call Opthalmology to screen fundus) and erythematous skin nodules (Bx shows characteristic fungal elements). Rx c empiric fluconazole or echinocandin.

"Cold comfort"—the risks and benefits of cooling blankets

When an ICU patient spikes a high fever, there is a good chance that they will end up on a "cooling blanket"—a modern version of "sponging" down the patient in order to lower body temperature. The wisdom—and utility—of this approach remains in question—modern thinking suggests that a "little bit of fever" may actually be a good thing (see Chapter 14) and that overly aggressive control of fever may lead to adverse outcomes. Controlled trials in patients with "sepsis" suggest *higher mortality* in those with aggressive temperature control. Most patients on cooling blankets develop "Shivering"—this *increases* metabolic demand and is associated with considerable patient discomfort. Although there is some controversy, aggressive temperature control may be appropriate in the following situations:

- ✓ **Extreme hyperthermia** due to drug toxicity (e.g. malignant hyperthermia; neuroleptic malignant syndrome) or heat-related disorders (heat stroke; heat exhaustion)
- ✓ **"Central" neurological fever:** Lowering temperature in patients with "central fever" due to stroke or brain injury may have a survival advantage
- ✓ **Excessive metabolic demand:** In patients with severe CHF or respiratory failure, control of temperature can minimize metabolic demand and prevent worsening organ failure.

In general, studies suggest that there is little benefit to aggressive external cooling measures (e.g. cooling blankets) in patients with infection-induced hyperthermia. When compelled to treat fever in these patients, try to avoid the cooling blanket and instead—when fever lowering is deemed necessary— aim to control temperature with oral or rectal acetaminophen.

ID Checklist: Managing an ICU or Post-operative fever

When faced with a prolonged ICU or postoperative fever, examine the patient thoroughly and review the above checklist. The following measures may be helpful in those with a prolonged unexplained ICU/postop fever:

- ❑ **Repeat the physical examination** with special attention to the following…
  - ***Examine all intravenous lines*** looking for tenderness, phlebitis or purulent drainage; whenever possible, change any catheters that have been in place for over 72 hours.
  - ***Uncover and examine any wounds***; roll the patient over and examine the back to rule out a decubitus ulcer.
  - ***Roll the patient over and perform a rectal examination*** looking for a perirectal or prostatic abscess (males) in all patients—especially in those with indwelling foley catheters or rectal tubes. Obtain a *C. difficile* toxin assay when diarrhea is present.
- ❑ **Consider the possibility of deep venous thrombosis** in all bedridden patients with fever—obtain a lower extremity venous duplex and/or lung scan (CT angiogram) if you suspect a pulmonary embolism.
- ❑ **Review the medication list**—minimize unnecessary drugs and consider switching antibiotics to an alternate class if you suspect antibiotic-associated drug fever (most common with sulfa and B-lactam antibiotics).
- ❑ **Obtain an abdominal CT scan** in patients with abdominal pain or a recent history of intraabdominal surgery—this will help exclude occult intraabdominal abscess or pancreatitis. A RUQ abdominal ultrasound is a good screen for patients with possible acalculous cholecystitis.
- ❑ **Order a chest CT scan** in patients with persistent pneumonia if you suspect underlying lung cavitation (abscess) or pleural effusion—if a significant effusion is present, perform a diagnostic thoracentesis to rule out an underlying empyema.
- ❑ **Reculture the patient** looking for bacterial or fungal superinfection; however, be careful about interpreting culture results—look for evidence (new pulmonary infiltrate, change in Gram stain, increased pyuria) suggesting that any new organism is a true pathogen rather than a "harmless" colonizer.
- ❑ **Look for fungal superinfection** in those receiving prolonged antibiotics. Check for growth of *Candida* from multiple sites and perform a dilated fundiscopic examination looking for *Candida* endophthalmitis. In "at-risk" patients with persistent fever—and no obvious source—consider a trial of anti-fungal therapy—a prompt defervescence suggests disseminated candidiasis.
- ❑ **Don't forget other non-infectious causes of fever:** Persistent fever may be secondary to the patient's primary disease process, especially if they have underlying disseminated cancer, rheumatologic conditions or endocrine disorders (thyroid disease). In a patient with delirium and fever, don't forget the possibility of alcohol withdrawal in a patient with previously concealed alcohol addiction.
- ❑ **Be wary of cooling blankets**: Avoid the use of cooling blankets, except in "hyperthermic" patients (Temperature > 40ºC) with non-infectious conditions (e.g. malignant hyperthermia; heat stroke/exhaustion; drug toxicity). In patients with infection-induced fever, if you feel you need to control the temperature, utilize round-the-clock oral or rectal acetaminophen.
- ❑ **Avoid "antibiotic roulette"**—frequent changes in antibiotics—unless you have a high suspicion of a bacterial/fungal superinfection or an overlooked pathogen. Remember, ICU fever has many non-infectious causes and doesn't always require a "change" in antibiotics

Fever in the ICU—what you need to know…

- Fever in the ICU is a common problem—over 50% of patients develop a fever sometime during their stay. Although "infectious " conditions are common, keep in mind that up to 50% of fevers may be secondary to "non-infectious" conditions such as drug fever, pulmonary embolism and atelectasis.
- Patients with ventilator-associated pneumonia (VAP usually have an elevated leukocyte count, a new infiltrate and evidence of "purulent" sputum. Other "respiratory" causes of ICU fever include sinusitis (associated with nasogastric or nasotracheal intubation), atelectasis (in post-operative patients) and pulmonary embolism.
- Intravenous lines are a common source of ICU fever— examine the line for local site infection (e.g. "exit" or tunnel infection) and obtain two sets of blood cultures, with at least one set from the suspect line. While staphylococcal species are the most common organisms associated c line infection, gram negative bacilli—and on rare occasions *Candida* species—may be the responsible pathogen.
- Obtain a urinalysis/urine culture and examine the genital region—in males with an indwelling Foley catheter, look for epididymo-orchitis or evidence of purulent drainage at the site of the urethral meatus.
- In patients with recent surgery, uncover the wound and look for evidence of local wound infection. Make an effort to role the patient over examine the back for evidence of a decubitus ulcer.
- The immobilized, critically ill patient in the ICU is at risk for deep venous thrombosis, pulmonary embolism and catheter-associated thrombophlebitis. In patients with unexplained fever, carefully examine IV sites for phlebitis and consider a venous duplex (of the lower extremities) with followup CT angiogram in those with pulmonary symptoms.
- Common intra-abdominal causes of "ICU fever" include acalculous cholecystitis (√ liver tests and RUQ ultrasound), drug-associated pancreatitis (check serum lipase), pseudomembranous colitis (ask about diarrhea) and occult intraabdominal abscess (especially in patients with recent intraabdominal surgery).
- Transfusions may be a cause of ICU fever due to associated transfusion reactions or infection (e.g. CMV, *Yersinia*, malaria) acquired from a contaminated unit. If the fever follows recent transfusion, check for evidence of hemolysis and make sure to examine a peripheral blood smear.
- Drug reactions remain an important cause of fever in the ICU—although any drug may be responsible, drug fever is especially common with B-lactam agents (penicillins and cephalosporins), anti-seizure medications and a number of cardiac drugs (hydralazine; procainamide).
- "Drug withdrawal" secondary to unrecognized alcohol addiction may initially manifest as delirium tremens in the hospitalized patient—ask the patient's family and friends about the possibility of occult alcohol or drug use.
- The ICU patient runs the risk of "superinfection" with resistant bacteria such as methicillin-resistant Staph *aureus* (MRSA), resistant gram-negative bacilli (ESBL, CRE and MDR GNRs) and *Candida* infection. Review the most recent cultures (looking for colonization with resistant organisms) and consider broadening the antibiotic coverage, especially in critically, hypotensive, "septic" patients.
- Not all patients with fever automatically require an antibiotic alterations—pending the results of a repeat evaluation, a "change" in antibiotic therapy may be delayed in the "normotensive", clinically "stable" patient with a low grade (< 38.7°C [102 °F]) temperature.
- Avoid use of "cooling" blankets unless the patient has "extreme" hyperthermia (T ≥ 104 °F) due to stroke or external factors such as heat stroke or medication reaction (e.g malignant hyperthermia; neuroleptic malignant syndrome). If temperature control is necessary in patients with infection-related fever, opt for oral or rectal acetaminophen—this is as effective as external measures (e.g. cooling blanket) and likely to be better tolerated by the patient.

Chapter 4

The "Power of polys"… Neutropenic Fever

You are called to the oncology ward to see a leukemic patient who has just "spiked" a fever of 38.7 ° C—it's a 35 year old "neutropenic" male (leukocyte count of 300 cells/mm^3) who is undergoing an initial round of chemotherapy. This is known in the trade as a "neutropenic fever" and—if not treated properly—is a potentially life-threatening situation that demands prompt evaluation and therapy.

What is the epidemiology of neutropenic fever? What are the likely associated infections? This next section will explore these issues and provide an effective and efficient approach to ensure that these patients receive an appropriate evaluation and therapy.

ID Jargon

The many faces of "Neutropenic" fever

Infectious disease specialists have developed a special set of "jargon" when describing neutropenic fever—as you evaluate patients, keep in mind the following definitions…

- **Neutropenia:** A neutrophil count of <500 cells/mm^3, or a count <1000 cells/mm^3 with a predicted decrease to <500 cells/mm^3
- **Neutropenic fever:** A single temperature ≥ 38.3ºC (101ºF) or a temp ≥ 38.0ºC (100.4ºF) for ≥ 1 hour in patient with neutropenia.
- **Persistent neutropenic fever:** Neutropenic fever that persists longer than 5 days, despite appropriate antibiotics.
- **Recurrent neutropenic fever:** Recurrent fever in a neutropenic patient, usually occurring after they have already defervesced following treatment for an earlier episode of neutropenic fever.

1. Neutropenic fever—principles and pitfalls

Following the advent of chemotherapy for hematological malignancies, it became clear that neutropenia-associated infection was an important complication, accounting for significant morbidity and mortality. A team at the National Cancer Institute (NCI) in the early 1970's provided the first systematic description of **"febrile neutropenia"—**their pioneering work described the condition and established a number of important principles in the management of the syndrome that remain true to this day…

- **Acute bacterial infection** remains the greatest initial risk to patients with chemotherapy-induced neutropenia—if not promptly treated it may well kill the patient before culture results have returned!
- **WBC predicts risk:** The absolute neutrophil count (ANC) provides a guide to the risk of infection — infection rates rise when the ANC falls below 1000 cells/mm^3, with the greatest risk in those with a count less than 100 cells/mm^3 (see Table 1—next page).

- **"Prolonged" versus "brief" neutropenia:** The duration of severe neutropenia helps predict the risk of infection and mortality—in the original NCI studies, patients with prolonged neutropenia (> 3 weeks) had close to 100% mortality compared to a 60% mortality in patients with a shorter duration of one week.
- **Fungal infection** emerges as a more significant problem in patients with prolonged neutropenia, especially those who have remain febrile despite administration of appropriate broad-spectrum antibiotics.

Table 1: Episodes of severe infection related to leucocyte counts

Absolute blood neutrophil count (cells/mm^3)	Episodes of severe infection*
>2000	5
1501-2000	5
1001-1500	5
501-1000	12
101-500	19
< 100	43

*Episodes per 1000 days without severe infection.
Table modified from Bodey G. Journal of Antimicrobial Chemotherapy (2009) 63, Suppl. 1, i3–i13

Remember… **Deadly delays:** Low neutrophil counts make patients especially vulnerable to bacterial infection. Evaluate fever as soon as possible and don't hesitate to start empiric antibiotics immediately—significant delays (6-12 hours) can lead to potentially irreversible septic shock!

2. What are the most common sites of infection in the neutropenic patient?

Most new-onset fevers in neutropenic patients are due to underlying bacterial infection and respond to broad-spectrum antibiotic therapy. While there are numerous potential sources of fever in the neutropenic patient, most sources fall into one of several infectious or non-infectious categories:

- **~20% → Bacteremia** or bloodstream infection
- **~20% → Focal site/+ Cultures:** On clinical examination, patients have a focal site of infection (e.g. pneumonia, catheter, dental or abdominal infection) with a site culture.
- **~20% → Focal site/negative cultures**: Although the patient has an apparent site of infection, the cultures are negative (or cannot be collected).
- **~20% → Non-infectious source** including underlying tumor or transfusion reaction
- **~20% → No clear source:** Patient will have a fever with negative cultures and no clear source of infection

The absence of leukocytes reduces the amount of inflammation and may make it difficult to appreciate the site of infection in a patient with a neutropenic fever. Keep in mind that certain sites (e.g. pneumonia, catheter site, dental infection) represent special risks in these patients and "target" your exam towards the most likely sources. While an extensive exam is not always necessary, pay special attention to the areas noted in the following table—these represent especially "common" sites of infection in neutropenic patients:

Site	Comments
Head	Check for evidence of fungal sinusitis (nasal discharge, bleeding or black eschar)
Mouth	? Dental abscess ? oral ulcers or mucositis
Chest	R/O pneumonia—check a routine chest radiograph
IV Sites	Check catheter for phlebitis or "tunnel" infection—poor function suggests clot or catheter infection
Heart	Rare cases of tricuspid endocarditis related to central catheter…check for murmur
Abdomen	RUQ: ? hepatomegaly and tenderness…consider hepatosplenic candidiasis…check UTZ or CT RLQ: ? tenderness/mass…consider neutropenic colitis…check CT and add metronidazole Diarrhea: ? pseudomembranous colitis…check *C. difficile* toxin…add metronidazole
Genital/rectal	*Gentle* rectal exam looking for ulcers (?HSV) , fissures or perirectal abscess
Skin	Careful exam for maculopapular rash (? Drug fever) or erythematous nodules (? Fungi)
? Transfusion	Fever associated with RBC or platelet transfusion
? Drug fever	Due to chemotherapy (cytarabine, bleomycin) or antibiotics (sulfa drugs, B-lactams)

Remember… Examine the patient carefully on a daily basis—new findings may appear and help identify the source of infection.

3. What is the epidemiology of bacteremia in the neutropenic patient?

Although only 20% of neutropenic patients in clinical trials have documented positive blood cultures, recognition of the likely pathogens helps to predict bacteria at other sites and aids the clinician in selecting empiric antimicrobial therapy.

Early studies of neutropenic fever (1960s) demonstrated a special risk from gram-negative facultative bacteria (*E. coli*; *Pseudomonas* sp.)—these pathogens most commonly originated from the patient's own intestinal microflora and led to recommendations for use of "combination" antibiotic therapy (carbenicillin + aminoglycoside) targeted towards gram-negatives. More recent studies (see Table 3) have documented a greater prominence of gram-positive organisms such as staphylococci and viridans streptococci.

Table 3: Causes of bacteremia in patients with febrile neutropenia

Organism	% cases	Organism	% cases
Staphylococcus aureus	5	*Escherichia coli*	15
Coag.-negative staphylococci (CNS)	40	*Pseudomonas aeruginosa*	9
Enterococci	2	*Klebsiella* species	1
Streptococci	11	Other gram-negative bacteria	6
Other gram-positive bacteria	2		
		Gram-positive bacteria (single)	60
		Gram-negative bacteria (single)	31
		Polymicrobial bacteremia	9

*** Based on 227 cases of bacteremia in 760 febrile episodes cited in Del Favero et al. CID 2001;33:1295-301.**

Factors responsible for this "gram positive" trend include the following…

- **Implantable central venous catheters:** These are a special risk factor for bacteremia with coagulase-negative staphylococci (and *Staph aureus*).
- **Antibiotic prophylaxis regimens:** Antibiotic prophylaxis with drugs such as quinolones has served to reduce the incidence of bacteremia with gram-negative pathogens, at the risk of promoting a higher incidence of infection with resistant organisms.

- **Intensive chemotherapeutic regimens:** Intensive chemotherapy regimes have led to a higher incidence of mucosal ulceration, increasing the risk of bacteremia with oral viridans streptococci.

Remember: The spectrum of pathogens and antibiotic susceptibilities varies from institution to institution—familiarize yourself with local susceptibility patterns in order to predict the organisms likely to be a problem in your patient population.

4. What antibiotic therapy is indicated in neutropenic fever?

Start empiric antibiotics as soon as possible after evaluating the patient and obtaining blood cultures—time is of the essence and significant delays in therapy could prove life-threatening. Any one of several possible antibiotic regimens could be used for initial empiric therapy; however, most hospitals have a standard regimen based local antibiotic resistance patterns and some version of the following IDSA guidelines:

The Infectious Disease Society of America (IDSA) has recommended the following antibiotic regimens in patients with neutropenic fever…

Regimen #1	Regimen #2	Regimen #3
B-lactam monotherapy	Combination therapy Aminoglycoside (or quinolones) + B-lactam	Carbapenem alone
Cefepime or Piperacillin/tazobactam	AG + Ceftazidime Quinolone + Ceftazidime	Imipenem, Doripenem or Meropenem

OVMC regimen: Cefepime (2 gm IV Q 8hr) ± Vancomycin*

***Add vancomycin in seriously ill, septic patients (e.g. hypotension, severe toxicity) and in those with clear evidence of line infection (e.g. purulent discharge; peri-catheter erythema**

Modify empiric antibiotic coverage based on the following situations…

Situation	Additional antibiotic coverage
IV Catheter or skin/soft tissue infection; Hx MRSA	Add Vancomycin (1 gm IV q 12 hr)
Perirectal abscess or intraabdominal source	Use Piperacillin/tazobactam or add metronidazole
Oral ulceration (? HSV)	Check viral culture and consider adding Acyclovir (although severe oral ulceration may be secondary to chemotherapy-induced mucositis)
Nephrotoxicity	Avoid aminoglycosides—consider use of B-lactams and quinolones (with dose adjustment)
Sepsis/ARDS	Add Aminoglycoside or carbapenem Dose with vancomycin till C/S available

In choosing therapy in the neutropenic patient, remember the following…

- ✓ **All antibiotics are "local":** The initial choice of antibiotics varies from institution to institution, depending upon local bacterial susceptibility patterns and practitioner choice. Familiarize yourself with the facility's antibiogram and local antibiotic guidelines.
- ✓ **? Anaerobic coverage:** Although anaerobic bacteremia is less common in neutropenic patients, be sure to include antibiotics with good anaerobic activity (e.g. piperacillin/tazobactam; carbapenems or

addition of metronidazole) in patients with perirectal abscess/ulceration or evidence of neutropenic colitis (LLQ pain/tenderness).

- ✓ **? Vancomycin:** Although most standard guidelines do not recommend vancomycin "up front" for neutropenic fever, the increasing incidence of gram-positive bacteremia is a concern and we recommend "early" empiric use of vancomycin in the following situations: 1). Patients with clear evidence of line infection 2). Severely ill or septic (hypotensive) patient 3). Patients who are MRSA carriers.
- ✓ **? Previous neutropenic fever:** In those who have received previous cefepime or piperacillin/tazobactam, keep in mind the possibility of resistant pathogens and—pending culture results—consider using a carbapenem or addition of an aminoglycoside (e.g.amikacin) to the regimen. This is especially important in critically ill patients who appear to be slipping into septic shock.

5. What are the causes of persistent fever in the neutropenic patient?

You've started appropriate antibiotic therapy but the fever "fails to respond"—what's next? Don't be too quick in changing antibiotics—remember that the neutropenic patient typically has a slower response to treatment, sometimes taking 3-5 days to "respond" to treatment with defervescence.

Nevertheless, patients with persistent fever—beyond 3-5 days—merit additional evaluation. With **persistent neutropenic fever** (despite antibiotic therapy), a different set of pathogens and condition comes to mind. In addition to resistant bacteria pathogens, invasive fungal infection and "non-infections" syndromes (e.g. drug fever, neoplastic fever) take on greater importance. When confronted with the persistent fever, keep the following in mind:

- **Resistant bacteria:** Repeat the physical examination and review the patient's cultures—add additional agents if resistant organisms are identified; however, in the patient with no obvious source of infection, keep in mind that changes in antibiotic therapy rarely lead to defervescence. If the patient has an indwelling central venous catheter, consider adding vancomycin—even if the cultures are so far negative.
- **Undrained abscess:** Examine the patient carefully (sinuses, IV sites, abdomen, perirectal region) for areas that may hide an undrained abscess or focus of infection.
- **Invasive fungal infection:** Patients may have invasive candidiasis or aspergillosis. Reexamine the sinuses, order fungal blood cultures and obtain a high resolution CT scan of chest (look for the "wedge shaped" infiltrates or nodules of invasive aspergillosis). Consider adding empirical antifungal therapy to the patient's antibiotic regimen.
- **Drug fever:** Think about drug fever in those who "look good" despite the persistent fever—presence of a skin eruption or relative bradycardia are additional clues to the syndrome. Although any drug may be associated with drug fever, it is most commonly seen with B-lactam and sulfa agents. If drug fever is possible, consider substituting a drug from another class (e.g. quinolone; aminoglycoside)—patients with drug allergy should defervesce within 48-72 hours.
- **Pseudomembranous colitis:** If the patient has diarrhea, consider the possibility of pseudomembranous colitis and send off a *C. difficile* toxin test on a stool sample. If you strongly suspect the condition, start the patient on empirical oral metronidazole or vancomycin.
- **Neutropenic colitis:** These patients usually complain of right lower quadrant abdominal pain or have tenderness on examination. Obtain an abdominal CT scan which will demonstrate the typical ileocecal thickening seen in "typhilitis".
- **Tumor fever:** The patient's underlying tumor or leukemia may be the cause of the persistent fever—reevaluate treatment with your hematology colleagues to assess the adequacy of treatment.

Recurrent Neutropenic Fever (RNF)—a member of a "select" club

An even more select syndrome is recurrent neutropenic fever—fever that recurs *after* a patient has been successfully treated for their initial neutropenic fever. These fevers occur in approximately 15% of all neutropenic patients and on average, start roughly 10 days after the onset (and successful treatment) of the initial, primary fever syndrome. A recent study reviewing this syndrome suggested that two thirds of these patients had a documented infection as the cause of the fever. Among these infections, invasive fungal infection (IFI) accounted for almost 50% of the cases, with two thirds of these related to invasive molds such as *Aspergillus* or *Mucorales* species. The lower incidence of *Candida* species infection may be secondary to wide use of azole prophylaxis in this study. Despite an aggressive diagnostic approach, over a third of patients had "unexplained fever" (FUO) that seemed to defy attempts to pin down a cause. This study stresses the risks of long term neutropenia—even after successful treatment of a primary fever, patients remain at risk for a "secondary" infection, with invasive fungal infection being an important consideration.

Source: Akova M et al. Secondary Infections in Febrile, Neutropenic Patients with Cancer. Clin Infect Dis. 2005;40:239-45.

6. "Mugged by a mold"—fungal pathogens in the neutropenic patient

Approximately 10% of neutropenic patients with persistent fever will develop documented invasive fungal infection. *Candida* and *Aspergillus* species are the most common pathogens; however, there appears to be an increasing incidence of invasive aspergillosis, possibly a consequence of more widespread prophylaxis against *Candida* (e.g. use of fluconazole).

Clues to a fatal fungus

As you evaluate the neutropenic patient with persistent (or recurrent fever), keep in mind the following "clues" which suggest invasive fungal infection:

- ✓ **Persistent fever:** Obviously, persistent fever—*despite* broad-spectrum antibacterial therapy—strongly increases the likelihood on underlying fungal infection.
- ✓ **Previous fungal infection:** If a patient had a documented (or suspected) fungal infection during a previous neutropenic episode, there is a good chance that it will return again. This might occur even if the patient has received anti-fungal prophylaxis during the intervening period. Review past hospitalizations and look for clues (e.g. + fungal cultures; characteristic radiograph findings; response to anti-fungal therapy) that might shed additional light on the current situation.
- ✓ **Pulmonary infiltrates/nodules:** Over 90% of invasive fungal infections (IFIs) present with some degree of pulmonary involvement—since plain chest radiographs may be insensitive, obtain a high resolution lung CT scan looking for new infiltrates, nodules or effusions. Specific signs ("halo" sign around nodule; lung cavitation; "crescent" sign) suggest fungal infection but may not be fully evident till leukocyte counts return.
- ✓ **Sinus and skin involvement:** Evidence of sinus complaints (e.g. sinus tenderness; nasal bleeding; nasal or palatal eschar) suggests invasive aspergillosis or mucor infection—in suspected cases, order a head CT scan and consult ENT for a more careful exam and possible biopsy . Examine the patient carefully for any skin lesions—biopsy any new nodules, papules or ulcers since these may be the first sign of a disseminated invasive fungal infection.

In patients with persistent pulmonary infiltrates, obtain sputum cultures and request a pulmonary consultation—bronchoscopy with bronchoalveolar lavage (BAL) may isolate a fungus that is likely the cause of the problem. Advent of fungal antigen detection tests offer an additional means of diagnosing invasive fungal infection—consider ordering a serum galactomannan or B-glucan test. Although sometimes

difficult to interpret, these tests are especially helpful if the patient has had a previously documented "negative" baseline test.

A guide to empiric anti-fungal therapy

Unless there is an some other, obvious cause, persistent fever (> 5 days) generally warrants addition of empiric antifungal therapy. If fever persists, add one of the following agents:

Drug	Dosing
Voriconazole:	6 mg/kg IV q 12 hr x 2 doses…then switch to 4 mg/kg IV q 12 hr If drug well absorbed…after 48 hr rx, switch to PO Rx 200 mg PO q 12 hr
Liposomal Amphotericin B	3 mg/kg IV q 24 hr
Caspofungin	70 mg IV load, then 50 mg IV q day

When using these drugs, keep in mind the following…

- **Voriconazole:** Active against most *Aspergillus* and most *Candida* species but lacks activity against *Murcorales* (e.g. mucormycosis). Start with IV treatment and switch to oral route as soon as possible.
- **Caspofungin:** Active against resistant *Candida* species (*C. krusei*, *C. glabrata*), but not necessarily ideal for aspergillosis (although there is some *in vitro* activity).
- **Amphotericin B:** Because of lower nephrotoxicity and infusion related side effects, most specialists are using some form on liposomal amphotericin B

Remember: Invasive fungal infection remains an important cause of mortality in the neutropenic patient—cultures are often negative and sometimes diagnosis is not confirmed until the infection is discovered at post-mortem exam. In a patient with persistent neutropenic fever, if you suspect fungal, do not hesitate to add empiric anti-fungal therapy—it may prove life-saving in selected cases!

ID Checklist: *What to do in the patient with neutropenic fever…*

- **Evaluate the patient as soon as possible!** Patients with neutropenic fever can deteriorate quite rapidly with a high associated mortality—when called about a case, don't delay and see them as quickly as possible. Likewise, if antibiotic therapy is indicated, make sure treatment is delivered as soon as possible, without delay.
- **Perform a physical exam:** The lack of leukocytes reduces inflammation and minimizes the extent of physical findings—examine the patient carefully and don't overlook "minor" findings that could represent the source of the infection. In most cases, a brief, "targeted" examination will often reveal the most likely sites. On examination, pay special attention to the following "high-yield" areas…
  - ✓ **Oral cavity:** Look for oral ulceration (common c chemotherapy), occult dental abscess/gingivitis and palatal eschar/hemorrhage (invasive mucormycosis).
  - ✓ **Nasal/sinuses:** Examine the nasal passages for hemorrhage or eschar suggesting mucormycosis.
  - ✓ **IV sites:** Examine IV sites including the any long-term central catheter—presence of tenderness, erythema and/or purulence suggests line infection and the need for empiric vancomycin.
  - ✓ **Heart/Lungs:** With a brief exam, check for pulmonary findings as well as presence of tricuspid murmur (rare endocarditis in patient with indwelling central line).
  - ✓ **Abdomen:** In addition to checking for hepatosplenomegaly (seen with disseminated candidiasis), check for the RLQ tenderness seen with neutropenic colitis.
  - ✓ **Genitourinary:** Check for indwelling Foley and epididymitis
  - ✓ **Rectal:** No need for a "full-bore" rectal exam—role the patient over and gently palpate the anal verge and surrounding perianal tissues. Rectal fissures and perirectal abscess are surprisingly common in patients with leukemia and remain an important source of fever and bacteremia.
  - ✓ **Skin:** Look for necrotic lesions (e.g. Ecythma gangrenosum in *Pseudomonas* bacteremia), vesicles (disseminated HSV or VZV) and nodules/papules (disseminated fungal infection). In unexplained fever, biopsy of these lesions may demonstrate an underlying pathogen (or recurrent leukemia).
- **Obtain cultures:** Automatically order two sets of blood cultures—if the patient has a central line try to obtain one set through the line (a positive culture will be a marker for line sepsis). Obtain additional cultures (sputum; urine) based on the initial evaluation.
- **Review radiographs**, especially the chest radiograph in patients with pulmonary findings. More sophisticated studies (e.g. CT scans) may be appropriate in patients with abdominal pain (Abd/pelvic CT scan is the test of choice for neutropenic colitis) or pulmonary complaints (Chest CT will help provide early diagnosis of invasive fungal infection).
- **Consider non-infectious causes** such as transfusion reaction (did the patient just receive a transfusion prior to the fever spike), drug fever (especially B-lactam drugs and specific chemotherapy agents) and fever related to underlying malignancy.
- **Review past episodes of fever** including culture/susceptibility results—the presence of "resistant" pathogens will likely influence the empiric therapy that is necessary in your case.
- **Start empiric antibiotics** based on the above recommendations. Keep in mind that modifications may be necessary depending upon findings on exam and the patient's previous antibiotic exposure. Antifungal therapy is not usually started during the "initial" febrile episode but may be appropriate in selected cases if there was a past history of invasive fungal disease.

ID Warning: Once you have made the decision to start antibiotics, write your order and make sure it is carried out as soon as possible (within the hour)—significant delays (6-12 hours) in antibiotic administration may well lead to increased mortality!

What you need to know about fever in the neutropenic host…

- Patients with neutropenia due to underlying disease (e.g. aplastic anemia) and/or chemotherapy are at significant risk for both bacterial and fungal infection. This risk increases with the depth of the neutropenia and requires prompt empiric antibiotic therapy in order to minimize mortality.

- Neutropenic fever (NF) is defined as a single temperature ≥ 38.3ºC (101ºF) or a temp ≥38.0ºC (100.4ºF) for ≥ 1 hour in a host with a low (<500 cells/mm^3), or declining (<1000 cells/mm^3 with a predicted decrease to <500 cells/mm^3) neutrophil count.

- Although only 20% of individuals with febrile neutropenia are bacteremic, bacterial infection plays a role in the majority of infections (60-80%) in this population. Common portals of infection include mucositis, pneumonitis, enteric infection (colitis; perirectal abscess) and intravenous line infection.

- Up to 20% of patients with "neutropenic fever" will have fever secondary to a "non-infectious" cause such as drug fever, transfusion reaction and/or the patient's underlying malignancy. In 20% of cases, no source will be found for the fever—since many respond to antibiotics, it is assumed that these fevers are due to bacteria from the patient's own intestinal flora.

- In patients with documented bacteremia, gram positive bacilli such as straphylococci and streptococci account for over two thirds of isolates—this likely reflects the common use of prolonged intravenous catheterization (e.g. staphylococcal species) and increased incidence of mucosal ulceration associated with aggressive chemotherapy regimens (e.g. viridans streptococci). Gram negative bacilli—including *Pseudomonas aeruginosa*—remain important potential pathogens and require empiric therapy until culture results are known.

- In the febrile, neutropenic patient, pay special attention to the sinuses, oral cavity (mucositis), chest exam (? Pneumonitis), abdominal exam (? Neutropenic colitis) and perirectal region (? Abscess or fissure). Make note of any skin lesions (? Disseminated fungal infection) and carefully examine the intravenous site looking for local or tunnel infection.

- Depending upon your local bacterial flora, treat the febrile neutropenic patient with a broad-spectrum regimen which includes antibiotics with activity against both gram positive organisms (staphylococcal and streptococcal species) and gram-negative bacilli. Suggested regimens include: 1). Cefepime *or* 2). Aminoglycoside + piperacillin/tazobactam *or* 3). Carbapenem (e.g. imipenem, doripenem or meropenem).

- In septic patients or those with evidence of line infection (erythema/purulent discharge surrounding the catheter; tenderness of the catheter "tunnel"), add vancomycin (to cover for MRSA) until culture results are available. In those with suspected intraabdominal or perirectal infection, add metronidazole to the regimen or use an agent (e.g carbapenem or piperacillin/tazobactam) with good anaerobic activity.

- In patients with persistent fever (≥ 5 days), consider the possibility of invasive fungal infection, neutropenic colitis, drug fever and fever associated with the underlying malignancy. In those with suspect invasive fungal infection, obtain a chest CT scan (~ 90% of patients will have pulmonary infiltrates or nodules) and request a pulmonary consultation for possible bronchoscopy.

- *Candida* species and aspergillosis are the most common causes of fungal infection in neutropenic patients. There is an increasing frequency (~ 5-10% of patients) of mucormycosis, especially in individuals with prolonged neutropenia who have received previous anti-fungal prophylaxis.

- In patients with persistent fever and suspected fungal infection, start empiric therapy with an anti-fungal agent such as voriconazole, liposomal amphotericin B or an echinocandin (e.g. caspofungin).

Chapter 5

A puzzling pyrexia—Fever of Unknown Origin (FUO)

ID specialists are "fever" doctors; evaluating—and diagnosing—a perplexing fever is one of the challenges of the specialty. In ID parlance, this syndrome merits a special name—**Fever of Unknown Origin** (or "FUO")—and has a specific set of criteria (and causes) the separate it from the usual spectrum of common fevers. The following chapter outlines the definition of this condition and provides a systemic approach to managing this sometimes elusive and frustrating condition.

1. What is the definition of FUO?

When infectious disease specialists use the term "Fever of Unknown Origin", they are referring to a very specific condition with a well-defined set of criteria as initially described by Petersdorf. The following tables define the "criteria" that need to be met in order to call a fever an"FUO".

Table 1: Criteria-Classic FUO
Temperature >38.3°C (100.9°F) Duration of >3 weeks Evaluation of at least 3 outpatient visits or 3 days in hospital—etiology still unclear

Table 2: "Classic FUO"—common causes
Infection (Tuberculosis, SBE, Occult abscess) Malignancy (Lymphoma) Collagen vascular disease (Still's, vasculitis) Miscellaneous (see below)

Remember: Try to avoid using the FUO term to describe any unexplained fever—the term implies that the case meets the specific criteria described above (e.g. Table 1) and suggests an increased likelihood of an associated list of conditions (see Table 2):

ID History: Robert Petersdorf and the "birth" of the FUO

Although physicians had long recognized cases of prolonged, unexplained fever, clinicians owe a debt of gratitude to Robert Petersdorf (1926-2006), an infectious disease specialist who provided a systematic approach to the syndrome and popularized the term "FUO". As a chief resident at Yale University medical center in the early 1960s, Petersdorf (with his mentor Paul Beeson) described a series of 100 patients with persistent, unexplained fever. They outlined a set of clinical criteria that emphasized the persistence of the fever (at least 3 weeks) and the "unknown" nature of the condition (no diagnosis despite one week of hospitalization). Furthermore, the ultimate results of their evaluation led to a list of diagnoses that provides a roadmap to any clinician confronted with a similar situation. Even today, their work and definitions remain pertinent—except for minor changes in the "criteria" (patients no longer require a full week of hospital investigation) the clinical approach and disease distribution is remarkably similar to the "initial" 100 cases described by Petersdorf.

Source: Petersdorf RT, Beeson PB. Medicine 1961;40:1-30

2. What are the most common causes of "classic" FUO?

This depends on factors such as the nature of the patient population, geographic location (e.g rural vs urban) and type of hospital (primary vs tertiary care). Several generalizations can be made:

- **Tuberculosis** remains an important infectious cause of FUO—although the incidence of pulmonary tuberculosis has fallen in industrialized countries, extrapulmonary tuberculosis remains a problem and continues to be a cause of "FUO", especially in immigrants from TB-endemic regions.
- **Infective endocarditis (IE):** Despite the great advances in blood culture techniques and imaging technology (e.g. echocardiography), IE remains an important cause of FUO.
- **Occult malignancy**—especially lymphoma—is a common cause of FUO in the industrialized world; always keeps in mind the possibility of underlying malignancy in patients with FUO.
- **Rheumatologic diseases** remain an important cause of FUO, especially SLE, rheumatoid arthritis and Still's disease. In older adults, keep in mind the possibility of temporal arteritis (giant cell arteritis), one of the most common causes of FUO in this population.
- **AIDS:** Even in patients at "low risk" for HIV, always consider the possibility of AIDS or underlying HIV infection —request "routine" serological testing and look for clues that might suggest the condition (e.g. unexplained adenopathy; lymphopenia, oral hairy leukoplakia, previous zoster).
- **Miscellaneous** conditions have been associated with prolonged fever including drug fever (carefully review the patients medication lists), recurrent pulmonary emboli (especially in bed-ridden patients) and alcoholic hepatitis.

14 disorders ~ 2/3 of the diagnoses…

Although there are over a hundred causes of "FUO", most studies suggest that a handful of conditions are responsible for most of the cases:

Infections	Malignancies	Inflammatory disorders	. Miscellaneous disorders
• Endocarditis • Tuberculosis • Abdominal abscess • EBV/CMV infections	• Lymphoma • Leukemia	• Adult-onset Still disease • SLE (lupus) • Polymyalgia rheumatic (Giant cell arteritis) • Sarcoidosis • Crohn's disease	• Habitual hyperthermia • Drug fever • Subacute thyroiditis
Source: Vanderschueren S. et al. From prolonged febrile illness to Fever of Unknown Origin: The challenge continues. Arch Intern Med 2003;163:1033.			

"Words of Wisdom" from a master clinician…

"Most patients with FUO are not suffering from unusual diseases; instead they exhibit atypical manifestations of common illnesses." Robert Petersdorf

3. Location, age and "duration"—FUO variations on a theme:

Studies demonstrate a variation in "FUO" depending upon geographic region and nature of the patient population. In general, "infection" is more common in developing countries or regions with high immigrant populations; "inflammatory" conditions, more likely in the "developed" world.

In evaluating FUO, remember your patient population and keep the following in mind…

FUO diagnosis in comparative clinical settings/studies

Author	Petersdorf et al	Kazanjian	Kejariwal et al	Vanderschueren
Date	1961	1992	2001	2003
Country	US	US	India	Belgium
Treatment setting	Tertiary care hospital	Community hospital	Developing world	Tertiary care hospital
# patients	100	86	100	290
		% Patients		
Infection	36	33	53	20
Neoplasm	19	24	17	10
Inflammatory	15	26	11	23
Miscellaneous	23	8	5	13
Undiagnosed	7	9	14	34

A review of these studies suggests the following observations…

- ✓ **Infection:** Infection remains an important cause of FUO, especially in hospitals located in the "developing" world or in those caring for a largely "immigrant' population from these regions.
- ✓ **TB/endocarditis:** Even in the modern era, tuberculosis (extrapulmonary) and endocarditis continue to be important causes of FUO.
- ✓ **Intraabdominal abscess:** As a cause of unexplained fever, the incidence of occult intraabdominal abscess has decreased, probably because of the widespread availability of abdominal CT scanning.
- ✓ **Rheumatologic disease:**, Inflammatory disorders (e.g. collagen vascular, granulomatous diseases) appear to be of increasing in importance as a cause of FUO.
- ✓ **"Undiagnosed" FUO:** In modern, tertiary care referral centers, the incidence of "undiagnosed" FUO has increased—this likely reflects a referral bias (easier cases have been screened out at other facilities), not necessarily a true change in the epidemiology of the condition. For these type of cases (negative workup despite extensive evaluation), news is often good—many have a relatively benign case and eventually resolve.

FUO in the older patient: The following table offers some insights into the differences in FUO between between younger and older patients:

Table 4: FUO—Older vs younger patients

Condition	Elderly (# pts; %)	Young (# pts; %)
Infection	72 (35)	33 (22)
- Tuberculosis	20 (10)	4 (3)
- Abscess	25 (12)	6 (4)
- Endocarditis	14 (7)	2 (1)
- Viral infections	1 (0.5)	8 (5)
Malignancies	38 (19)	8 (5)
NIID (Inflammatory)	57 (28)	27 (17)
Miscellaneous	17 (8)	39 (26)
No diagnosis	18 (9)	45 (29)
Total	204	152

Source: Norman D. Clin Inf Dis 2000;31:148

A review of these studies suggests the following observations….

- ✓ **Infection** remains an important cause of FUO in older patients; moreover, they are less likely to have "viral infection" and more likely to present with tuberculosis, occult abscess and endocarditis.
- ✓ **Malignancies** are also more common in the older population; although "solid" tumor (e.g. adenocarcinoma) may present with fever, look especially for lymphoma and occult hematological malignancy.
- ✓ **Inflammatory disease:** Non-infectious inflammatory disease—especially temporal arteritis (polymyalgia rheumatic) are important causes of fever in the older population—question the patient carefully about headache and always obtain an erythrocyte sedimentation rate.

4. Clinical pearls for patient evaluation

The initial history and physical are critical in generating a differential diagnosis and likely etiology. Keep the following considerations in mind during the initial evaluation:

- **History:** Nothing takes the place of a careful history and meticulous physical examination. Pay special attention to the following…
  - ✓ **Onset:** Try to define exactly when the illness *really* began—ask the patient when they last felt well and make sure you've nailed down the detail of the disease's onset and progression.
  - ✓ **Epidemiological clues.** As an ID specialist, your inquire about some of the exposures that could provide a clue to the condition—ask about travel history, animal/pet exposure, unusual food ingestion, employment history, recreation/hobbies, sexual activity and illnesses in the patient's close family or friends.
  - ✓ **Family and friends:** Don't rely completely on the patient for the clinical history; with patient permission, ask their family and friends for further information about the illness. They may recall details forgotten by a patient who may be too sick—or frustrated—to remember all the pertinent facts.
  - ✓ **Review the medical record:** Always make efforts to obtain and review old records from previous hospitalizations— this will save time and may unearth the results of a critical test that got lost or delayed in the filing room!

- **Physical examination:** Nowhere is a careful physical examination more important—easily overlooked findings on physical examination may provide important clues to the underlying cause. Pay special attention to the following "high yield" areas:
  - ✓ **Eye exam:** Many of the causes of FUO are associated with opthalmological findings—perform a fully dilated fundiscopic examination (or send the patient to an ophthalmologist) looking for choroids tubercles (miliary TB), "wax droppings" (sarcoidosis) and retinal vasculitis or hemorrhage (Roth spot in SBE).
  - ✓ **Lymphadenopathy:** Carefully examine all major lymph node groups for evidence of localized or generalized lymphadenopathy—biopsy of these nodes may help diagnosis occult granulomatous or neoplastic disease.
  - ✓ **Cardiopulmonary exam:** Listen carefully for heart murmurs, cardiac friction rubs (e.g pericarditis) and pleural friction rubs (pulmonary embolism; SLE or inflammatory conditions).
  - ✓ **Abdomen:** Although often picked up on CT scan, check the patient for evidence of hepatosplenomegaly, an important finding in any FUO evaluation.
  - ✓ **Genito-rectal exam:** Don't skip the GU/rectal exam—look for epididymoorchitis (TB, brucellosis, polyarteritis nodosa), perirectal/rectal inflammation (perirectal abscess) or fissures (inflammatory bowel disease). In females, take the time to do a pelvic exam looking for pelvic tenderness (pelvic thrombophlebitis; PID) or masses .

- ✓ **Joints:** Rheumatological problems are especially important causes of FUO—examine joints for presence of swelling and warmth.
- ✓ **Skin:** A careful skin examination may reveal important lesions that might provide a diagnosis on biopsy.

- **Prioritize and plan laboratory testing:** Be wary of scattershot testing trying to cover all the "causes" of FUO. Order an initial package of "screening tests" and then perform subsequent testing based on the patient's clinical presentation and likely differential diagnosis. In FUO, the package of "standard" tests usually includes the following…
  - ✓ **Cultures:** Order 2 sets of blood cultures and a urine culture
  - ✓ **? TB:** Always order a PPD or IGRA test (Quantiferon gold) to check for TB exposure.
  - ✓ **Rheumatology workup:** Check an ESR, ANA, Rheumatoid factor (may be + in infective endocarditis) and Ferritin (high in Still's); additional serological studies will depend upon the clinical presentation.
  - ✓ **Viral:** HIV Antibody test; HIV viral load (? 1° HIV infection), EBV and CMV serology
  - ✓ **"Exotic" serologies:** Depending upon the exposure history, consider ordering serologies for zoonotic pathogens such as Coxiella burnettii (Q fever), Brucella and rickettsial disease.
- **Radiology/scanning:** Following routine x-rays (e.g. chest radiographs), the next level of testing includes CT scans, cardiac echocardiography and nuclear medicine scans. As you contemplate additional studies, keep the following in mind…
  - ✓ **CT scans:** An abdominal and chest CT scan is appropriate for most FUO evaluations—it helps to pick up occult intraabdominal abscess and may provide additional findings (e.g. hepatosplenomegaly; retroperitoneal or hilar adenoapathy) that provide an opportunity for diagnostic biopsies.
  - ✓ **Echocardiography:** Infective endocarditis remains an important cause of FUO—even if the patient has a "normal" cardiac exam, a routine echocardiogram is often performed in cases of unexplained fever.
  - ✓ **Nuclear medicine scans:** While they rarely "make the diagnosis", nuclear medicine scans (e.g. Indium labeled WBC scan; Gallium scan) may point to pathology in specific areas or help sort out infectious from neoplastic conditions (e.g. PET scan).

  Again, these are likely to have a higher yield if ordered in a "targeted" fashion in light of previous clinical and laboratory findings. Although sometimes indicated, in general avoid "blind" scanning without a clear reason.
- **Biopsy:** The fourth level of testing requires crosses the "invasive" divide and includes biopsy of such tissues as lymph node, liver and bone marrow. Again, these are more likely to yield useful information in patients with findings that point to these organ systems.
- **Putting the case together:** You've acquired all this information—take the time to think about the case in order to generate a differential diagnosis and plan your next move. Use the following in particularly puzzling cases…
  - ✓ **Make a timeline:** Make a timeline of the patient's illness and carefully note the results of pertinent laboratory and radiographic tests. Such a chart may give you new insights into the patient's illness and will certainly help subsequent physicians once you leave the service.
  - ✓ **Call an expert:** Don't be afraid to ask for help from other colleagues, especially if the clues point to diagnosis outside of your specialty—a rheumatologist or hematologist (? Bone marrow exam) may provide additional insight into the case. All FUO patients should have a thorough fully dilated eye examination by an ophthalmologist—a careful exam with sophisticated instruments may pick up clues missed by others. .
  - ✓ **Take a break:** Protracted fever sometimes remains a puzzle despite a hospital admission and a thorough workup. If the patient is not critically ill, it may be possible to discharge the patient and

revisit the case in the office, when there has been time for other tests to come back. Ask the patient to keep a record of their temperature and symptoms—such patient "involvement" might prompt additional thought unusual exposures and clues to the case.

ID Pearl

FUO "psychology" for doctor and patient: An FUO is frustrating for both patient and doctor—an unexplained fever is a daily reminder of the doctor's fallibility and the patient's possible mortality. Counsel patience to patient, family and doctors—remind them that fever—although a sign of underlying disease—is rarely harmful, in and of itself. Patients with prolonged, unexplained fever often do quite well and the fever may disappear "by itself", regardless of our efforts!.

6. Time for a trial…Empiric antibiotic therapy?

In clinically stable patients, avoid the urge to "do something"—don't start antibiotics unless there is a clear need to treat a septic or deteriorating patient. If you choose to start an empiric antibiotic, have a clear rationale and set parameters to evaluate the trial.

Despite the above admonition, it is common for many FUO patients to already have received a course of therapy. Use this to your diagnostic advantage—a response—or failure to respond—to a specific agent may provide clues to the underlying condition. In some situations, a "trial" of empiric antibiotic therapy may be appropriate, since a response to a specific agent may "confirm" a diagnosis…

- **? Tuberculosis:** A common cause of FUO in patients from developing countries, miliary tuberculosis actually has a relatively low bacterial burden, making confirmation by culture or tissue biopsy sometimes difficult. If the patient responds, add additional agents and reevaluate the patient in 8-12 weeks when cultures are available.
- **? Rickettisial and zoonotic disease:** "Rickettsial" disease such as murine typhus, ehrlichia and anaplasmosis often responds promptly to doxycycline in suspect cases. Doxycycline may also be helpful in other "zoonotic" conditions such as Q fever, brucellosis and tularemia, pending diagnostic tests.
- **? Corticosteroids:** If there is a high index of suspicion for rheumatological disease such as SLE or vasculitis, a trial of corticosteroids may be indicated, provided that the likelihood of an infectious etiology is relatively low.

Warning: Be cautious if a patient "responds" (e.g. becomes afebrile) on a quinolone or aminoglycoside—these agents have anti-mycobacterial activity and sometimes provide a false sense of clinical response.

Fever of unknown origin (FUO)—what you need to know…

- In infectious disease "jargon" the term Fever of Unknown Origin (FUO) implies a specific syndrome with the following criteria: 1). Temperature >38.3°C (100.9°F), 2). Duration of fever $\geq$ 3 weeks and 3). Etiology remains unclear despite evaluation consisting of at least 3 outpatient visits, or 3 days in the hospital.

- In retrospective studies, the frequency of various etiologies of FUO depends upon the hospital and patient population—although "infectious" causes are more common in the developing world, they remain an important cause of FUO in industrialized countries.

- Tuberculosis, infective endocarditis and occult abscess are the "top three" causes of infection-related FUO in most studies. Other important conditions include viral etiologies such as EBV (atypical mononucleosis), CMV and HIV –especially primary HIV infection where initial antibody tests may be negative.

- Hematological malignancies such as lymphoma are the most common causes of neoplastic-associated FUO; however, other persistent fever is a specific characteristic of selected "uncommon" malignancies such as hypernephroma; pheochromocytoma and hepatoma).

- "Inflammatory" or rheumatologic conditions remain important causes of FUO; however, the incidence of systemic lupus erythematosus (as a cause of FUO) is much less because of the ready availability of serological testing (e.g. ANA; anti-DS DNA). Syndromes such as Still's Disease and temporal arteritis lack simple serological tests and remain important causes of "inflammatory" FUO.

- Miscellaneous causes of FUO account for 10-20% of cases and include endocrinological causes (e.g.subacute thyroiditis), clotting disorders (e.g. deep venous thrombosis and recurrent emboli) and drug fever. "Genetic" or familial causes of FUO (e.g. familial Mediterranean Fever; Hyper IgD syndrome) often have a history of recurrent bouts of "unexplained" fever that started in childhood or adolescence.

- Proper evaluation of an FUO always begins with a careful history and physical examination. Avoid extensive "scattershot" laboratory testing—try to focus your evaluation based on clues obtained from the initial history and physical examination.

- Try to avoid "empiric" antibiotic therapy unless a patient is clearly deteriorating and withholding antibiotics could prove deleterious. Alternative, if a patient has already received specific agents, failure to respond to a treatment may be a clue that will help to exclude specific entities.

- While persistent fever is disturbing, it is not always a harbinger of more serious disease. In major clinical series, up to 30% of FUOs remained "undiagnosed", and some disappeared without a cause ever being determined.

- Although the clinician—and patient— have a great desire for an "answer" to an unexplained fever, sometimes a decision for "watchful waiting" may be the best approach if initial studies are negative and the patient is clinically stable.

Chapter 6

Fever of Unknown Origin (FUO) in the AIDS patient

Despite the advent of powerful new anti-viral agents, we still see patients with low T-cell counts and advanced HIV infection. When these patients present with an unexplained fever, we look for the suspected culprits (e.g. *Pneumocystis*, community-acquired pneumonia, cryptococcal disease) but are sometimes stymied when the initial tests come up "negative". These patients turn into a modern version of "fever of unknown origin"—HIV or AIDS related "FUO" (AIDS-FUO). This chapter is dedicated to "AIDS-FUO" and will provide a practical approach with diagnostic "questions" and clues that will lead to a correct diagnosis.

1. HIV/AIDS-related FUO—definition and common causes:

Not all "unexplained" fever meets the definition of "FUO"—AIDS-FUO has a specific definition that generally *requires* the following features…

- **Temperature** > 38.3°C (101 °F) on multiple occasions
- **Fever** of > 4 weeks duration (outpatients) or > 3 weeks duration (inpatients)
- **Diagnosis uncertain** after 3 days of investigation

Utilizing the above criteria, the following study from *Clinical Infectious Diseases* (CID 1999;28:341-6) outlines the most common underlying etiologies of this syndrome:

Table 1: Etiology of fever in 70 patients with HIV-associated FUO

Etiology	# pts (%)	Etiology	# pts (%)
Infection		Neoplasia	
Mycobacterium avium-intracellulare	22 (31)	Lymphoma	5 (7)
Pneumocystis jirovecii	10 (13)	Kaposi's Sarcoma	1 (1)
Cytomegalovirus (CMV)	8 (11)		
Histoplasmosis	5 (7)	Miscellaneous	
Viral (not CMV)*	5 (7)	Drug fever	2 (3)
Bacterial	4 (5)	Castleman's disease	1 (1)
Mycobacterium tuberculosis	4 (5)		
Parasitic†	2 (3)	No etiology determined	14 (20)

* HepC/B;adenovirus pneumonia; HSV esophagitis; Varicella zoster encephalitis
† Cerebral toxoplasmosis; disseminated cryptosporidiosis
Source: 72 fever episodes Armstrong et al., CID 1999;28:341-5

With regard to this study, keep in mind these important caveats….

- ✓ **Geographic diversity:** These patients were seen at two academic medical centers in the United States—depending upon the "site" of the study, regional variations in the etiology of "FUO" are likely to be present. *Mycobacterium tuberculosis* is more likely to be a problem in the developing world and

selected fungal infections (e.g. histoplasmosis in the Midwest and Central America) in patients from other locations.

- ✓ **Advanced disease:** It this series, most of these cases had "advanced" HIV infection (mean CD4=58 cells/mm^3; range: 0-457 cells/mm^3) and were receiving anti-retroviral therapy. Patients with well-controlled, "early" HIV infection (e.g. CD4 counts > 500 cellsmm^3) are more likely to fit the profile of the "standard" FUO case seen in the non-HIV population.
- ✓ **Prolonged duration:** The average duration of fever was 42 days (range: 16-220 days)—diagnosis can be a challenge, even in an era with fairly sophisticated diagnostic techniques.
- ✓ **Infection is "king":** In standard non-HIV FUO, infection accounts for approximately 30% of cases. In the above study of AIDS-FUO, almost 80% of patients had an infection, sometimes with more than one pathogen.

As stated above, fever is common in HIV patients, either as part of the presenting illness, or secondary to a later complication. Before you label a patient "AIDS-FUO", keep in mind the following during your initial evaluation.

- ➢ **Primary HIV infection** itself is associated with a fever (sometimes lasting up to several weeks) along with a "mononucleosis-type" syndrome of pharyngitis, lymphadenopathy and a diffuse maculopapular rash (up to 50% of cases). Since the initial HIV ELISA antibody may be negative during the "window" period prior to seroconversion, always check a p24 antigen (part of the 4^{th} generation HIV ELISA) or HIV PCR viral load to exclude primary HIV infection.
- ➢ **"Common" bacterial infections:** Although we think of "exotic" opportunistic infections, HIV patients are at greater risk for "common" infections such as pneumococcal pneumonia and bacillary dysentery. Check routine cultures (HIV patients have a 5-fold greater risk of pneumococcal bacteremia) and—depending on the presumed site of infection—consider an initial trial of standard antibacterial therapy.
- ➢ **Opportunistic pathogens:** In patients with low CD4 counts, the "standard" opportunistic pathogens still remain common causes of unexplained fever. Depending upon the clinical presentation, keep in mind the possibility of pneumocystis (pneumonitis), cryptococcal disease (meningitis) and toxoplasmosis (focal CNS disease). Again, the likelihood of these organisms depends upon the CD4 count and site of infection—patients with "high" T-cell counts (> 500 cells/mm^3) can still, rarely be afflicted with these pathogens.
- ➢ **Miscellaneous causes:** Although we may be quick to blame infection, keep in mind the other "non-infectious" causes of fever in HIV-FUO. These include drug fever (Was the patient recently started on TMP/SMX?), immune reconstitution syndrome (Were they started on anti-retroviral therapy) and neoplastic disease.

2. Pathogen profile—specific conditions associated HIV FUO

In your evaluation of HIV-associated FUO, keep in mind the following entities…

- **MAI infection:** In the industrialized world, *Mycobacterium avium-intracellulare* (MAI) infection is the most common cause of FUO in HIV/AIDS. This is usually seen in patients with low CD4 counts (< 100 cells/mm3) and is often accompanied by lymphadenopathy and hepatosplenomegaly. In suspect cases check both stool and blood AFB cultures and consider an empiric trial of anti-MAI therapy (clarithromycin + ethambutol)—a prompt clinical response with defervesence will lend further support to the diagnosis.
- ***Mycobacterium tuberculosis*:** In immigrants from the "developing" world disseminated *Mycobacterium tuberculosis* is probably more common than MAI infection. In these patients ask about previous TB exposure (any family members with MTB?) and remember that the PPD (and Quantiferon Gold) may well be negative in patients with active disease. Review the chest radiograph and consider a

chest CT scan. Remember that ~5% of AIDS patients with tuberculosis have a *negative* chest radiograph and have a low threshold for obtaining sputum AFB samples despite the seeming absence of pulmonary disease.

- ***Pneumocystis* infection:** Despite the widespread use of pneumocystis prophylaxis, PJP infection remains an important cause of FUO in HIV/AIDS. Ask about pulmonary symptoms and check a CT of the chest—presence of "ground glass" infiltrates are a clue and suggest the need for more definitive testing (e.g. induced sputum or bronchoscopy with DFA for *Pneumocystis*).

- **CMV infection:** Most commonly seen in patients with advanced HIV/AIDS (CD4 < 100 cell/mm3), cytomegalovirus usually targets eyes (retinitis), gastrointestinal tract (colitis; esophagitis) and nervous system (encephalitis; peripheral neuropathy). In patients with persistent fever, check serology (almost all patients are IgG positive) and request a fully dilated fundiscopic exam to help identify subclinical retinal disease. In gastrointestinal disease, definitive diagnosis of CMV requires biopsy with evidence of tissue invasion.

- **Fungal infection: Cryptococcus** can be seen in any population, but specific fungi such as **histoplasmosis** (Midwest; Central America), **coccidioiodomycosis** (Southwest US) and *Penicillium marneffei* (Southeast Asia) are more limited to specific geographic regions—ask about past residence or travel to these areas.

> **ID Clue:** The risk of underlying *Pneumocystis* in a patient taking prophylactic antibiotic therapy (e.g. TMP/SMX, dapsone, atovaquone) is low—but not zero! Some of the patients in the above study claimed to be taking pneumocystis prophylaxis, yet turned out to have active PJP infection on further evaluation. Despite being prescribed the meds, problems associated with compliance (Is the patient faithfully taking the medicine?), absorption (? Diarrhea or underlying GI disease) and efficacy (atovaquone is less efficacious than TMP/sulfa) may lead to drug "failure".

- **"IRIS" reaction:** When patients with low CD4 counts are started on anti-retroviral therapy, they may develop immune reconstitution inflammatory syndrome (IRIS) associated with control of viral load and improvement of T-cell counts. The IRIS reaction usually implies a reaction to an underlying "subclinical" opportunistic infection/neoplasm such as mycobacterial disease (MAI), fungal (Cryptococcus) or CMV infection.

- **Neoplasm:** HIV/AIDS patients are at specific risk for **non-Hodgkin's lymphoma (NHL)**—look for hepatosplenomegaly/lymphadenopathy, unexplained hematologic abnormalities (anemia, pancytopenia). Check an LDH (often elevated in lymphoma) and consider a bone marrow. **Kaposi's Sarcoma** by itself is rarely associated with fever, unless it becomes apparent as part of an "IRIS" reaction to anti-retroviral therapy.

- **? HIV infection:** Persistent low-grade fever/sweats may be secondary to poorly controlled HIV infection (e.g. low CD4 count; high HIV viral load)—this usually disappears following institution of effective anti-retroviral therapy.

- **Parasitic infection:** Parasitic disease is rarely the cause of prolonged unexplained fever in HIV/AIDS, except for the occasional case of CNS **toxoplasmosis** (usually clinically apparent) and the rare patient disseminated **strongyloidiasis** (usually seen with concomitant steroid use). **Visceral leishmaniasis** is an important cause of FUO in patients from the Mediterranean basin—look for unexplained hepatosplenomegaly and pancytopenia that mimics histoplasmosis.

What is the T-cell count? The standard "OIs (opportunistic infections) associated with AIDS (e.g. PCP, cryptococcus, CMV MAI) are much more common in patients with CD4 counts less than 200 cells mm^3—patients with higher counts are more likely to have infection with "standard" pathogens seen in the general population. The clinical presentation is also conditioned by T-cell count—patients with tuberculosis reactivation and low CD4 counts (< 200) have "atypical", non-specific pulmonary infiltrates whereas patients with higher counts generally present with radiographic patterns (e.g. upper lobe infiltrates/cavitation)more typically associated with TB.

3. What are the patient's symptoms?

As with most of clinical medicine, carefully question the patient about previous infections, duration of symptoms and the likely site of organ involvement. See if the patient's clinical presentation fits any of the following "patterns"—this will help guide further testing and may provide clues to the underlying cause:

√ **Headache/CNS:** Think cryptococcus, toxoplasmosis and CNS lymphoma. Obtain a CT scan (if possible, with contrast) and—if not contraindicated—a lumbar puncture.

√ **Pulmonary:** The chest radiographic pattern may be helpful in sorting out the causes…

-Focal pulmonary infiltrates→bacterial pneumonia

-Diffuse pulmonary infiltrates→PCP, cryptococcosis, MTB, histoplasmosis

-Diffuse pulmonary nodules (miliary nodules)→TB, histoplasmosis, coccidioidomycosis

-Hilar adenopathy: TB, fungal disease, lymphoma

√ **Gastrointestinal:** Ask about the following…

-Esophagitis: CMV, HSV or *Candida albicans*

-Diarrhea: AIDS patients at risk for *Salmonella, Shigella and Campylobacter*

-Bloody diarrhea (Heme + stool): CMV(esp in pts with low [<100] CD4 counts)

-Chronic watery diarrhea: √ stool for C/S (? *Salmonella*), AFB (?MAI), O+P) and C.difficile toxin

-Hepatosplenomegaly: May be seen with HIV alone; however, think disseminated TB, histoplasmosis, lymphoma or bacillary angiomatosis

√ **Neuropathy:** May be due to HIV, vitamin deficiency (B12) or meds (DDI, D4T) but—in a febrile patient with low CD4 counts, think about the possibility of CMV infection.

√ **Anemia:** Think lymphoma, parvovirus B19, histoplasmosis and drug toxicity (AZT, TMP/SMX)

√ **Effusions:** (pleural, pericardial, abdominal): Primary body cavity lymphoma (+HHV8); crypto; TB; histoplasmosis.

4. Are there any exposure or geographic factors?

Recent or remote travel/residence is an important clinical clue to the cause of an "unexplained" fever in an HIV/AIDS patient. Be sure to take a careful travel and history and consider alternative pathogens, based on the following exposures:

- **Midwest US:** Histoplasmosis (usually has hepatosplenomegaly with lymphadenopathy)
- **History of TB exposure:** Immigrants from TB endemic areas; ask about previous PPD or family TB history
- **Travel to Southwest** (e.g. Las Vegas, Palm Springs, Lancaster, Bakersfield): risk for coccidiodomycosis

- **Latin America:** Consider the possibility of histoplasmosis, Chaga's disease (Focal CNS lesions) and visceral leishmaniasis (skin lesions; hepatosplenomegaly; pancytopenia).
- **Southeast Asia:** *Penicillium marnefei,* meliodosis (*Pseudomonas pseudomallei*)
- **Cat exposure or homeless:** Bacillary angiomatosis in AIDS pts: fever, HS megaly c focal lesions, vascular skin lesion--√ serology for *Bartonella henselae* or *Bartonella quintana* (Trench fever in homeless)

5. Could this be "IRIS" or drug fever?

Sometimes fever emerges *after* the patient has been started on anti-retroviral or prophylactic antibiotics. In those situations keep in mind the possibility of immune reconstitution syndrome (IRIS) and/or drug fever. Common features of these syndromes include the following…

- **IRIS:** Immune reconstitution inflammatory syndrome is a condition that usually occurs within 3-4 months after starting effective anti-retroviral therapy—control of HIV (decreased viral load) with a rise in CD4 count leads to inflammation associated with emergence of an underlying "occult" opportunistic infection. Common underlying "OIs" associated with this condition include MAI infection, cryptococcal disease and/or CMV (e.g. uveitis; iritis). In addition to a careful evaluation and treatment of the underlying infection, an empiric course of corticosteroids may be appropriate if IRIS appears to be a likely possibility.
- **Drug fever:** Despite the impaired immunity, HIV/AIDS patients have a higher incidence of drug allergy than the general population. As you evaluate the HIV "FUO" patient, keep in mind the following "common" causes of drug allergy in AIDS:

  - TMP/SMX or dapsone: Maculopapular rash and/or fever

  - Anemia with hemolytic anemia: G6PD def iciency due to sulfa drugs or dapsone

  - Abacavir: Fever, rash, abdominal pain, usually within 12 weeks of starting Rx
  Chance of fatality with rechallenge
  +HLA B5701 test predicts risk for abacavir hypersensitivity syndrome

  - Nevirapine: Maculopapular rash after starting drug in 25% of patients

HHV-8—a wily HIV co-pathogen

Human Herpes virus type 8 (HHV-8)—the virus associated with Kaposi's Sarcoma—was first isolated from the tissue of an AIDS patient in 1994, by a team working at Columbia University. Although generally benign, HHV-8 can lead to aggressive forms of Kaposi's sarcoma in HIV/AIDS and has been associated with a number of additional "febrile" syndromes in AIDS patients. HHV-8 is thought to be the cause of **Castleman's syndrome**, an inflammatory, lymphoma-like condition that presents with persistent fever and lymphadenopathy. HHV-8 plays an important role in **Primary effusion lymphoma (PEL),** an HHV-8 "positive" HIV-associated neoplasm that presents with unexplained ascites, pleural or pericardial effusions. When evaluating persistent fever in HIV patients, keep in mind the possibility of HHV-8, especially in patients with unexplained effusions or lymphadenopathy. Make sure the pathologist orders HHV-8 staining on any biopsy/cytology specimens—while mortality is high in patients with "lymphoma", early diagnosis with subsequent chemotherapy can be life-saving.

Here's what to do in the HIV/AIDS patient with an unexplained fever…

- **Take a careful history:** Pay special attention to the following…
  - ✓ **AIDS treatment history and last T-cell count:** Has the patient been taking their medications? Where they recently started on a new regimen (? Possibility of IRIS).
  - ✓ **PCP prophylaxis—is the patient taking the meds?** PCP is clearly a possibility in the patient with a low CD4 count who hasn't been taking their prophylaxis therapy.
  - ✓ **Place of birth and past residency:** Look for potential recurrent infections (e.g. histoplasmosis; TB) based on previous residence and risk factors
  - ✓ **Unusual exposures:** Pets, travel and unusual foods.
- **Eye examination:** Perform a dilated funduscopic exam looking for subclinical CMV retinitis
- **Check a PPD or MTB IGRA (Interferon gamma releasing assay)** in all HIV/FUO cases.
- **Chest radiograph:** Look for focal pneumonitis, diffuse infiltrates and hilar adenopathy (see above—consider bronchoscopy (or sputum induction) for PJP, AFB or fungi. √ PPD in all patients
- **√ Liver tests:** An elevated alkaline phosphatase may be clue to disseminated infection (e.g. TB, histo) or lymphoma
- **? Anemia:** Check a hemoglobin and LDH in all patients—an elevated LDH in combination with significant anemia may be a clue to underlying lymphoma or parvovirus infection. Consider a bone marrow biopsy (with culture) in those with significant findings.
- **Abdominal CT scan:** An abdominal CT scan is a "routine" part of most FUO evaluations—look for hepatosplenomegaly (MAI, MTB, histoplasmosis, lymphoma), "focal" liver lesions (Bacillary angiomatosis), and evidence of colitis (CMV, *C. difficile*)
- **Serology:** √ Serum cryptococcal antigen, urine histo antigen (in at risk pts), RPR, CMV IgG, toxoplasmosis serology.
- **Biopsy:** Obtain a **core biopsy** (or fine needle aspirate) or any large lymph node to rule out lymphoma and/or granulomatous disease. Consider a **colonoscopy** (with biopsy) in those with evidence of colitis or chronic diarrhea. Examine a **peripheral sme**ar for evidence of parasitic infection (malaria; Chaga's disease); examination of a **"buffy coat"** peripheral smear may lead to an early, rapid diagnosis of histoplasmosis (look for small inclusions in mononuclear cells).
- **Antibiotic trial:** While it is always better to "make a diagnosis" before treatment, an empiric trial of antibiotics may be appropriate, especially if the patient is deteriorating or you have a strong suspicion of a specific pathogen. In selected situations, consider the following:
  - ✓ **Pneumonia** → trial of TMP/SMX and 3rd generation cephalosporin (e.g. ceftriaxone)
  - ✓ **Diarrhea** → Obtain stool cultures and consider oral quinolone
  - ✓ **Low CD4 count** → If you are suspicious of MAI infection, obtain appropriate cultures (e.g. blood; stool AFB) and consider a trial of clarithromycin (or azithromycin) + ethambutol.
- **? Corticosteroid trial:** In patients with possible IRIS (and you have done your best to rule out underlying occult infection/lymphoma), a trial of corticosteroids may be appropriate.

Fever of unknown origin (FUO) in HIV/AIDS—what you need to know…

- AIDS-associated Fever of unknown origin (HIV-FUO) is a specific syndrome in AIDS patients defined as fever (T > 38.3°C), lasting at least 3 weeks (outpatient: 4 weeks), that remains unexplained despite 3 days of investigation.
- HIV patients with fever are more likely to have infection compared to non-AIDS FUO cases (HIV: 80% vs non-HIV: ~30%), and also more likely to have "multiple" pathogens (~10-20% of HIV cases) accounting for unexplained fever.
- The level of the CD4 count is important in evaluating FUO in HIV/AIDS patients—individuals with well controlled infection and "high" or normal CD4 counts (e.g. CD4 > 500 cells/mm3) are much more likely to have FUO due to some of the "standard" FUO causes rather than HIV-related opportunistic pathogens (e.g. MAI; CMV; PJP).
- In the United States, mycobacterial disease—especially *Mycobacterium avium-intracellulare* infection (MAI) is the most common cause of prolonged fever in the HIV/AIDS patient. In addition to fever, look for hepatosplenomegaly, anemia and chronic diarrhea. In suspect cases, obtain blood/stool AFB cultures, a bone marrow (with AFB cultures) and consider a trial of anti-MAI therapy (e.g. clarithromycin + ethambutol).
- In the developing world (or immigrant populations), *Mycobacterium tuberculosis* is more likely to account for FUO—look for evidence of pulmonary involvement (e.g. infiltrates ± hilar adenopathy) as well as infection of other organ systems (e.g. meningitis; lymph nodes).
- Despite *Pneumocystis* prophylaxis, *Pneumocystis jiroveci* (PJP) remains an important cause of prolonged fever in HIV, especially in patients with T-cell counts less than 200 cells/mm^3. Question the patient carefully about pulmonary symptoms and look for diffuse "ground glass" pulmonary infiltrates on chest radiograph or CT scan.
- CMV infection is an important cause of persistent fever in patients with advanced HIV infection—look for evidence of "target" organ presentations including visual symptoms (CMV retinitis), abdominal pain/diarrhea (CMV colitis) and nervous system complaints (neuropathy, back pain, altered mental status).
- Occult non-Hodgkin's lymphoma (NHL) is the most common neoplastic cause of HIV-FUO—look for unexplained lymphadenopathy, hepatosplenomegaly and pancytopenia. In these cases, obtain chest/abdomen CT scan looking for adenopathy or unexplained "masses"—biopsy of these lesions (along with bone marrow biopsy) may clinch the diagnosis.
- Patients recently started anti-retroviral therapy may develop "Immune reconstitution inflammatory syndrome" (IRIS), an inflammatory syndrome associated with immune response to an underlying "occult" infection. In these cases, look carefully for underlying mycobacterial, fungal (Cryptococcus) or viral disease (CMV; VZV) and consider a course of corticosteroids, provided that the opportunistic infection is also treated.
- In addition to the above conditions, keep in mind the possibility of drug fever in AIDS patients, especially fever due to "sulfa" drugs (e.g. TMP/SMX; dapsone) and rarely, anti-retroviral agents (e.g. abacavir; efavirenz; nevirapine). In most of these situations, the patient will have a concomitant rash or eosinophilia.
- In general, avoid empiric antibiotic therapy in HIV-associated FUO unless the patient presents with a clinical syndrome that points to a specific pathogen; in that situation, a response to therapy may well be diagnostic of the underlying infection.

Chapter 7

What every MD should know about antibiotics

It all seems pretty confusing, there are literally hundreds of antibiotics—including new ones being released daily—and it is difficult to keep them all straight. Try to think of them as families with each member having their own peculiar quirks. What follows is a brief overview of each family highlighting important points about their use and abuse.

1. Penicillins

Despite the passage of time, the penicillin agents remain some of the most common antimicrobials prescribed by physicians. When using these drugs, keep the following in mind:

A brief history of penicillins…

"Natural" penicillins (1940s)
Pencillin G
Phenoxymethyl PCN (PenVK)-oral

The "first" penicillin (**Penicillin G**) is still good for treatment of streptococcal infections and less common diseases such as syphilis and actinomycosis. **PenVK** (phenoxymethyl penicillin) was subsequently developed to provide adequate serum levels following *oral* administration.

Anti-staphylococcal PCNs (1950s)
Methicillin
Oxacillin/Nafcillin
Dicloxacillin (oral)

"Poor activity of PCN G against *Staph* aureus led to development of the "anti-staphylococcal penicillins" such as (**methicillin, oxacillin** and **nafcillin**). Although methicillin is no longer used (+ kidney toxicity), it survives as a laboratory "marker" to this class of agents. When "stepping down" to an oral agent, use **dicloxacillin** (250-500 Q6hr) for oral therapy.

"Gram-negative" PCNs (1950s)
Ampicillin
Amoxicillin (oral)

Ampicillin was developed as the first clinically useful "gram-negative" penicillin with activity against gram negative facultative bacilli such as *E. coli.* It retains activity against streptococci (including most enterococci), and is the drug of choice for listeria (meningitis). **Amoxicillin** has a similar spectrum but improved oral absorption compared to ampicillin.

Extended-spectrum PCNs (1970s)
Piperacillin
Ticarcillin

Known as an extended spectrum penicillin, **Piperacillin** and related drugs (e.g.**Ticarcillin)** have an even better gram-negative spectrum, including activity against organisms such as resistant *E coli, Enterobacter*—and in some cases-- *Pseudomonas aeruginosa.* They are effective against streptococci, and have considerable activity against most anaerobic pathogens. .

B-lactam/B-lactamase inhibitors (BL/BLI) (1980s)
Amoxicillin/clavulanate (Augmentin)
Ampicillin/sulbactam (Unasyn)
Piperacillin/tazobactam (Zosyn)

In an effort to "broaden" activity of "extended spectrum penicillins" , chemists combined standard penicillins with a B-lactamase "inhibitors" (BLI) such as tazobactam or clavulanic acid. These agents (BL/BLI) have improved gram-negative coverage, activity against *Staph aureus* (MSSA) and increased efficacy against intraabdominal anaerobes (including *B. fragilis*). Think of these drugs as broad-spectrum agents useful for "mixed" aerobic/anaerobic infections such as aspiration pneumonia; head/neck infection; intraabdominal infection and diabetic foot infection.

Here are a few key points about using penicillins…

- **Ampicillin:** The "original" *E.coli* drug (commonly used for urinary tract infections), about 60% of community isolates are now resistant to ampicillin—don't rely on this drug in critically ill patients unless you have a susceptibility in hand**. Amoxicillin (500 mg PO Q 6hr)** has a similar spectrum, better absorption and is the "drug of choice" when an oral penicillin is required.
- **Oxacillin/nafcillin:** The anti-staphylococcal penicillins are the "drugs of choice" for MSSA (methicillin susceptible *Staph aureus*) but *do not* have activity against methicillin-resistant *Staph aureus* (about 50% of community isolates).
- **BL/BLI agents:** These agents have "broad" activity against streptococci, *Staph aureus,* gram negative bacilli and anaerobes, an appropriate spectrum for "mixed" infection such as intra-abdominal and diabetic foot infection.
  - **Ampicillin/sulbactam** (Unasyn) is a good broad spectrum but *lacks* activity against *Pseudomonas aeruginosa* and MRSA. **Amoxicillin/clavulanic acid** (Augmentin) has similar activity and is a good drug for a "step down" oral agent.
  - **Piperacillin/tazobactam (**Zosyn) has even broader activity (~ 50% of *Peudomonas aeruginosa* isolates) but is expensive (~50-$100 per day) and is usually "overkill"—once you get a positive culture, cut back to a more selective (and cheaper) agent if possible (most patients with "community-acquired" infection really don't need *Pseudomonas* coverage!)

Watch Out!

Penicillin allergy: The main potential "downside" of penicillin therapy is allergy—especially the possibility of IgE mediated "hives" or "anaphylaxis. Before you use these agents, always ask the patient (or a close family member) about a previous history of rash or penicillin allergy. This is not a minor problem—in the United States, an estimated 250-400 patients die each year following penicillin anaphylaxis. Although many cases can be avoided by a proper history, an acute allergic reaction can occur in anyone, even in those who have previously tolerated the agent.

2. Cephalosporins

The cephalosporins are safe, reliable and are some of the most common antibiotics used in the hospital. Here is a quick way to keep the many agents in mind, thinking of them as different "generations" with successive variations in coverage:

The "Quick" Cephalosporin spectrum

Good staph/strep → Good anaerobe → ↑ GNR:+ Pneumo;+CSF → + Pseudo activity → + MRSA

1st Generation	2nd Generation	3rd Generation	4th Generation	5th Generation
Cefazolin Cephalexin (PO) Cephradine (PO) Use for cellulitis and MSSA infections	Cefotetan Cefoxitin Good for mixed infections (Intraabd; diabetic foot) c anaerobes	Cefotaxime Ceftriaxone Cefdinir(PO) Cefixime (PO) Cefpodoxime (PO) Ceftibuten (PO)	Cefepime + *P. aeruginosa* but no MRSA or anaerobe; useful for nosocomial infections	Ceftaroline + MRSA; pneumo E. coli (No Pseudo)

Here are a few key points about using these drugs…

- **Cefazolin:** This drug is quite inexpensive and has excellent strep and staph (MSSA) coverage—it remains quite useful for management of skin/soft tissue infection (except MRSA) and surgical antibiotic prophylaxis.

- **Anti-anaerobic cephalosporins:** Cefotetan and cefoxitin have the best anti-anaerobic activity of any cephaloporins—they remain good agents for "mixed" infection including intraabdominal (appendicitis; diverticulitis; cholecystitis), aspiration pneumonia (lung abscess) and "mixed" skin/soft tissue infection.
- **CNS penetration:** The 3rd and 4th generation cephalosporins (cefotaxime; ceftriaxone; cefepime) have good (~20%) CSF penetration and excellent activity against *Streptococcus pneumonia*, they are a good choice for community-acquired meningitis but they don't cover *Listeria monocytogenes* (for this you need ampicillin in selected situations).
- **GNR bacteria**: "Higher" generation cephalosporins (3rd and 4th generation) have improved GNR coverage including (in the case of cefepime) coverage against *Pseudomonas aeruginosa*; this makes cefepime a good agent for "nosocomial" gram-negative infections (e.g. nosocomial pneumonia; febrile neutropenia; complicated UTI).
- **? MRSA:** The new drug ceftaroline is the first B-lactam with activity against MRSA making it a good choice for complicated skin/soft tissue infection (50% of community staph isolates are MRSA) when patients cannot tolerate vancomycin. The drug is active against penicillin resistant *Streptococcus pneumonia* and is now licensed for community acquired pneumonia.

Tough question

Can you use cephalosporins in PCN "allergic" patient? It depends. In general, avoid cephalosporins in patients with a strong history of anaphylaxis (e.g. hives, SOB, angioedema, hypotension); however, they are generally safe in patients with a history of a "maculopapular" penicillin skin rash (more likely to be cell-mediated reaction rather than IgE). Nevertheless, always use caution when giving cephalosporins to a patient with suspected PCN allergy (10% cross- reactivity)—if necessary, give the first cephalosporin dose in monitored setting.

3. Carbapenems

These B-lactam agents have extremely broad spectrum and are generally reserved for septic patients—especially in those with hx of recent hospitalization or possible nosocomial infection. Note…they ***do not*** have MRSA activity and pending culture results, you may need to add vancomycin in a critically ill patient.

Imipenem; Doripenem, Meropenem	Broad activity including nosocomial GNR (Pseudomonas; Acinetobacter; ESBL GNR), staph/strep (but not MRSA) and excellent anerobic activity. Watch out for seizures, especially with imipenem All these agents are pretty much the same—use what hospital has on formulary.
Ertapenem	Similar to other carbapenems except for no *Pseudomonas* activity. Once daily dosing is good for home administration when treating diabetic foot infection or ESBL bugs.

Here are a few key points about using these drugs…

- **Broad-spectrum drugs for nosocomial infection:** The top three drugs on the list (imipenem; doripenem; meropenem) are essentially equivalent (with minor variations) and have broad activity against most nosocomial GNR (including Pseudomonas: Acinetobacter), staph (MSSA), strep and anaerobes. Reserve these agents for seriously ill patients with suspect nosocomial pathogens.
- **"Once a day" Ertapenem:** This agents lacks *Pseudomonas* coverage but has the advantage of once-daily dosage—patients can be sent home on the convenient dosing of one gram daily (c NL renal function).
- **What they don't cover:** Emerging carbapenem-resistant *Enterobacteriaceae* (CRE)—usually strains of *E. coli* and *K. pneumonia*—are resistant to carbapenems and require alternative agents (e.g. colistin or tigecycline). Carbapenems are also inactive against MRSA (cover these with vancomycin).

- **Toxicities:** These drugs are similar to cepahalosporins—in addition to warnings regarding penicillin toxicity, they may cause seizures, especially when used in high doses in patients with underlying renal disease (this is most common with imipenem and less common with other agents in the class).

4. Quinolones

Because of their excellent absorption (PO levels are close to IV levels), and broad spectrum (including GNRs such as *Pseudomonas aeruginosa*), these have become commonly prescribed agents, especially for urinary tract and respiratory infections. Here is a quick review of the pertinent agents…

1st Generation	2nd Generation	3rd Generation
Ciprofloxacin	Levofloxacin	Moxifloxacin/Gatifloxacin
Mainly GNR (includes Pseudomonas) 50% *Staph aureus* Poor pneumococcal coverage	Respiratory quinolone Good S. pneumonia + Atypicals (mycoplasma; legionella) + *Pseudomonas aeruginosa*	Respiratory quinolones Excellent S. pneumoniae Good GNR (No *Pseudomonas*) Fair anaerobe (Moxifloxacin)

Some key points about using the quinolones…

- **"Once" or "Twice " daily pharmacokinetics:** These drugs are often given once daily (levofloxacin; moxifloxacin) or BID (ciprofloxacin). They have excellent PO absorption—levels similar to that with IV dosing.
- **Toxicity:** Be cautious with the use of these agents in older patients or those with risk factors for prolonged QT interval (electrolyte disorders; selected drugs)—these patients are at risk for ventricular tachycardia.
- **Clinical use:** Respiratory quinolones (levo; moxi; gati) have activity against *both* pneumococcus (including PCN resistant pneumococcus) and "atypical" pathogens such as *Mycoplasma*, *Chlamydophila* and *Legionella*. Ciprofloxacin has less "gram positive" activity and is usually reserved for gram negative infection.
- **Increased resistance:** Widespread use of these drugs in the community has led to increased resistance, both among staphylococci (over 50% of strains are now resistant) and *E. coli* (~ 20-30% of strains are resistant).

5. Aminoglycosides

Because of the potential for nephro- and ototoxicity, these drugs (gentamicin; tobramycin; amikacin) have lost some of their previous favor; however, with the rise of more resistant GNRs, they are making a comeback. Here are a few key points about using these agents…

- **Pharmacokinetics:** Aminoglycosides have "concentration-dependent" killing—they are as effective (and less toxic) when given as "once-daily" dosing when compared to Q8hr dosing.
- **Activity:** These drugs are active against "facultative" gram negative bacilli such as *Enterobacteriaceae* (*E.coli; Klebsiella; Enterobacter*) and *Pseudomona aeruginosa.* In general, amikacin seems to have the "best" activity and lowest rate of resistance when compared to other members of the class (gentamcin; tobramycin).
- **Toxicity:** Be careful using these drugs in older patients and those with underlying renal insufficiency—these individuals have a greater risk for ototoxicity and nephrotoxicity. Use aminoglycosides require serum monitoring (work with your pharmacist) and auditory monitoring (for patients receiving more prolonged therapy).
- **An antibiotic "combo"?** These agents have some gram positive activity and are useful as part of a "synergistic" regimen against endocarditis with enterococci, (AG + ampicillin), streptococci (AG + PCN G) and staphylococci (AG + oxacillin).

With increasing gram negative resistance, aminoglycosides are making a comeback—their use may well be necessary for patients with nosocomial GNR infection, provided organisms are demonstrated susceptible.

6. Macrolides

These agents have a long history of safety and tolerability making them excellent drugs for outpatient therapy. Their absorption is not always ideal (approximately 30% following oral administration) but the ability of the drug to concentrate within macrophages extends their potency. The following drugs are currently available:

Erythromycin	Still good for mild to moderate respiratory infection but tough to stomach
Clarithromycin	Similar to erythromycin (but better *H. influenza* coverage) Dosed twice daily—watch out for QT prolongation and drug interactions
Azithromycin	Once daily (Qday) dosing with high concentrations in macrophages *No* significant drug interactions or QT prolongation

Keep in mind the following key points…

- **Antibacterial spectrum:** These agents have primary activity against respiratory pathogens, including pneumococcus and "atypical" pneumonia organisms (*Mycoplasma, Chlamydophila, Legionella*). Both clarithromycin and azithromycin can be used for treatment of MAI (*Mycobacterium avium intracellulare*) infection.
- **QT prolongation:** Whenever using clarithromycin, be especially careful about QT interactions since these may lead to ventricular arrhythmias (this is much less a problem with azithromycin; however, always use caution in patients with a prolonged QT interval or meds/conditions that could lead to one).
- **Resistance:** There is increasing resistance to macrolides among pneumococcus and Group A streptococci (about 20%); be cautious about relying on these agents as sole agents in patients with life-threatening infections.

7. Anti-anaerobe agents

There are several agents that are especially active against anaerobes—these drugs are often valuable in patients with "mixed" (anaerobes + other bugs) infections such as aspiration pneumonia (lung abscess), intraabdominal and diabetic foot infection. Here are some key points about selected drugs:

Clindamycin	This drug is active against intestinal anaerobes , including *Bacteroides fragilis* and anaerobic strep For convenience, the drug can be dosed at 900 mg IV Q 8hr; oral dosing is 450 to 600 mg PO Q 6 hr. The main side effects of the drug are rash and *C. difficile* colitis (warn patients about diarrhea).
Metronidazole	Remains highly active against "strict" anaerobes such as *Bacteroides* and clostridial species; the drug has *poor* activity against microaerophilic anaerobes such as *Actinomyces*, *Propionobacteria* and streptococci—patients with "mixed" anaerobic infections require an additional agent (PCN or cephalosporin) to cover the "metronidazole-resistant" bacteria.
Cefoxitan	Along with cefotetan, these 2nd generation cephalosporins have the best anti-anaerobic activity
Amp/sulbactam	This drug (and piperacillin/tazobactam) also have excellent anti-anaerobic activity and are useful in mixed anaerobic infection.

Note: When using a BL/BLI drug (piperacillin/tazobactam; ampicillin/sulbactam), there is generally *no need* to add metronidazole for anaerobic coverage unless you need to treat *C. difficile* colitis.

8. Some "Old" standbys

As times change, sometimes "old" drugs make a comeback. Most of these agents are relatively inexpensive and non-toxic. Here are some agents that remain quite useful in selected situations…

Doxycycline	This drug has activity against *Strep pneumonia* (80% of isolates) and *Mycoplasma*—it is a cheap and effective agent for young patients with bronchitis and atypical pneumonias. Doxycycline also has activity against methicillin resistant *Staphylococcus aureus*—use it in suspected MRSA infection but remember that the drug has very little activity against group A streptococci
Minocycline	A drug with a long track record for treatment of acne, minocycline has made a comeback since it has good in vitro activity against MRSA. Minocycline has some unusual toxicities—patients may develop dizziness and rare patients develop a "lupus-like" syndrome (pneumonitis) on the drug.
Nitrofurantoin	Nitrofurantoin has excellent activity against community acquired *E. coli* (90%+ susceptible). It is considered a urinary "anti-septic"—it is useful for cystitis but shouldn't be used for serious invasive gram negative infection such as pyelonephritis. Main toxicities → Pneumonitis or peripheral neuropathy with prolonged Rx. Rare methemoglobinemia
Colistin	This drug is a membrane "detergent" , first used in the early 60s for treatment of GNR infections The drug had a relatively high rate (30%) of nephrotoxicity and fell out of favor when other agents (aminoglycosides) became available; however, it's not made a comeback as a treatment for highly resistant GNR infection (bugs resistant to all standard agents may remain susceptible to colistin).

Keep in mind the following key points…

- **Tick-borne infection:** Doxycycline is the drug of choice for many unusual "zoonotic" or tick-borne infections such as typhus, Rocky Mountain spotted fever, tularemia, plague, leptospirosis and Lyme disease. Think of adding the agent in critically ill patients with a potential animal exposure (hiking; camping; farms) who fail to respond to standard agents.
- **MRSA:** In addition to their use for respiratory pathogens (e.g. doxycycline for *Mycoplasma pneumonia* and *Chlamydophila*), both minocycline and doxycycline often have activity against MRSA and can be used for mild-moderate MRSA infection.
- **Nitrofurantoin:** This urinary tract agent is reserved for patients with cystitis—it cannot be relied upon for patients with pyelonephritis or more serious urinary tract infections. The drug often has excellent activity against *E. coli* and has the added benefit of safety during pregnancy.
- **Colistin:** A "drug from the past", this parenteral agent may be lifesaving in patients with highly resistant, hospital acquired gram negative infections (e.g. CRE; MDR GNR).

2. "Fancy" New Agents:

We've seen the introduction of a number of new agents during the past decade, including daptomycin, linezolid and tigecycline. Although these drugs tend to be fairly expensive ($50-$200 per day), their activity against "resistant" pathogens—and ease of administration—make them potentially "lifesaving" agents in selected situations. .

Daptomycin	This is a "once-a-day" parenteral drug with excellent activity against resistant gram positives such as methicillin-resistant *Staph aureus* (MRSA) and vancomycin-resistant enterococcus (VRE). Start with a 4 mg/kg IV dose (you can push the dose higher in more serious infections) and monitor for muscle "toxicity" (check a baseline CK and ask the patient about myalgias).
Linezolid	This is another agent "gram positive" drug active against resistant gram-positive organisms such as MRSA and VRE. The drug is quite expensive ($200 a day for two pills!) but available in a well-absorbed oral form (600 mg PO/IV q 12 hours) that may permit earlier hospital dischargeThe drug acts as an MAO-inhibitor so be careful about drug interactions that might lead to a "serotonin syndrome" (e.g. SSRI, anti-depressants; pseudoephedrine; meperidine). With more prolonged use (≥ 2 weeks) the drug can cause thrombocytopenia and optic neuropathy.

Tigecycline	This is a new tetracycline (related to minocycline) with activity against gram positives (including VRE and MRSA), resistant gram negatives (ESBL producing *E. coli*/*Klebsiella* sp; *Acinetobacter*) and anaerobes. It has poor activity against selective GNRs (*Pseudomonas* and *Proteus* sp) but is useful in patients with mild to moderately severe "mixed" (aerobic/anaerobic) intraabdominal and skin/soft tissue infection (e.g. diabetic foot infections). The drug has relatively few adverse effects; however, significant nausea/vomiting is seen in up to 30% of patients.

Here are a few key points about using these drugs…

- **MRSA pneumonia:** *Avoid* use of daptomycin in patients with MRSA pneumonia—pulmonary phospholipids absorb the drug and cause a higher failure rate when compared to other MRSA agents.
- **Tuberculosis:** In addition to its' use for gram-positive pathogens, linezolid has activity against *Mycobacterium tuberculosis* and is an important agent in the management of drug-resistant TB.
- **Tigecycline warning:** Although tigecycline may be life-saving in patients with resistant pathogens, use of the drug has been associated with a higher mortality rate in bacteremic patients, possibly due to the "static"—rather than "cidal" action of the agent.

When thinking about antibiotics, keep in mind the following…

- Although penicillin agents remain excellent drugs against a wide variety of pathogens, always ask about previous allergy prior to administering them—unexpected IgE- mediated anaphylaxis remains a serious, and potentially life-threatening—complication of the class.
- The anti-staphylococcal penicillins (oxacillin; nafcillin) as well as 1st generation cephalosporins (e.g. cefazolin) have excellent activity against methicillin-susceptible *Staph aureus* (MSSA) but are ineffective against the increasingly common methicillin resistant *Staph aurues* (MRSA) strains.
- Extended spectrum penicillins (e.g. piperacillin) have broad gram-negative activity, including activity against nosocomial gram negatives such as *Pseudomonas aeruginosa*. Combination of these drugs with a beta-lactamase inhibitor (BL/BLI drugs) broadens activity to include staphylococci (MSSA) and anaerobes. Use these agents (piperacillin/tazobactam; ampicillin/sulbactam) for coverage of "mixed" aerobic-anaerobic infection such as intraabdominal abscess, aspiration pneumonia and diabetic foot infection.
- First generation cephalosporins (cefazolin; cephalexin) have good activity against staphylococci, streptococci making them good agents for "cellulitis" (provided that MRSA is not present) and milder community acquired urinary tract infection (*E.* coli). Ceftaroline—a "5th" generation cephalosporin—is the first agent in this class with good activity against methicillin-resistant *Staph aureus* (MRSA) as well as drug resistant *Streptococcus pneumoniae.*
- Second generation cephalosporins such as cefoxitin and cefotetan add anaerobic coverage (and slightly better gram negative culture) to the spectrum of first generation cepahalosporins; they are useful for treatment of "mixed" aerobic-anaerobic infection such as intraabdominal abscess and diabetic foot infection.
- The "third" generation cepahalosporins such as cefotaxime and ceftriaxone have improved gram negative coverage (except for *Pseudomonas*) and good activity against *Streptococcus pneumoniae* and most *Enterobacteriaceae* (*E. coli; Klebsiella*). In addition they have good CSF penetration, making them a good choice for management of CNS infection with susceptible (pneumococcus) organisms.

- Cefepime is a “fourth” generation cephalosporin with good activity against hospital-acquired gram negatives (including *Pseudomonas aeruginosa*), gram positives (MSSA; strep) but has poor activity against anerobes and MRSA.

- Carbapenems (imipenem; doripenem; meropenem) are broad spectrum agents with activity against nosocomial pathogens such as *Pseudomonas aeruginosa, Acinetobacter* and ESBL producing gram negative bacilli (ESBL *E. coli* and *K. pneumonia*). Ertapenem also has “broad” antibacterial activity (except for Pseudomonas aeruginosa), and has the advantage of once-daily administration.

- Ciprofloxacin is primarily a “gram-negative” drug—although there is increasing resistance, it has excellent oral absorption and reliable activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa* (60% of strains). “Respiratory quinolones” such as levofloxacin and moxifloxacin are active against both “typical” (*Strep pneumonia*) and “atypical” (*Mycoplasma; Legionella; Chlamydophila*) pathogens, making them a good choice for community-acquired pneumonia and respiratory infection.

- Aminoglycosides have primary activity against gram-negative pathogens such as *Enterobacteriaceae* and *Pseudomonas*—they must be used with caution (monitoring required) because of problems with nephro- and oto-toxicity.

- Macrolides have activity against both pneumococci and “atypical “ pathogens (e.g. *Mycoplasma; Legionella* species), making them a good choice for non-severe respiratory infections. Be cautious about use of these drugs in patients with underlying cardiac conditions—prolongation of the QT interval (especially with clarithromycin) can lead to life-threatening ventricular tachycardia (e.g. *torsades de* pointes).

- Doxycycline remains an important agent for management of zoonotic and tick-borne infections such as plague, tularemia, psittacosis, typhus and spirochetal disease (leptospirosis; Lyme disease). Both doxycycline and minocycline also have excellent activity against MRSA and can be sued for outpatient treatment of staphylococcal skin and soft tissue infection.

- Anti-anerobe agents include clindamycin, metronidazole, the “beta-lactamase inhibitor” penicillins (e.g. piperacillin/tazobactam; ampicillin/sulbactam; amoxicillin/clavulanic acid). These agents are often useful for patients with “mixed” aerobic-anaerobic infections such as intraabdominal abscess (diverticulitis; appendicitis; cholecystitis), diabetic foot infection and lung abscess/aspiration pneumonia.

- Newer “gram-positive” antibiotics including daptomycin (IV) and linezolid (IV and PO)—because of their cost, these agents are generally reserved for infections with “resistant” gram positives such as MRSA, VRE and drug-resistant *Strep pneumonia*.

- Tigecycline—a broad spectrum tetracycline—has good activity against anaerobes, resistant gram positives (MRSA; VRE) and some resistant gram negative bacilli (e.g. *Acinetobacter;* ESBL *E.*coli). This drug is often used employed in “mixed” aerobic-anaerobic infections where resistant pathogens are present or other agents (B-lactams) are contraindicated because of resistance or allergy.

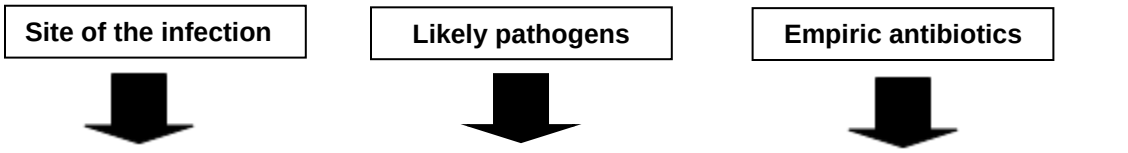
Chapter 8

Empiric antibiotic therapy—a brief primer for housestaff

You are working in the emergency room or on the wards. A patient "spikes" a fever and you think they are infected…how do you go about choosing the "right" empiric antibiotic therapy? What follows is a brief summary of an approach I've found effective. Use the "antibiotic grid" (at the end of this section) and ask yourself the following questions…

1. What is the site of the suspected infection?

The first step is to try to define the possible site of infection—while not always possible, if the patient has a clear "site" of infection, you can narrow down the possible pathogens and better choose empiric therapy. In most cases, a brief history, physical exam and ancillary studies (radiology) will allow you to determine the most likely site of the infection. From here—using your knowledge of the most likely "pathogens" at selected sites (see tables in next chapter or appendix)—you can choose the antibiotics most likely to cover the infection.



Site	Microbiology	Suggested antibiotics
Community-acquired pneumonia (Mild-moderate severity)	*Streptococcus pneumoniae, Mycoplasma pneumoniae Chlamydia pneumoniae*	Ceftriaxone (1 gm IV) + doxycycline (PO/IV) or macrolide (PO) OR Levofloxacin 750 PO Qday

Unknown source: Sometimes patients present with "sepsis" and no obvious localizing site or organ. Common bacterial organisms in this scenario are *Streptococcus pneumoniae, Staphylococcus aureus, E. coli* and rarely, *Neisseria meningiditis.* As outlined in the antibiotic grid, a broad spectrum antibiotic "cocktail" (ceftriaxone + vancomycin) should prove adequate pending culture results.

2. Immediate versus delayed treatment—can you wait?

This is a judgment call that depends upon the likely diagnosis and how sick the patient appears to be. Not all febrile patients immediately require antibiotics; however, prompt therapy (within an hour of the initial evaluation is especially important in the following situations:

- **"Toxic", septic patients:** Patients that look "toxic"—or appear septic (see box)—generally merit "immediate" (within 1-2 hrs.) empiric antibiotic therapy. "Triggers" for immeidate treatment include physical findings (hypotension, fever > 40 °C, confusion), laboratory results (WBC > 15K; lactic acidosis) and "severe" toxicity (patient appears critically ill).

- **Immuncompromised patients:** Patients with underlying immune defects due to neutropenia, chemotherapy, corticosteroids and various forms of immunodeficiency (e.g. HIV/AIDS; hypogammaglobulinemia) have a higher mortality rate with "sepsis"—have a lower threshold in these cases for immediate antibiotic therapy.
- **Complicated medical problems:** Those with complicated underlying medical problems (cancer, congestive heart failure, renal failure) also demonstrate a lower tolerance for bacteremia/severe infection—start empiric therapy when patients have "high" f ever (Temp ≥ 38.7 ° C [102 °F), especially if accompanied by shaking chills, leukocytosis or lactic acidosis.

Non-infectious fever: While we are often "quick" to start antibiotics, remember that not ot all fever is associated with infection—keep in mind the possibility of non-infectious conditions such as pulmonary emboli, metastatic cancer and drug fever. In these situations, it may be perfectly reasonable to withhold antibiotic therapy until culture results are available—especially if patients "look good" and have relatively low grade temperatures (< 38.7° C).

3. Oral versus parenteral therapy—what's best?

Once you have made a decision to treat the patient, you have to decide on the best "route" of therapy—most hospitalized patients are best treated (initially) with intravenous antibiotic. In general, parenteral therapy is best in the following situations…

- **Septic patients:** Patients who appear "septic" (e.g. high fever, toxic appearance, rigors, hypotension, WBC > 15K), generally require immediate IV antibiotic therapy.
- **Nausea/vomiting/GI disease:** Patients with persistent nausea and vomiting—or those with underlying gastrointestinal disease where drug absorption is a problem—should receive parenteral treatment until the initial response is assured. Oral therapy may well be reasonable but make sure the patient can take the medication without vomiting it up.

Clinical Pearl

Oral therapy: "Non-toxic" patients can often be treated with oral antibiotics. Certain agents (quinolones, metronidazole, clindamycin) have excellent oral absorption and may be perfectly appropriate for the "less sick", non-septic, patient. Following oral administration, some drugs (e.g. quinolones) provide serum levels that are equivalent to those seen after parenteral administration.

.

4. Is there a possibility of resistant organisms?

Has the patient been recently hospitalized within the past 3-6 months? Have they recently taken a course of antibiotics? If the answer to these questions is "yes", there is a possibility that they might have a more "resistant" nosocomial pathogen such as MRSA or a resistant gram negative rod. In these situations, "broader" antibiotic coverage—with a carbapenem, aminoglycoside or BL/BLI drug (piperacillin/tazobactam) may be appropriate until culture results are available.

With regard to "resistant" bacteria, keep in mind the following…

- ***Pseudomonas aeruginosa*** is an uncommon cause of community-acquired infections unless the patient has specific risk factors such as recent hospitalization, nursing home residence or specific immune defects (e.g. neutropenia).
- **MRSA (methicillin-resistant *Staph aureus*)** now accounts for close to *50%* community-acquired staphylococcal isolates—include an antibiotic active against MRSA (e.g. vancomycin) in seriously ill patients with suspected staphylococcal infection.

- **ESBL** organisms are common gram-negative bacilli (*E coli; Klebsiella* sp) with resistance to 3rd generation cephalosporins (e.g. ceftriaxone; cefotaxime) secondary to an extended spectrum B-lactamase that confers resistance to 3rd generation cephalosporins. Infections with these bugs usually require a carbapenem such as imipenem, doripenem or meropenem.
- **CRE** (Carbapenemase-resistant *Enterobacteriaceae*) organisms (usually *E. coli* and *Klebsiella* species) are mostly hospital-acquired and resistant to carbapenems—although there may be a significant mortality (in part due to the patient's underlying medical problems), they may be treated with colistin or polymyxin.

Again, unless the patient has been recently hospitalized or treated with antibiotics, these bugs (except for MRSA) are uncommon in community-acquired infections.

5. Does the patient have any drug allergies?

Ask the patient about previous history of drug allergy—a history of anaphylaxis to a B-lactam antibiotic (e.g. penicillins; cephalosporins) is especially important since an IgE mediated immediate hypersensitivity reaction could well be life-threatening. Keep in mind the following…

- **Anaphylaxis:** Ask about a history of hives, tongue swelling, difficulty breathing or hypotension following drug administration—these symptoms suggest an IgE mediated reaction.
- **? Cephalosporins:** Although they are often safe, avoid cephalosporins in patients with a history of an acute, severe anaphylactic reaction to penicillins.

If you are uncertain about allergy and the safety of a specific antibiotic, make sure the patient receives the agent in a monitored setting with immediate access to a "crash cart".

6. When choosing a drug, are there any special considerations?

Not so fast…there are several additional factors that should help determine antibiotic choice and dosing:

- **Renal dysfunction:** Most agents require altered dosing in patients with underlying renal dysfunction. In general, try to avoid nephrotoxic agents (e.g. aminoglycosides, amphotericin B) in individuals with renal insufficiency.
- **Drug interactions:** Check the patient's medication list to make sure there will be no adverse drug interactions with the chosen antibiotic. Selected drugs (e.g. coumadin) are notorious for drug interactions (both increased and decreased levels, depending upon the agent); likewise, agents such as rifampin, azoles and macrolides are also well know for drug interactions.
- **Convenience, ease of administration and cost:** In the current health care climate (increasing needs; limited resources) we always have to strive for more cost-effective therapy. When choosing antibiotic therapy, keep in mind the following:
  - ✓ **Once-daily administration:** Whenever possible, use drugs that can be administered once or twice daily (e.g. ceftriaxone, aminoglycosides, quinolones)—this saves nursing time and is likely to be more cost effective. Drugs such as piperacillin/tazobactam—while effective for empiric therapy—are quite costly when you consider the need for multiple dosing.
  - ✓ **New agents vs. "old standbys":** In most situations, older, generic drugs are perfectly adequate for most infections. Newer, recently released drugs (these are ones usually heavily promoted by pharmaceutical representatives) tend to be expensive (usually between $50 to $150 per day!) and may not be any better than standard, generic agents.

- ✓ **Oral antibiotics:** In most situations, oral antibiotics are cheaper than parenteral medication—once a patient has responded to IV medications, whenever possible (see below) switch to oral agents with good PO absorption.

A checklist for empiric antibiotic therapy…

When faced with a febrile patient, use the following checklist to help decide the best, initial empirical antibiotic therapy:

- ❑ **Identify the site of infection:** This if the first key step in making a decision on empiric antibiotic therapy—if you can identify the likely "site", you've got a better chance of choosing appropriate therapy.
- ❑ **Consider site-specific pathogens:** With most infectious disease conditions, the list of pathogens stays pretty much the same from year to year.
- ❑ **Could there be resistant pathogens?** Has the patient been recently hospitalized or received any antibiotics within the past few months? The answer to this question alerts you to the possibility of more resistant pathogens (e.g. MRSA, multi-drug resistant GNRs) seen in nosocomial infection.
- ❑ **How sick is the patient?** This question helps you decide where to send the patient (ward vs ICU) and the route of treatment (Intravenous vs oral therapy). For the hospitalized patient, initial parenteral therapy is almost always mandatory in the critically ill individual (sepsis; hypotension) or those with significant nausea and vomiting.
- ❑ **Could the patient have a non-infectious cause of fever?** While we are quick to start antibiotics on the febrile patient, keep in mind the possibility of a non-infectious cause of fever—in such individuals, inappropriate antibiotics could prove harmful (e.g. increased bacterial resistance; antimicrobial toxicity; C. difficile infection).
- ❑ **Choose empiric antibiotics** based on the likely "site" of the infection and empiric antibiotic grid (see appendix)
- ❑ **? Antibiotic allergy:** *Always* ask the patient (or the patient's family members) about a history of drug allergy, especially to common offenders such as B-lactam agents (Penicillins; cephalosporins) and sulfa drugs.
- ❑ **With regard to antibiotic dosing, keep in mind** the following…
  - √ **Renal dysfunction:** If your antibiotic choice is renally excreted, make sure you have made adjustments for any underlying renal insufficiency.
  - √ **Potential drug interactions:** Review the patient's "med" list and make sure there are no potential serious drug interactions.
  - √ **Cost/convenience considerations:** Once daily or BID administration is generally cheaper than Q 4-6 hour dosing. Whenever possible, try to avoid "expensive" parenteral agents (~ $75-$100 per day) except in special circumstances where less expensive, "generic" agents can't be given.
- ❑ **Reevaluate the patient at 24-48 hours—**if cultures reveal a single pathogen, it may well be possible to narrow therapy to a more specific, selective agent.

Empiric antibiotic therapy—what you need to know…

- Use the initial history and physical examination to identify the suspected "site" of the infection—this will allow you to determine the likely pathogens and the most appropriate empiric antibiotic therapy.
- Administer "immediate" (vs. delayed) empiric antibiotic therapy in severely ill patients (e.g. "toxic", septic, hypotensive) and those with moderate-severe immunodeficiency syndromes (neutropenia; HIV/AIDS; chemotherapy).
- Consider immediate therapy in patients with "complicated" underlying medical problems such as CHF, COPD and renal failure— these individuals have less "reserve" and are less likely to tolerate an extended delay in treatment.
- In the febrile patient, always keep in mind the possibility of "non-infectious" cause of fever—if stable, these individuals may be able to forgo immediate therapy until culture results and additional studies are available.
- Non-infectious conditions that may cause fever include vascular events (pulmonary embolism; myocardial infarction), drug fever (and drug withdrawal) and fever associated with neoplastic or rheumatological disease (lupus, temporal arteritis, vasculitis).
- In the severely ill patient, administer parenteral therapy until the patient is clinically stabilized; this ensures that the patient attains adequate antibiotic levels at the most critical time in the case.
- Initial oral therapy may well be appropriate, provided that the patient is clinically stable (not "septic" or hypotensive) and is able to take oral medications (does not have significant nausea/vomiting) .
- Always ask the patient about recent (within the past 3 months) hospitalization or antibiotic use—an "affirmative" answer raises the possibility of more resistant pathogens that could influence the choice of empiric therapy.
- Before you give an antibiotic, always ask about any drug allergies—in many cases, a careful history will help you avoid penicillin anaphylaxis, the most common severe allergy.
- Additional considerations regarding antibiotic choice include: 1). Renal failure (need to dose adjust the drug), 2). Drug interactions (especially with agents such as warfarin) and 3). Cost considerations (whenever possible use a less expensive "generic" drug versus an expensive "brand" agent).
- Reevaluate your antibiotic selection 24-48 hours after the start of therapy—at this time you may have additional information (e.g. culture results) that may allow you to narrow therapy.

Chapter 9

Using the antibiotic "grid" …choosing empiric therapy

The previous chapter gives you an idea of some of the considerations that come into play when choosing an antibiotic—the following section outlines the rationale behind "site specific" empiric antimicrobial therapy. After you've identified a potential infection site, use the "antibiotic grid" to choose the initial empiric antibiotic therapy…

A. CNS infection

True "bacterial" CNS infections are uncommon, but fall into the "Don't want to miss" category. In a patient with suspect meningitis (fever with headache, meningismus and an abnormal spinal fluid), empiric antimicrobial therapy is indicated until additional studies are available.

CNS Infections		
Site	**Microbiology**	**Suggested antibiotics**
Meningitis	*S. pneumoniae* (? PCN resistance†) *N. meningiditis* *Listeria monocytogenes* (Risk: age>50; steroids, subacute, summer)	Ceftriaxone + Vancomycin (Add ampicillin if *Listeria* risk factors or pt. immunocompromised)
Brain abscess	Streptococci + anaerobes	Ceftriaxone + metronidazole

- ✓ ***Streptococcus pneumoniae*** is the most likely pathogen for "community acquired**"** bacterial meningitis in adults. Most strains are susceptible to ceftriaxone; however, until cultures (and bacterial susceptibilities) are available, experts recommend addition of vancomycin to cover for the uncommon "highly-resistant" strains pneumococcal strains (MIC $\geq$ 1 ug/ml).
- ✓ **Meningococcal disease** (*Neisseria meningiditis*) is also a concern—especially among younger individuals living, playing or working in crowded conditions (e.g. college students or military recruits in dormitories; sports teams; concert/nightclub attendance) that increases the likelihood of epidemic transmission. In the United States, these organisms remain quite susceptible to B-lactam agents such as penicillin G and ceftriaxone.
- ✓ ***Listeria monocytogenes*****,** a food-borne pathogen, is uncommon but remains a special concern in immunocompromised patients, especially individuals on drugs (corticosteroids) that suppress cell mediated immunity. Consider adding ampicillin to the regimen in the following situations…
  - ➢ **Cell-mediated immunity defects**: Patients on medications (e.g. corticosteroids) or with conditions (e.g. lymphoma) that impair cell mediated immunity.
  - ➢ **Extremes of age:** Both neonates—and older individuals (> age 50)— have a higher risk of listeriosis; empiric coverage is generally indicated unless there is another clear etiology.
  - ➢ **"Summer" meningitis:** Listeriosis is a food-borne infection and more common during summer months.

- **"Subacute" presentation:** Compared to pneumococcal meningitis, patients with *Listeria* meningitis are more likely to have a subacute illness (over several days) and present with ataxia and myoclonic jerks.

✓ **Brain abscess:** Dental abscess and gingival disease (periodontitis) are the most common source of pyogenic brain abscess. Infection with "single" organisms—or "multiple" mixed bugs—including viridans streptococci and oral anaerobes (anaerobic streptococci; *Actinomyces* species; *Porphyromonas*; *Fusobacterium* species) are seen in this situation. If your patient has focal neurological findings—or a "focal" lesion on CT/MRI—consider a pyogenic brain abscess and administer "broad-spectrum" coverage (ceftriaxone + metronidazole) until the situation is clearer.

B. Pneumonia

Community acquired pneumonia is divided into several categories depending upon severity (mild/moderate vs. severe), likely etiology (aspiration; drug use) and the likelihood of recent hospitalization (e.g. Healthcare associated pneumonia). Despite widespread use of pneumococcal vaccine, *Streptococcus pneumonia* remains the most common diagnosed cause of community-acquired pneumonia (CAP), followed by "atypical" pathogens such as *Mycoplasma* or *Chlamydophilia.*

Pneumonia		
Site	**Microbiology**	**Suggested antibiotics**
Community-acquired (Mild-moderate severity)	*Streptococcus pneumoniae,* *Mycoplasma pneumoniae* *Chlamydia pneumophila*	Ceftriaxone (1 gm IV) + doxycycline (PO/IV) or macrolide (PO) OR Levofloxacin 750 PO Qday
Community-acquired (Severe-ICU)	Above pathogens + CA-MRSA *Legionella pneumophila*	Ceftriaxone (2 gm) + azithromycin (IV) + vancomycin Or Levofloxacin 750 mg IV
Aspiration/ANO$_2$	Oral anaerobes	Clindamycin *Or* Cefoxitin Or Ceftriaxone + metronidazole *Or* Ampicillin/sulbactam *Or* Piperacillin/tazobactam
Intravenous drug use	*Staphylococcus aureus*	Ceftriaxone + vancomycin*
Healthcare-associated (Nosocomial and ventilator)		
< 4 days hosp.	CAP pathogens	Rx Community-acquired pneumonia (see above)
≥ 4 days hosp.	Resistant GNR + S. aureus (MSSA and MRSA)	Pip/taz +vancomycin (Add Amikacin or carbapenem if severe sepsis)
* If patient has methicillin susceptible *Staph aureus,* can switch to B-lactam agent (oxacillin nafcillin or 1st generation cephalosporin)		

√ **Community-acquired pneumonia (CAP):** Although most CAP studies identify pathogen in only 50-75% of cases, research suggests that three pathogens (e.g. *Sreptococcus pneumoniae, Mycoplasma pneumoniae* and *Chlamydia pneumophila*) account for the lion's share of cases.

√ **Severe CAP:** Pneumococcus remains the most common cause of "severe" community acquired pneumonia; with a reduction of "atypical" pathogens such as *Mycoplasma* and *Chlamydophila pneumoniae.* In this situation,

Staphylococcus aureus (community-acquired MSSA and MRSA), gram-negatives (*Klebsiella pneumoniae*) and *Legionella pneumophila* become increasingly important considerations.

√ **Healthcare-associated pneumonia:** Infections acquired early in admission (< 4 days) are usually related to the "standard" CAP pathogens such as pneumococcus—infections acquired later (≥ 4 days) are more likely to include "hospital flora" pathogens such as gram negatives (*Enterobacteriaceae;Pseudomonas aeruginosa*) or *Staphylococcus aureus* (MSSA; MRSA).

√ **Other pathogens:** Specific risk factors raise the possibility of other pathogens. Patients with **lung abscess** and/or **aspiration** (loss of consciousness; history of seizure; alcohol or drug intoxication) have a higher incidence of anaerobic infection and may require addition of metronidazole or clindamycin to the regimen. *Staphylococcus aureus* (both MSSA and MRSA) is a special problem in **intravenous drug users**—in this situation, add staphylococcal coverage (e.g. vancomycin) until you can rule out infection with MRSA.

C. Intraabdominal infection

Because of the nature of the intestinal microflora, intraabdominal infections usually contain a mixture of gram negatives, streptococci and strict anaerobes (e.g. *Bacteroides fragilis*). Antibiotic therapy needs to be relatively "broad" to cover the "mixed" infection seen in these cases.

Intraabdominal infection		
Site	**Microbiology**	**Suggested antibiotics**
Local GI infection (Appy/chole/divertic)	E. coli, strep, anaerobes	Cefotetan (2 gm IV q 12 hr) *or* Cefoxitin (2 gm IV Q 6 hr) *or* Ceftriaxone + metronidazole
Abdominal sepsis (peritonitis;shock)	*E. coli*, enterococci, anaerobes	Gentamicin + Pip/taz or Gentamicin + amp + metronidazole
Pancreatitis (severe)	GNR + streptococci	Imipenem
SBP (peritonitis)	GNR, *S. pneumoniae*	Ceftriaxone (2 gm IV Q 24 hr)
Diarrhea	*Salmonella, Shigella, Campylobacter*	Ciprofloxacin PO or IV

√ **Intraabdominal "sepsis** generally requires coverage for mixed aerobic-anaerobic bacteria including facultative anaerobic gram negatives (e.g. *E. coli; Klebsiella*), streptococci and strict anaerobes (e.g. *Bacteroides, Fusobacterium, Clostridia* species).

√ **"Severe" intraabdominal sepsis**, includes patients with severe peritonitis and those with intraabdominal infection requiring ICU admission. Since many of these cases may acquire hospital "flora", add an anti-pseudomonal antibiotic (e.g. aminoglycoside; quinolone; carbapenem) until culture results are available.

√ **Pancreatitis:** In general, "standard" cases of pancreatitis (mild-moderate illness) on a general medicine ward *do not* require antibiotic coverage—patients with "severe" pancreatitis (e.g. "septic"; + pancreatic necrosis on CT scan) or those with evidence of a pancreatic abscess should receive broad coverage with a carbapenem (e.g. imipenem).

√ **Diarrhea:** Patients admitted with enteric fever type syndromes (e.g. fever, diarrhea, abdominal pain/distension) have ahigher incidence of *Shigella, Salmonella* or *Campylobacter* and are more likely to benefit from quinolone therapy. When in doubt, cover with ceftriaxone + metronidazole until stool cultures are available.

D. Urinary tract/GYN infection

Gram negative bacilli (*Enterobacteriaceae*) are the most common pathogens in urinary tract infection, along with occasional cases of enterococcal infection, especially in older males. The grid also makes the important distinction between "complicated" and "uncomplicated" infections—patients with "complicated" infection are more likely to have resistant pathogens.

Urinary tract Infections including PID		
Site	**Microbiology**	**Suggested antibiotics**
Pyelonephritis (uncomplicated)	GNR (*E. coli*)	Ceftriaxone (1 gm IV Q day)
Pyelonephritis (complicated) e.g. foley, instrumentation,males, underlying disease	GNR + enterococci	Gentamicin + ampicillin (Consider carbapenem in patient withsevere sepsis/septic shock)
Prostatitis	GNR + enterococci	Gentamicin OR Cipro + ampicillin
Pelvic Inflammatory Disease	GC, *Chlamydia*, mixed infection	Cefotetan + doxycycline (IV/PO)*
* May also use single dose azithromycin (1 gram PO) for coverage of Chlamydia species		

√ **Pyelonephritis:** This infection is usually seen in relatively young women and is most commonly due to community-acquired *E.coli.* These organisms are almost always susceptible to a 3rd generation cephalosporin (e.g. ceftriaxone); however, keep in mind more resistant pathogens if the patient has been previously treated with the drug or been admitted to the hospital (increases risk for resistant nosocomial gram negative bacilli).

√ **Complicated UTI:** This suggests urinary tract infection (usually pyelonephritis) in patients with indwelling hardware (e.g. Foley catheter; urinary stent), males (usually older individuals with some degree of urinary tract obstruction) and individuals with other "complicating" factors (e.g. GU cancer, stones etc.). In these cases, you are more likely to see resistant GNRs (e.g *Pseudomonas*) or enterococci (especi*ally males).

√ **Pelvic Inflammatory Disease (PID):** Pelvic inflammatory disease is usually secondary to sexually transmitted pathogens (e.g. *Neisseria gonorrhea*, *Chlamydia* species) or mixed aerobic/anaerobic infection.

E. Skin/soft tissue infection

Gram positive organisms—especially staphylococcal and streptococcal species—predominate in "cellulitis" and related soft tissue infections. In the current era, the role of MRSA (methicillin resistant *Staphylococcus aureus*) is an important consideration—initial empiric coverage for this organism is especially important for those with "focal" skin infection (e.g. boils, carbuncles) or "purulent" cellulitis ("culturable" pus actually present). Most routine, "simple" cases of cellulitis are due to streptococcal species and generally do not require MRSA coverage.

Soft Tissue Infection		
Site	**Microbiology**	**Suggested antibiotics**
Cellulitis*	Grp A streptococci, *S. aureus*	Cefazolin (+clindamycin in nec fasc)
Cellulitis with skin abscess *	*S. aureus* (MRSA)	IV Vancomycin or Clindamycin Outpt: TMP/SMX (2 DS BID) ± rifampin
Diabetic foot infection	Mixed bacteria (GNR, staph/strep, ANO_2)	Ceftriaxone + Metronidazole (PO)
Diabetic foot infection (Severe illness or sepsis)	Mixed bacteria (GNR, staph/strep, ANO_2)	Piperacillin/tazobactam + vancomycin
Note: Add vancomycin in patients with life-threatening disease until cultures are available.		

√ **Cellulitis and skin abscesses:** When you initially see the patient, try to determine whether they have a simple spreading cellulitis (usually due to Group A streptococci) versus a "focal" infection like a skin abscess or boil. Patients with "focal infection" are more likely to have staphylococcal infection which raises the possibility of MRSA—organisms resistant to B-lactam antibiotics (e.g oxacillin or cefazolin) that now accounts for over 50% of community-acquired staphylococcal infection.

√ **Necrotizing soft tissue infection:** In critically ill patients with suspected necrotizing soft tissue infection (e.g. gas gangrene, necrotizing fasciitis), give "broad" initial coverage that includes an antibiotic active against MRSA such as vancomycin. In these situations, many specialists also recommend addition of clindamycin for 72 hours since the it inhibits protein synthesis and "turns off" production of toxins as seen in severe Group A streptococcal infection .

√ **Diabetic foot infection:** Until cultures are available, administer "broad spectrum" antibiotics with activity against gram negative bacilli, streptococci and anaerobes. Initial coverage for *Pseudomonas aeruginosa* and MRSA is rarely necessary unless previous cultures show these pathogens or the patient appears critically ill.

F. Endocarditis/vascular infection

In previous eras, endocarditis was most commonly due to viridans streptococci and usually a condition seen in patients with valvular heart disease due to previous rheumatic fever. In the current era, while viridans streptococci remain an important cause of endocarditis, staphylococci are increasingly important pathogens, especially in "nosocomial" endocarditis (endocarditis associated with infected lines or implanted devices) or those with a history of intravenous drug use.

Endocarditis and vascular infection

Site	Microbiology	Suggested antibiotics
Endocarditis-Native valve	*S. aureus*, viridans strep, HACEK	Ceftriaxone + vancomycin
Endocarditis-prosthetic valve	*S. aureus*, coag-neg staph, viridans strep,	Ceftriaxone + Gent (q8 hr) + rifampin
IV site	*S. epidermidis*, *S. aureus,* rare GNR	Vancomycin (add cefepime in septic patients till cultures available)

*HACEK organisms: *Hemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenalla corrodens*, *Kingella*.—gram-negative bacilli that tend to be susceptible to penicillin G
Abbreviations: RHD: Rheumatic heart disease; GNR: Gram negative rods;

√ **Endocarditis-Intravenous Drug User:** In these cases, *Staphylococcus aureus* is by far and away the most common pathogens—use vancomycin "up front" to cover for the possibility of MRSA until antibiotic susceptibilities are available. On rare occasion, intravenous drug users will develop endocarditis due to gram negatives such as *Pseudomonas aeruginosa*—administer an aminoglycoside (or cefepime) until culture results have returned.

√ **Endocardits—preexisting valve abnormalities:** Viridans streptococcal species and "HACEK" bugs (*Hemophilus* species and related penicillin-sensitive organisms) are the most common pathogens in individuals with preexisting valvular abnormalities; this includes patients with a history of rheumatic heart disease and those with congenital valve abnormalities (e.g. Bicuspid aortic valve; mitral valve prolapse). In these situations, a combination of gentamicin, ceftriaxone and vancomycin is appropriate until culture results are available.

G. Febrile neutropenia

While gram negative bacilli (especially *Pseudomonas aeruginosa*) were the most common pathogens in the "early" days of chemotherapy (e.g. 1960s), in the current era, gram positive bacilli (especially streptococcal species and *Staphylococcus epidermidis*) have become increasingly important. Whatever the cause, prompt, early therapy is necessary in order to reduce mortality, since these patients tolerate the "septic" state quite poorly.

Febrile neutropenia		
Site	**Microbiology**	**Suggested antibiotics**
Febrile neutropenia	GNR, viridans strep, staph sp.(IV site)	Cefepime (2 mg IV Q 8hr) *or* Piperacillin/tazobactam *or* Carbapenem (add vancomycin if line infection)

√ **Febrile neutropenia:** Patients with neutropenia (Neutrophil count < 500 cells/mm3) run the risk of bacteremia with both resistant gram negatives (e.g. *Pseudomonas aeruginosa*) and gram positive pathogens (e.g. viridans streptococci; staphylococcal species). In the febrile patient, prompt empiric coverage is critical to reduce mortality. When making the initial antibiotic choice, keep in mind the following caveats:

- **Initial coverage:** A broad spectrum B-lactam agent (e.g. cefepime; piperacillin/tazobactam or carbapenem) is appropriate till cultures are available.
- **? Vancomycin:** Add vancomycin if the patient is critically ill (hypotensive; ICU case) or has clear evidence of a soft-tissue infection or an infected central line.
- **? Anaerobic coverage:** In general, anaerobic bacteria are less likely to be seen as a cause of fever in the neutropenic patient, except in the individual with a perirectal abscess or evidence of neutropenic colitis. If you suspect one of these conditions, use piperacillin-tazobactam or add metronidazole to the patient receiving cefepime.
- **? Resistance:** Keep in mind "past" antibiotic exposure in those with multiple episodes of febrile neutropenia—in critically ill patients, include an aminoglycoside (e.g. amikacin) for 48 to 72 hours until the culture results are available.

H. Sepsis-Unknown source

Although your patient appears "septic" and requires immediate antibiotic antibiotic therapy, there will be occasions when you are unable to identify a potential source. In these situations, the most common organisms include *Streptococcus pneumoniae*, *Staphylococcus aureus,* gram negatives such as *E. coli* or *Klebsiella pneumoniae*—and—rarely, *Neisseria meningiditis.*

Sepsis—unknown source		
Site	**Microbiology**	**Suggested antibiotics**
Source unknown (community)	*S. pneumo.,S. aureus*, group A strep, GNR	Ceftriaxone + vancomycin + [gent or levofloxacin]
Source unknown (nosocomial)	*Staphylococcus aureus,* resistant GNR (*Pseudomonas, Enterobacter, Acinetobacter etc)*	Piperacillin/tazo + vancomycin (Use carbapenem or add aminoglycoside if previous pip/taz exposure)

√ **Community-acquired "sepsis":** Pathogens such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, gram negatives (*E. coli* or *Klebsiella pneumonia*) and—rarely, *Neisseria meningiditis* represent some of the most common sources of the "septic" patient in the emergency room. A combination of ceftriaxone and

vancomycin should provide broad coverage for these organisms—add a dose of aminoglycoside or quinolone if the patient is hypotensive and you do not want to miss the rare resistant gram negative organism.

√ **Hospital-acquired sepsis:** In this situation, more resistant gram negatives (e.g. *Pseudomonas, Acinetobacter*) and staphylococcal species (e.g. MSSA, MRSA, MRSE) are especially common—broader coverage with antibiotics (e.g. piperacillin/tazobactam; carbapenems) is appropriate until cultures are available.

Using the antibiotic grid—what you need to know…

- *Streptococcus pneumoniae* is the most likely pathogen for "community acquired**"** bacterial meningitis in adults—initial coverage includes both ceftriaxone and vancomycin, to cover the possibility of penicillin-resistant strains.

- In selected cases of suspect meningitis (e.g. neonates; age > 50 yrs; corticosteroid use; immunocompromised patient; "summer" meningitis), include high dose ampicillin to cover *Listeria* until culture results are available.

- Initial coverage of community-acquired pneumonia (CAP) should include drugs with activity against *Streptococcus pneumonia* (ceftriaxone) and "atypical" pathogens such as *Mycoplasma* and *Legionella pneumophila* (e.g. macrolide or doxycycline).

- For patients with penicillin allergy, a "respiratory" quinolone such as levofloxacin or moxifloxacin provide coverage for most of the major CAP pathogens, including the "atypical" pathogens.

- Community-acquired intraabdominal infections (appendicitis, choecystitis, diverticulitis) usually contain a "mixture" of facultative gram negatives (e.g. *E. coli*), streptococci and strict anaerobes (e.g. *Bacteroides fragilis*)—appropriate empiric therapy requires "broad spectrum" drugs (e.g. cefoxitan; ceftriaxone + metrodnidazole) ampicillin/sulbactam) with coverage against mixed aerobic/anaerobic infection.

- For patients with "severe" or "complicated" intraabdominal infection (e.g. septic ICU patient), consider more broad-spectrum agents (e.g. carbapenems; pipracillin tazobactam; aminoglycoside + metronidazole + ampicillin) to cover more resistant gram-negative pathogens.

- *E. coli* is the major pathogen for community-acquired urinary tract infection (e.g. pyelonephritis) and usually sensitive to 3rd generation cephalosporins (e.g.ceftriaxone) and aminoglycosides. For critically ill patients admitted to the ICU, consider the possibility of ESBL gram negatives (*E. coli; Klebsiella*) and start initial therapy with a carbapenem until susceptibilities are available.

- "Simple" cellulitis is usually due to group A streptococci and can be treated with intravenous cefazolin. Patients with "focal" soft tissue infections (e.g. boils, carbuncle, "purulent" cellulitis) often have *Staphylococcus aureus* and should have coverage against methicillin-resistant *Staphylococcus aureus* (e.g. vancomycin) until culture and susceptibility results are available.

- In addition to staphylococci and streptococci, diabetic foot infection may also have be due to "mixed" infection with faculatative gram negatives (*E. coli*) and anaerobes—utilize "broad spectrum" treatment (e.g. ceftriaxone + metronidazole *or* cefoxitin *or* ampicillin/sulbactam) until cultures are available.

- In critically ill patients with gas gangrene or necrotizing fasciitis, include coverage for *Pseudomonas aeruginosa* (e.g. carbapenem *or* piperacillin/tazobactam) and MRSA (e.g. vancomycin), and consider adding clindamycin to minimize "toxin" production by group A streptococcal strains.

- Staphylococci are playing an increasingly important role in endocarditis (IVDU; noscocomial bacteremia)—cover these patients with gentamicin + vancomycin until culture results are available. Viridans streptococci are important pathogens in those with endocarditis on a previously damaged valve (e.g. rheumatic fever; bicuspid valve)—start these patients on ceftriaxone + vancomycin while awaiting cultures.

- Gram negative pathogens have a high associated mortality in the febrile neutropenic patient—use a drug with activity against *Pseudomonas aeruginosa* (cefepime; carbapenem or piperacillin/tazobactam) as initial empiric therapy and consider adding vancomycin (for MRSA *Staph aureus* coverage) in seriously ill, "septic" patients (e.g. hypotensive; ICU) or those with clear evidence of indwelling catheter infection.

- In patients with "community-acquired" sepsis where there is no evident source, start the patient on ceftriaxone + vancomycin until cultures are available. For those who are "critically ill" with hypotension and septic shock, include coverage for *Pseudomonas* (aminoglycoside, piperacillin/tazobactam or carbapenem) until culture results are available.

Chapter 10

Antibiotic dosing for "Dummies"

What concentration of antibiotic is necessary to kill a specific pathogen? What about the correct dose and frequency required when treating a specific infection? Antibiotic dosing questions (How much drug to give to get a specific level?) fall under the category of **antibiotic pharmacokinetics**. Additional considerations (How does the drug act to kill the bacteria at the site of infection?) are addressed by the rapidly burgeoning field of **antibiotic pharmacodynamics**. Not surprisingly, proper antibiotic choice plays an important role in treatment with appropriate dosing helping to determine the ultimate response to therapy.

This chapter aims to give you a brief, practical overview of **antibiotic dosing**—things you need to know if your patient is to receive the proper antibiotic dosing in order to cure their infection. Learn these basic concepts and you will be far ahead of most physicians practicing medicine today!

1. The ABCs of "MICs" —Determining antibiotic susceptibility

Microbiologists have developed a laboratory test—the **MIC** or **Minimal Inhibitory Concentration**—to measure bacterial susceptibility to a specific antibiotic. For most clinically relevant bacteria, the MIC for an organism is the lowest concentration of antibiotic required to ***inhibit*** growth of the bacteria in a test tube (see diagram below). To an infectious disease clinician, the MIC of an organism indicates whether the antibiotic treatment is likely to be effective—if the MIC is higher than antibiotic levels at the site of the infection, the treatment may well fail.

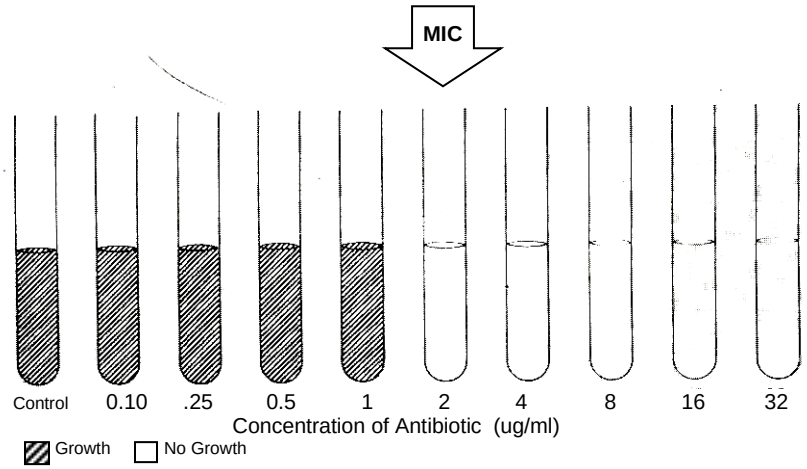


Figure 1: MIC testing

In thisexample, the tubes contain a serial dilution of antibiotic along with a standard inoculation of bacteria. The MIC of the organism (MIC=2 ug/ml) is the *lowest* concentration of antibiotic that will inhibit growth of the pathogen.

The **MBC** or **Minimal Bactericidal Concentration** is another value you might hear about on rounds—this is the minimal concentration (in the test tube) of antibiotic required to ***kill*** a specific bacteria rather than just inhibit it. While the MBC is rarely measured, these "**cidal**" agents are especially important for treating infections at hard-to-reach or "protected" sites such as the CSF (meningitis) and heart valve (endocarditis).

Practical points on antibiotic susceptibility testing…

√ **Automated microdilution:** No need to have rows of test tubes--in the modern microbiology laboratory, MICs are determined using "automated microdilution" techniques (that's a fancy way of saying it is done automatically by a computer run machine). Once a bacteria is growing, the susceptibility results are usually available within 18-24 hours.

√ **Choosing an antibiotic:** Whenever possible, find out the MIC (for a specific antibiotic) of the bacteria you are treating and choose the antibiotic based on susceptibilities of the organism.

√ **? "Cidal" antibiotics:** Certain infections—endocarditis and meningitis—required "bactericidal" antibiotic levels at the site of the infection.

KNOW THE JARGON

MIC (minimal inhibitory concentration): The concentration of antibiotic required to *inhibit* growth of a specific bacterium.

MBC (minimal bactericidal concentration): The concentration of antibiotic required to *kill* a specific bacterium.

Breakpoint: The "breakpoint" is the antibiotic concentration that serves to separate "sensitive" from "resistant" organisms. Breakpoints are chosen by experts using several criteria including antibiotic *in vitro* susceptibility data, known serum antibiotic levels and clinical outcome studies.

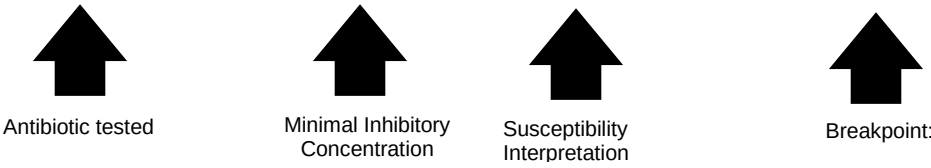
Know how to read the antibiotic susceptibility report

Now that you know what an MIC is, you need to know the basics of reading an antimicrobial susceptibility report. In the report below (figure 2), a series of antibiotics are tested against a single isolate (E.coli) with a susceptibility interpretation based on the

Case #1: 51-year old female presenting with fever, dysuria and pyelonephritis. Urinalysis demonstrated pyuria and the culture was + for *E. coli*.

URINE CULTURE: *E. coli*

ANTIBIOTIC	MIC	INTERPRETATION	BREAKPOINT*
AMPICILLIN	4	RESISTANT	≤ 0.5
CEFAZOLIN	1	SUSCEPTIBLE	≤ 0.5
CEFTRIAXONE	1	SUSCEPTIBLE	≤ 1
GENTAMICIN	< 1	SUSCEPTIBLE	≤ 1
CIPROFLOXACIN	2	RESISTANT	≤ 0.25
TMP-SULFA	≤ 1	SUSCEPTIBLE	≤ 1/19



***Note:** Although it may not be included in your laboratory's report, we've included the MIC "breakpoint" to help provide the rationale behind the interpretation (resistant vs. susceptible).

Interpreting antibiotic susceptibilities in case #1…

- ✓ **Ampicillin resistance:** With an MIC= 4 ug/ml, this isolate is above the established "breakpoint" (≤ 0.5 ug/ml and considered resistant. Because of widespread use, only 40% of community-acquired *E. coli* strains are susceptible to ampicillin, making it a poor choice for empiric therapy of serious UTI.
- ✓ **Cefazolin or ceftriaxone** would be appropriate choices for therapy in this situation.
- ✓ **Quinolone resistance:** Community-acquired quinolone resistance (~ 20% of *E. coli*) raises concerns about the use of this drug for empiric UTI therapy. In this patient, an alternate agent (? Gentamicin or ceftriaxone) should be administered until culture results are available..
- ✓ **Other agents:** When it is time for discharge, trimethoprim-sulfamethoxazole or cephalexin (similar to cefazolin) would be appropriate choices for oral therapy.

Outcome: The patient was admitted and started on empiric ceftriaxone. Her flank pain improved and she defervesced over the next 48 hours; the patient was discharged on oral cephalexin to complete a 10 day course of therapy.

Case #2: A 45 yr old male intravenous drug user with fever, chills and a new murmur. Blood cultures grew 2/2 sets of *Staphylococcus aureus.*

BLOOD CULTURE: *Staph aureus*

ANTIBIOTIC	MIC	INTERPRETATION	BREAKPOINT*
PENICILLIN G	> 2	RESISTANT	≤.05
OXACILLIN	> 1	RESISTANT	≤ 0.25
CEFAZOLIN	2	RESISTANT	≤ 0.5
VANCOMYCIN	< 0.5	SUSCEPTIBLE	≤0.5
CLINDAMYCIN	≤ 0.5	SUSCEPTIBLE	≤ 0.25
TETRACYCLINE	≤ 1	SUSCEPTIBLE	≤ 1
TMP-SULFA	≤ 10	SUSCEPTIBLE	≤ 10 (0.5/9.5)
CIPROFLOXACIN	> 0.5	RESISTANT	≤ 0.5

Interpreting antibiotic susceptibilities in case #1…

- ✓ **Oxacillin resistance:** This isolate is a methicillin-resistant *Staph aureus* (MRSA) meaning that it is resistant to anti-staphylococcal penicillins (e.g. oxacillin; nafcillin) as well as cephalosporins. Despite the cephalosporin resistance, the organism is likely to be susceptible to ceftaroline, a new "5th" generation cephalosporin.
- ✓ **Vancomycin:** This drug is the drug of choice for initial treatment of suspected MRSA infections.
- ✓ **Trimethoprim-sulfamethoxazole:** Although not the first choice for bacteremia, TMP-SMX could be used to treat less severe skin and soft tissue infections.
- ✓ **Other agents:** Both clindamycin and doxycycline frequently have activity against MRSA—if the organism is susceptible, they might be appropriate choices in the patient with less severe skin/soft tissue infection. There is a high rate of resistance among MRSA strains to quinolones.

Outcome: The patient was admitted and started on empiric vancomycin. A second set of blood cultures (Day #2) was positive but he gradually defervesced and a third set of blood cultures were negative. He was found to have a 1 cm tricuspid valve vegetation on echocardiogram and subsequently received a full 4 week course of vancomycin for MRSA tricuspid endocarditis. Although the organism was susceptible to several other agents (clindamycin; doxycycline; TMP/SMX), these drugs are "bacteriostatic" and would be less appropriate for management of endocarditis. (See "Cidal" vs "Static" on page 10-6).

3. Understand antibiotic dosing—Time vs Concentration-dependent killing

Don't be scared by the term "**antibiotic pharmacodynamics**"—this turns out to be a new field of pharmacology that's investigating how antibiotics go about the business of killing bacteria *in the patient*. Recent research suggests that the effects of these agents can be divided into three major categories: Type 1, Type 2 and Type 3 antibiotics (this shouldn't be a surprise!). Knowing which category the drug falls into will help determine dosing schedules.

To understand these categories, you need to know a few additional terms (pharmaceutical jargon) that will help predict the patterns…

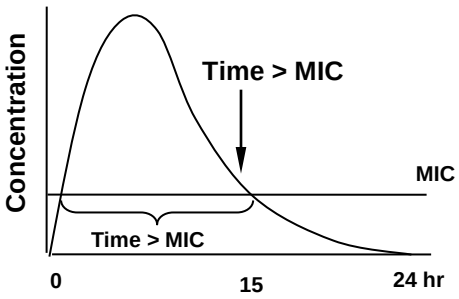
Know the jargon…

- **C_{peak}**: This is the peak blood concentration attained by the antibiotic following the dose.
- **AUC (Area under the curve):** Derived from research studies (see graph below), this is the total amount of antibiotic in the blood, measured over 24 hours.
- **AUC/MIC:** The AUC divided by the MIC (see definition above) seems to predict efficacy of quinolones, macrolides and vancomycin.
- **PAE (Post antibiotic effect):** Look upon this as an antibiotic "knockout" punch—drugs with a prolonged PAE (e.g.aminoglycosides) prevent bacterial regrowth for some time (many hours),even if antibiotic concentrations fall below the MIC. In antibiotics with a "minimal" PAE (e.g. β-lactams), bacterial growth rapidly returns to normal as soon as antibiotic concentration falls below the MIC.

The way antibiotics kill the target organism helps to determine the best dosing intervals and goals of therapy. —"**time-dependent**" bacterial killing and "**concentration-dependent**" bacterial killing (see Figure 3 next page). These features have major (and practical!) implications for antibiotic dosing.

Time-dependent killing

(Time > MIC makes the difference)

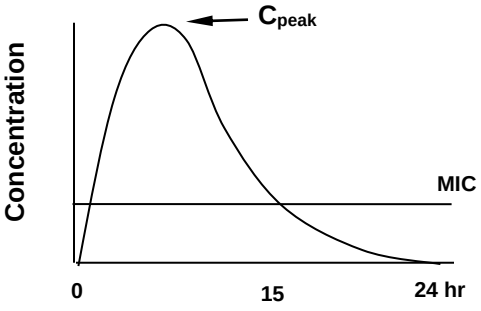


Time above MIC (Time > MIC)

The amount of time the serum level is *above* the MIC of the organism—in this case about 15 hours.

Concentration-dependent

(Peak concentration makes the difference)



C_{peak}: MIC ratio

The height of the peak concentration (C_{peak}) seems to be the deciding factor—aim for a Cpeak:MIC ratio of 10:1 for optimal activity.

■ Getting time on your side…"Time-dependent killing"

With some antibiotics, **Time-dependent killing** (Time > MIC) is the key parameter—these agents work best when the antibiotic concentration is above the MIC for as long as possible. B-lactam drugs (penicillins and cephalosporins) fall into this category—in this case, all that is necessary is to maintain the concentration of antibiotic above the MIC for an extended period of time (usually greater than 12 to 15 hours).

Dosing implications: Many B-lactam agents have relatively short half -lives (e.g. 30 min) and rapidly disappear from the serum following infusion. With these agents, frequent dosing is necessary in order to continuously maintain a level above the MIC for as long as possible.

■ The power of the "peak"…"Concentration-dependent" killing

Drugs which work via **Concentration-dependent killing** depend upon reaching "peak" serum levels that are 8 to 10 x the MIC of the target bacteria. Once the bacteria are hit by a high concentration of antibiotic (the C_{peak}), the bugs are killed outright or their growth is suppressed for many hours (This is called "post antibiotic effect" if you want to impress your friends and colleagues!).

Dosing implications: Agents in this class—including aminoglycosides or quinolones—can often be dosed on a less frequent basis (once or twice daily) as long as they reach high "peak" serum levels.

Table 1: Antibiotic pharmacodynamics—Time vs. Concentration dependent dosing

	Time-dependent killing	Concentration-dependent killing
Antibiotics	B-lactam agents Carbapenems Cephalosporins Penicillins I	Aminoglycosides Macrolides Metronidazole Quinolones
Pharmacodynamics	These drugs work best as long as serum concentration is maintained above the MIC for long periods of time (> 12 hrs)	These drugs work best in "large" doses that maximize the peak concentration (C_{peak}) and C_{peak}/MIC ratio.
Key parameter	Time > MIC	C_{peak}/MIC

Practical points on antibiotic pharmacodynamics…

- **B-lactam dosing:** Except for certain agents with long serum half-lives (e.g. ceftriaxone, ertapenem), most B-lactam agents require fairly frequent dosing (Q 4-6 hr) in order to maintain drug levels above the MIC of a specific pathogen. In the modern era, some experts have advocated administering these agents via "continuous infusion" (using an intravenous pump) in order to maximize T>MIC and take advantage of the time-dependent pharmacodynamics of these agents.
- **Aminoglycosides/quinolones:** Because of the "concentration-dependent" pharmacodynamics of these drugs, administration on a once or twice daily basis is usually adequate—a factor in treatment success is the ability to attain a peak serum level of 8-10 x the MIC of the infecting organism. This is the rationale behind "once-daily" aminoglycoside regimens.

4. Combination antimicrobial therapy—ordering an antibiotic "combo"

Are two drugs better than one? In sick patients it is sometimes tempting to pile on more drugs, hoping that a "combination" of agents will do the job better than a single antibiotic. While there is often a rational for multiple antibiotic therapy (covering more than one pathogen), there are very few situations where we need two drugs (or more) to treat a single pathogen.

In those situations where combination therapy is beneficial (see below) the drugs usually work together (**synergistic**) to lower the concentration of each agent required. This doesn't always happen when we combine antibiotics—in some situations, the combination makes little difference ("**indifferent**") or makes things worse ("**antagonistic**").

The following clinical conditions represent situations where combination antibiotic therapy is indicated:

- **Endocarditis:** Enterococci are usually "tolerant" to penicillin agents—the drug concentrations required to "kill" the bugs are many times higher than concentrations to suppress growth. In **enterococcal endocarditis**, there is a high failure rate unless two agents (ampicillin + aminoglycoside) are used.

  Endocarditis due to **viridans streptococci** represents another situation where synergistic therapy makes a difference—in patients with uncomplicated infection, treatment with two agents (penicillin + aminoglycoside) halves the length of therapy (2 weeks) compared to penicillin-alone (4 weeks). Other forms of endocarditis, including **prosthetic valve endocarditis**, may benefit from antibiotic combinations, depending upon the organism.

- **Pseudomonas bacteremia:** Early studies in neutropenic patients suggested that survival outcomes of *Pseudomonas* bacteremia were improved when two agents (broad spectrum penicillin + aminoglycoside) were employed. More recent studies seem to imply the opposite—survival may be equivalent (or better) in patients receiving monotherapy with one of the new B-lactam agents (e.g. carbapenems).

  The best therapy for ***Pseudomonas* pneumonia** remains unclear—studies suggest that combinations therapies may lead to improved survival. This is one of the few situations in gram-negative infection where "combination" antibiotic therapy is of definite benefit.

- **Other conditions:** Of course combination therapy is well established for a number of other conditions including **tuberculosis**, **HIV** infection and treatment of **viral hepatitis**.

In occasional situations (e.g. endocarditis with resistant pathogens), laboratories look for synergistic antibiotic combinations using trays that allow for "checkerboard" susceptibility testing of two drugs together.

5. A view to a kill—"Cidal" vs. "Static" Antibiotics

Antibiotics have different effects on bacteria depending upon their mechanism of action…

- ***Bacteriostatic*** antibiotics such as tetracyclines, macrolides (e.g. erythromycin; clindamycin), sulfa drugs and linezolid slow down microbial growth but don't necessarily kill the pathogen. Control of the infection requires a robust immune response (e.g. neutrophils, antibodies etc.) in order to eliminate surviving bacteria.
- ***Bactericidal*** antibiotics such as B-lactam drugs (e.g. penicillins/cephalosporins), quinolones, and aminoglycosides can kill the pathogen outright and are less dependent on the immune system to complete the job.

In most clinical situations, the distinction doesn't make much difference; however, with selected infections, bactericidal antibiotics are likely to be more effective and should be the treatment of choice:

- **Endocarditis:** In bacterial endocarditis, the organisms are sequestered inside a vegetation and relatively "protected" from penetration of antibiotics and immune cells. In this situation, bactericidal antibiotics (B-lactams; aminoglycosides; quinolones)—sometimes in combination—are almost always necessary for cure of the infection. In general, bacteriostatic drugs such as tetracyclines and macrolides *should not* be used to treat infective endocarditis.
- **Meningitis:** The cerebrospinal fluid compartment is a sequestered space with reduced entry of antibiotics and immune cells due to the blood-CSF barrier. Because of this "protected" status, bacterial infection of the CSF (meningitis) is more difficult to treat and generally requires high dose parenteral antibiotic therapy in order to attain adequate levels within the CSF. In bacterial meningitis, bactericidal antibiotics—rather than static agents—have a higher cure rate.

Remember: ***When treating endocarditis and meningitis, use "cidal" agents (B-lactams) and avoid "static" drugs such as tetracyclines, macrolides and clindamycin.***

6. Deep penetration—successful treatment of "intracellular" infection

Selected bacterial pathogens are "intracellular" and directly infect leukocytes such as macrophages. This includes infection with organisms such as *Legionella pneumophila*, brucellosis, *Salmonella* species and rickettsia. Although these pathogens may be sensitive to "extracellular" antibiotics such as B-lactam agents, successful therapy usually requires antibiotics with the capability of intracellular penetration.

B-lactam agents (penicillins; cephalosporins) and aminoglycosides generally have minimal intracellular penetration—antibiotics such as tetracyclines, macrolides and quinolones attain adequate intracellular levels and are generally better choices for these "intracellular" infections. "Intracellular" antibiotics are usually recommended for therapy of the following infections:

- **Salmonellosis:** Although 3rd generation cephalosporins can be used for treatment of *Salmonella* infection, agents with good intracellular penetration such as quinolones are more effective and have lower relapse rates, provided the pathogen is susceptible.
- **Brucellosis:** *Brucella* species are predominantly intracellular pathogens—therapy requires agents with intracellular penetration such as tetracyclines, rifampin and trimethoprim-sulfamethoxazole.
- **Legionnaire's disease:** Although *Legionella pneumophila* is susceptible, in vitro, to β-lactam agents, the organism is an intracellular pathogen requiring "intracellular" antibiotics (e.g. macrolides, quinolones, doxycycline/rifampin) able to penetrate macrophages.
- **Rickettsial infection:** *Rickettsial* organisms are energy parasites that multiply in protected intracellular compartments—tetracyclines have good intracellular penetration and are the "drugs of choice for these infections.

7. Beyond the blood-brain barrier—Managing CNS infection

In addition to using a bactericidal antibiotic, choosing an agent with adequate CSF penetration is critical in management of CSF infections such as bacterial meningitis (see Table 2 below). Passage of an antibiotic through the blood-CSF barrier depends on several factors include antibiotic size (small compounds > large compounds), lipid solubility (lipid soluble > water soluble) and the presence of specific transport channels.

Table 2: CSF Penetration characteristics of various antibiotics (% serum levels)

Very Good[1] (> 50%)	Good (10-20%)	Fair-Poor (< 10%)
Choramphenicol*	Penicillins	Aminoglycosides
Linezolid*	Cephalosporins (2nd/3rd/4th)	Cefazolin (1st Gen ceph)
Metronidazole	Carbapenems	Macrolides
Rifampin	Monobactam (Aztreonam)	Azithromycin*
TMP/SMX	Quinolones	Clarithromycin*
		Erythromycin*
		Vancomycin

1. Penetrate CSF well regardless of inflammation
2. Adequate CSF penetration achieved when meninges are inflamed
3. Penetration often inadequate even when meninges are inflamed.
* Not bactericidal

Table taken from Applied Therapeutics: The clinical use of drugs; ed. Young & Koda-Kimble; Sixth edition; Applied Therapeutics, Inc. Vancouver, WA 1995.

Practical Points on CNS infection pharmacodynamics…

√ **B-lactams:** In general, B-lactam agents (penicillins; cephalosporins) are the favored drugs for treatment of bacterial meningitis. Although CSF penetration may only be fair (approximately 20% of serum levels depending upon the agent), with susceptible organisms, higher doses generally result in adequate antibiotic concentration in the CSF.

√ **Aminoglycosides:** Aminoglycosides have relatively poor CSF penetration—*intrathecal* administration of these agents is required when treating bacterial meningitis due to resistant gram-negative bacteria.

√ **Macrolides/tetracyclines:** In addition to being "static" agents (a "no-no" in meningitis), tetracyclines and macrolides have relatively poor CSF penetration and represent a poor choice for treatment of bacterial meningitis.

√ **Quinolones:** Quinolone agents are "cidal" and have good CSF penetration (both features of a "good" meningitis agent); however, they have reduced effectiveness in the low pH environment of infected CSF.

√ **Vancomycin:** Although vancomycin has relatively poor CSF penetration, it may be necessary for treatment of bacterial meningitis with drug-resistant pneumococci or staphylococci (e.g. MRSA). In these situations, clinicians usually recommend higher dosing (1.5-2 gm IV Q 12 hr) and—in some situations—the addition of intrathecal vancomycin.

Remember: *When treating meningitis, avoid "static" drugs (tetracyclines, macrolides and clindamycin) and make sure your choice of antibiotic has adequate CSF penetration.*

Antibiotic pharmacodynamics and dosing—what you need to know…

- The Minimal Inhibitory Concentration (MIC) is a laboratory measurement of the susceptibility of specific bacteria to a selected antibiotic. For tested antibiotics, laboratory susceptibility reports generally cite MICs along with an interpretation (Sensitive-Intermediate-Resistant) based on serum antibiotic levels attained with standard dosing.
- The action of time-dependent antibiotics (B-lactam agents) depends upon maintaining serum antibiotic levels above the pathogen MIC for as long as possible. Successful therapy with these agents usually require frequent dosing (Q 4-6 hours depending upon the agent) in order to maintain antibiotic levels (Time > MIC) as long as possible (12 hours or greater) during the treatment period.
- Concentration-dependent antibiotics (aminoglycosides, quinolones) can be dosed less frequently (once or twice daily) and depend upon reaching adequate peak serum levels (Cpeak) approximately 10 x the MIC of the infecting organism.
- Treatment of endocarditis and meningitis requires bactericidal ("cidal") agents that specifically kill—rather than suppress growth—of the pathogen. In general, avoid bacteriostatic drugs (e.g. tetracyclines; macrolides; sulfa agents) when treating infections at these sites.
- Intracellular infections such as Legionnaire's disease, salmonellosis, brucellosis and rickettsial infection require antibiotics (quinolones, tetracyclines, macrolides) able to achieve adequate intracellular levels.
- Combination antimicrobial therapy is necessary for selected infections such as enterococcal endocarditis and possibly, *Pseudomonas* pneumonia in the immunocompromised patient.
- Successful management of bacterial meningitis requires treatment with antibiotics able to penetrate the blood-CSF barrier. B-lactam agents are often used since they are bactericidal and—if given in high doses—able to achieve adequate CSF concentrations.

Chapter 11

Practical aspects of antibiotic therapy—*what you need to know*

Choosing the right antibiotic is only half the battle—issues regarding "dosing", length of therapy and response to treatment are just as important but rarely covered in most texts. Although some of this falls under the "art of medicine" category, the following section addresses the most common questions regarding practical aspects of antibiotic therapy…

1. What situations require parenteral rather than oral antibiotic therapy?

In seriously ill patients, administer parenteral, intravenous antibiotics until the patient is clinically stable and able to take oral medications. Patients with sepsis/hypotension (or underlying gastrointestinal disease) may have inadequate absorption of oral antibiotics—although some agents may still be well absorbed in this setting, it's best to give drugs via a parental route to assure adequate drug levels.

Don't rely on oral antibiotics in any patient with significant nausea and vomiting—the danger of inadequate dosing is too great and it is better to administer parenteral therapy until a clear clinical response is apparent. Depending upon the clinical situation, certain deep-seated, life-threatening infections (endocarditis, bacterial meningitis) almost always require prolonged (2-6 weeks) parenteral therapy. While oral antibiotic therapy is sometimes underutilized, be cautious of oral administration in critically ill patients or those with significant nausea/vomiting.

ID Casefile: A 22 year old male recently returned from a trip to Thailand presented with falciparum malaria. The houseofficer started oral medications (quinine) but the patient experienced nausea and vomited up the medicine. Twelve hours later, the patient deteriorated and had to be sent to the ICU where he was intubated and started on intravenous quinidine.

Warning: *Do not rely on oral therapy in a patient who has significant nausea and vomiting!*

2. "Rescue me!"…immediate therapy in septic patients.

When a patient looks toxic and appears "septic" (e.g. low blood pressure, tachycardia, tachypnea), don't delay—obtain appropriate cultures and start parenteral antibiotic therapy as soon as possible. Significant delays in therapy (> 2-3 hours) could result in irreversible septic shock and increase the likelihood of patient mortality.

Immediate therapy is especially important in immunocompromised patients (e.g. AIDS, cancer, neutropenia)—because of immune impairment, these patients have less "reserve" and a higher mortality associated with bacteremia. If you write orders for antibiotics, make sure the order is acknowledged and carried out by hospital staff; in most circumstances, septic patients should receive antibiotics within a short period (< 1 hour) following the written order.

ID Casefile: A 45-year old male with testicular cancer on chemotherapy developed diarrhea and hypotension during an episode of neutropenia (WBC < 500 granulocytes). Since the patient was "afebrile", the on-call houseofficer ordered intravenous fluids and went back to bed. The next morning (7 hours later) the patient remained hypotensive but was now febrile—the resident ordered blood cultures and wrote for intravenous antibiotics. The patient finally received intravenous antibiotics at 1:00 PM, close to 12 hours after the initial sign of sepsis (e.g. hypotension). Later that day, the blood cultures turned positive for *E. coli* (sensitive to standard antibiotics). Despite appropriate therapy, the patient remained hypotensive and died 12 hours later from irreversible septic shock.

Warning: *In sepsis, there is a "golden" period—probably only a few hours—where appropriate antibiotic therapy can prevent the development of irreversible septic shock. While supportive measures (e.g. intravenous fluids, vasopressors) are important, they don't take the place of prompt, proper antimicrobial therapy. In the septic patient, order appropriate antibiotics and make they are administered* ***as soon as possible!*** *More immediate antibiotic treatment might have prevented the patient's death in the above case.*

3. What question should you always ask prior to starting an antibiotic?

In the United States, there is an estimated 200-300 deaths a year from antibiotic-associated anaphylaxis! Before starting therapy, always ask patients about a history of antibiotic allergy, especially to beta-lactam antibiotics and sulfa drugs, the agents most commonly associated with drug allergy. Although some of these deaths are unavoidable, many can be prevented with more careful questioning of the patient's previous allergy history. When a significant allergy history is present, if possible, use an alternative agent from a different class of antibiotic.

ID Challenge: Is it safe to administer a cephalosporin in a patient with penicillin allergy?

Estimates suggest that approximately 10% of patients with penicillin allergy will develop some type of reaction to subsequent cephalosporin administration—the real risk probably depends on the nature of the initial penicillin reaction and the likelihood that it was IgE-mediated anaphylaxis. For patients with a true history of a penicillin anaphylactic reaction (Immediate onset of hives, soft-tissue swelling, difficulty breathing, hypotension following penicillin adminstration), avoid cephalosporins unless they are absolutely necessary for treatment of the primary infection. For patients with other types of reaction to penicillin (maculopapular rash, vasculitis), cephalosporins are likely to be safe but should be administered with caution in a supervised setting. Fortunately, alternative agents are available for most infections and beta-lactam antibiotics are rarely necessary in a patient with a true history of penicillin anaphylaxis. In the rare case where penicillin is required despite such a history, consult an allergist for penicillin skin testing or consider penicillin/cephalsporin desensitization with careful monitoring in an ICU setting.

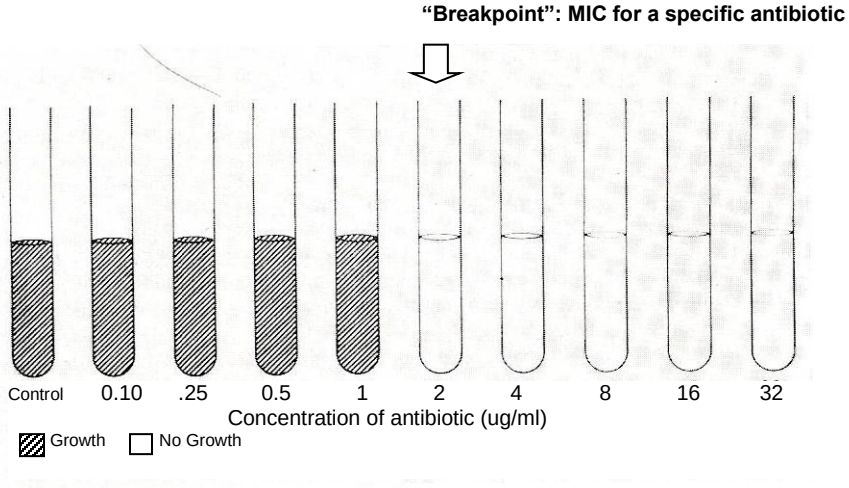
Warning: *Avoid cephalosporins in patients with a history of anaphylactic reaction to penicillin—try to choose an agent from a "non-B-lactam" class in this situation. If you feel you must challenge the patient, administer drugs in a monitored setting with appropriate support (e.g. epinephrine; crash cart)readily available.*

4. A matter of susceptibility—Know thy "MICs"!

If cultures are positive for a specific organism, it is critical to know whether the pathogen is susceptible to the chosen antibiotic. The laboratory routinely measures a Minimal Inhibitory Concentration (MIC) to see whether the bug is susceptible to standard antimicrobials. If culture results are available, check the MIC of the organism to make sure it is susceptible to your chosen antibiotic.

ID Labtalk: A matter of degree…Measuring the "MIC"

The standard "macrodilution" MIC is performed using a series of test tubes, each containing growth media and along with a standard inoculum of the bacteria being tested. Each tube also contains a concentration of antibiotic, part of a "serial" dilution from a low concentration (.01 ug/ml) to a high concentration (128 ug/ml). The Minimal Inhibitory Concentration (MIC) is the lowest concentration of antibiotic that will inhibit growth of the bacterial inoculum (in labtalk, this also know as the "breakpoint"); tubes with concentrations of antibiotic *below* the MIC will appear cloudy with bacterial growth.



- **Automated MICs**: In most clinical laboratories, MIC values are determined using an automated "microdilution" system that can read the MIC from bacterial growth in small wells containing bacterial broth and a series of antibiotic concentrations.
- **Fastidious organisms:** Some fastidious organisms (e.g. *Streptococcus pneumoniae, Hemophilus influenzae*) grow poorly in the automated microdilution trays—these bugs have to be tested with special techniques including the Kirby-Bauer test (antibiotic disk on agar plate) or E-test (strip with antibiotic gradient concentration on agar plate).
- **Susceptible bacteria:** Some organisms are known to remain quite susceptible to standard antibiotics (e.g. group A streptococcus and penicillin). In these situations, the laboratory may not perform susceptibility testing unless requested in special cases.

Watch out…

√ **MIC variability:** Different MICs may be obtained using different methods—if a patient is not responding to antibiotic, check with laboratory to make sure the MIC is correct and consider an alternative testing method (e.g. E-test, broth macrodilution) if there is a question about the results.

√ **Antibiotic pharmacokinetics:** Knowledge of antibiotic pharmacokinetics (e.g. blood, urine and CSF levels) is also important in judging response to a specific antibiotic—although an organism appears "sensitive", failure to attain adequate antibiotic concentrations—due to inadequate dosing or poor compartment penetration (see below)—may doom your therapy.

5. How rapidly can you expect a clinical response to antibiotics?

The "time to response" varies depending upon the pathogen and the nature of the infection. Although some patients became afebrile within 24 hours, don't expect an immediate response in all cases—patients with serious infections may require several days to defervesce despite administration of appropriate antibiotics. In most "uncomplicated" bacterial infections (e.g. cellulitis, pneumonia, UTI), expect to see a diminution of fever and clinical improvement within 72 hours.

Persistent fever suggests an incorrect diagnosis, inadequate therapy (e.g. inadequate dose, wrong antibiotic) or a "complicated" infection requiring surgical intervention. Although there are some exceptions to this rule, persistent fever is a concern and merits a careful evaluation to make sure the diagnosis is correct.

ID casefile: A 27-year old female was diagnosed with acute pyelonephritis after presenting with fever, urinary frequency and flank pain. Despite 72 hours of appropriate intravenous antibiotic therapy, she continued to have high fevers with little clinical improvement. The urine culture grew *E. coli*, sensitive to the antibiotic. An ultrasound demonstrated left hydronephrosis due to an intraureteral stone; the patient promptly defervesced following catheter drainage of the obstructed kidney.

Warning: *When a patient is receiving appropriate antibiotic therapy, persistent fever and clinical symptoms (beyond 72 hours) suggests the possibility of an incorrect diagnosis, a resistant organism or an infection requiring surgical intervention.*

6. How long should you treat most infections?

In many situations, length of treatment is based on severity of infection in combination with previous experience (what's worked in the past!). Unfortunately, we often don't know the optimal length of therapy and—for most common infections—the recommendation usually boils down to the standard "7-10 days". Selected serious infections generally necessitate longer courses of therapy—most patients with endocarditis generally need 4-6 week courses of parenteral antibiotics; patients with tuberculosis require prolonged 6-9 multi-drug treatment regimens.

When thinking about "common" infectious disease ailments, most treatments will fall into one of the following categories…

- **Single-dose therapy:** Bacterial cystitis/urethritis, gonorrhea, primary syphilis
- **10-14 days:** Most common infections including community acquired pneumonia, bronchitis, pharyngitis, urinary tract infection, cellulitis, diarrheal disease, meningitis (parenteral therapy required)
- **4-8 weeks:** "Deep-seated" infections including endocarditis, osteomyelitis, brain abscess and liver abscess
- **6 months-1 year:** Infections requiring extended therapy for cure including tuberculosis, actinomycosis, nocardiosis and some forms of osteomyelitis

Table 2: Standard recommendations for length of therapy

1-3 days	10-14 days	4-8 weeks	> 6 months
Bacterial cystitis Gonorrhea Primary syphilis	Cellulitis Meningitis Pneumonia Pyelonephritis Intraabdominal abscess*	Brain abscess* Endocarditis Liver abscess* Osteomyelitis	Actinomycosis Nocardiosis Tuberculosis HIV (indefinite) Disseminated fungal infection

*** With appropriate surgical drainage**

√ **Newer agents:** It is entirely possible that newer drugs (quinolones, 2nd generation macrolides) might permit shorter periods of treatment depending upon the infection. Short course, high-dose respiratory quinolones (e.g. levofloxacin-750 mg QD x 5 days) is just as effective as standard therapy (e.g. levofloxacin 500 mg PO QD x 10 days).

√ **When to break the rules:** Avoid rigid adherence to any treatment recommendation—in certain situations (poor clinical response, patient is immunocompromised) it may be appropriate to extend therapy beyond the usual guidelines.

ID history: The "Red Lake" trials—preventing rheumatic fever

In the late 1950s, the large "Red Lake" trial—performed on a Midwestern Indian reservation—examined the efficacy of penicillin in the prevention of rheumatic fever in those with Group A streptococcal infection. Investigators found that a 10-day course of penicillin was required to eradicate pharyngeal streptococcal infection—anything shorter led to persistent bacterial carriage with an increased risk of rheumatic fever. Although similar, large scale studies are not available for many other infections, extrapolation from this data led to the oft recommended "10-day" course of therapy for many common bacterial infections.

7. Time to "step down"— when to make the switch from IV to PO:

While a prolonged course of IV antibiotics may be necessary for certain infections (e.g. endocarditis), a switch to an oral antibiotic may well be appropriate in those who can take oral medication. When thinking about a switch to PO therapy, use Table 3 and keep in mind the following considerations …

- **Is the patient improving?** Most patients with common bacterial infections are better within 48-72 hours (e.g. decreased fever, increased well-being)—at this point in time, a switch to oral antibiotic therapy may well be appropriate. Before switching to PO antibiotic, make sure the patient is clinically improving and able to tolerate oral medication.
- **Can the patient take oral medications?** Presence of poorly controlled nausea/vomiting is a relative contraindication to oral antibiotic therapy—do not rely on oral agents in patients with vomiting or significant underlying gastrointestinal disease (e.g. ileus; malabsorption; short-bowel syndrome).
- **Which antibiotics have the best oral absorption?** Not all oral antibiotics are created equal—in the following table (Table 3), all the suggested antibiotics (except where indicated) have oral bioavailability of 90% or greater.
- **Additional considerations:** Before you make the final choice, keep in mind the following considerations…
  - **Antibacterial spectrum:** Is the bacteria susceptible to the proposed antibiotic?
  - **Frequency of dosing:** Compliance increases with less frequent dosing (Q day or BID).
  - **Cost of the drug:** Newer agents may cost $50-100 ($$$) per short-course regimen!

When choosing specific oral agents, keep in mind the following caveats…

√ **Penicillins:** Amoxicillin and amoxicillin/clavulanic acid have the best absorption and are generally the preferred agents when transitioning to an oral penicillin antibiotic. For patients with methicillin-susceptible *Staph. aureus* (MSSA), dicloxacillin is the drug of choice.

√ **Cephalosporins:** Cephalexin remains the best-absorbed cephalosporin and is the preferred agent in this class *except* when dealing with *Hemophilus influenzae* (cefuroxime) or more resistant gram-negative bacilli (use 3rd generation cephalosporins such as cefpodoxime, cefdinir or cefixime).

√ **Quinolones:** Ciprofloxacin is well absorbed and quite inexpensive and generally the recommended agent for most gram-negative infections. For respiratory infections, choose one of the respiratory quinolones (e.g. levofloxacin, moxifloxacin or gatifloxacin) that has better activity against gram-positive pathogens.

√ **Macrolides:** Although azithromycin has lower "serum" levels, this may be outweighed by its' excellent intracellular levels and ease of administration. Be cautious about drug interactions with clarithromycin—the drug may prolong QT interval, a potentially dangerous side effect in patients with underlying cardiac conditions.

√ **"Mixed" infection (aerobic-anaerobic):** For patients with anaerobic or "mixed" aerobic/anaerobic infection, there are several possible agents that can be used. Amoxicillin/clavulanic acid (Augmentin)has excellent anti-anaerobic activity and is a good choice for patients with "mixed" infection such as diabetic foot infection or diverticulitis. Metronidazole has excellent activity against strict anaerobes but should be combined with an additional agent with activity against facultative gram positive anaerobes and/or gram negative bacilli.

Table 3: "Step down" oral antimicrobial regimens for common infections

Infection	Likely pathogen	Suggested oral regimen* (Check susceptibilities)
CAP† (Pneumonia)	Pneumococcus	Amoxicillin (if pathogen confirmed) *or* Levofloxacin *or* Moxifloxacin *or* Azithromycin
Cellulitis—Grp A strep	Grp A Strep	Cephalexin *or* Amoxicillin *or* Clindamycin
Cellulitis--MSSA	Staph (MSSA)	Dicloxacillin *or* Cephalexin *or* Clindamycin
Cellulitis--MRSA	Staph (MRSA)	TMP/SMX *or* Clindamycin (susceptible isolates) *or* Minocycline (Note: may add rifampin to one of these agents in severe cases)
Diabetic foot infection	Mixed	Amoxicillin/clavulanate (Augmentin) *or* Ciprofloxacin + metronidazole *or* Ciprofloxacin + clindamycin
Abdominal (e.g. Diverticulitis)	Mixed	Amoxicillin/clavulanic acid *or* Ciprofloxacin + metronidazole **or** Ciprofloxacin + clindamycin *or* Moxifloxacin
UTI	E. coli	Ciprofloxacin *or* TMP/SMX (susceptible isolate) *or* Cephalexin (susceptible isolate)

***Oral bioavailability of agents is > 90% for all suggested drugs except azithromycin (35%) and ciprofloxacin (70%):.† Community-acquired pneumonia**

Practical aspects of antimicrobial therapy—what you need to know…

- For critically ill, septic patients, administer initial antimicrobial therapy via a parenteral route until you are certain that the patient is clinically stable—do not rely on oral antibiotic therapy in patients with serious nausea/vomiting or those with significant underlying gastrointestinal disease (ileus; malabsorption; short-bowel syndrome).

- Administer antibiotics promptly (within the hour) in seriously ill, septic or hypotensive patients—significant delays of even several hours can lead to increased mortality in sepsis.

- Before you administer antibiotics, always ask if the patient is allergic to any of the planned drugs in the regimen—unexpected anaphylaxis to B-lactam antibiotics (e.g. penicillins; cephalosporins) is estimated to account for close to 300 deaths a year in the United States.

- Once you have culture results, check the "MIC" (minmal inhibitory concentration) to determine if the pathogen is susceptible to the agents the patient is receiving. Along with a knowledge of serum antibiotic levels, the "MIC" is an important parameter that helps the infectious disease specialist choose the best antibiotic for a specific infection.

- Clinical response to antimicrobial therapy will vary depending upon the disease condition and the chosen antibiotic—most patients with "common" bacterial infections demonstrate some degree of defervescence and clinical improvement within 72 hours of initiation of antibiotics. Failure to improve following this period of time suggests the possibility of an antibiotic-resistant pathogen or presence of a complication (e.g. abscess; endocarditis) requiring surgical drainage or intervention.

- Although the length of antibiotic therapy remains uncertain for many infections, most "standard" bacterial infections (e.g. pneumonia, urinary tract infection, cellulitis) require approximately 10-14 days of treatment.

- Patients with "deep seated" bacterial infection—such as endocarditis or osteomyelitis—often require longer therapy (4-8 weeks) depending upon the case. Selected infections (e.g. tuberculosis; actinomycosis; nocardiosis) may require 6-9 months of treatment for effective cure.

- For most common bacterial infections, switch the patient to an oral antibiotic once they are clinically stable and able to take PO medications. Prolonged parenteral treatment may be necessary for selected infections such as bacterial endocarditis.

Chapter 12

Ten things doctors should know about oral antibiotics

Although most houseofficers become skilled in the use of parenteral antibiotics during their training, few leave residency feeling fully comfortable with oral antibiotic therapy, something they will be using for the rest of their career. This chapter gives an overview of oral antibiotic "basics"—general principles necessary for effective oral antimicrobial therapy along with some potential pitfalls.

As you think about oral antibiotic therapy, keep in mind the following benefits and "pitfalls":..

- **Oral agents are surprisingly effective:** Although we rely on parenteral therapy in hospitalized patients, oral antibiotics can be surprisingly effective in selected cases. Many agents (see below) have excellent oral bioavailability with some agents (e.g. quinolones) attaining serum levels that equal those following parenteral administration
- **How sick is the patient?** While oral antibiotic therapy is often quite effective, be cautious of oral treatment in critically ill, septic patients, especially during the first 24 hours of care where survival can depend upon getting adequate serum levels of the selected drug.
- **Nausea and vomiting—a red alert!** Don't rely on oral therapy in patients with poorly controlled nausea and vomiting or significant GI tract disease (e.g. ileus; malabsorption; short bowel syndrome)—attaining adequate serum levels is doubtful in this situation and could lead to clinical failure.
- **Cost and convenience:** A major advantage of oral therapy is the non-inconsiderable cost savings—oral drugs tend to be cheaper and oral therapy can often shorten or prevent a costly hospital admission.

With these benefits and precautions in mind, here are some of the practical aspects of oral antimicrobial therapy that physicians should know:

1. Know the basics of oral absorption and serum drug levels

When choosing an oral agent, keep in mind that not all antibiotics are created equal—oral bioavailability is variable depending upon the agent and may differ within the same class (see Appendix 3).

When choosing an oral antibiotic, keep the following in mind…

- **Amoxicillin** has the best bioavailability (90% of dose) of penicillin agents and is the logical choice when oral penicillin is indicated.
- **Cephalexin** (99%) has the best bioavailability of cephalosporins, but is hampered by the necessity for more frequent dosing (requires QID or Q 6hr dosing). Other oral cephaloporins (e.g. cefuroxime) are more convenient (once daily or BID dosing) but have lower absorption (50-80%) and often more expensive.
- **Quinolones** have excellent bioavailability (> 70%) —in patients with an intact gut, serum levels after oral administration often equal those seen following parenteral dosing.

- **Doxycycline** and **minocycline** are better absorbed (90% +) than tetracycline (60%) with the additional advantage of less frequent dosing (BID vs QID).
- **Macrolides:** Although absorption of most macrolides (Azithromycin; clarithromycin) is on the lower side (35-50% of a dose), their ability to "concentrate in the macrophage" makes up for some of the deficit and assures activity against intracellular bacteria such as *Legionella* species.
- **Trimethoprim-sulfamethoxazole:** This agent has generally excellent (95% +) bioavailability but should be taken on an empty stomach for optimal absorption.
- **"Anaerobe" agents: Clindamycin** and **metronidazole** have excellent oral absorption (approximately 90% bioavailability).

Word of Warning

Dosing dilemmas—oral β -lactam tolerance: Although some β-lactam agents (e.g. amoxicillin; cephalexin) have "excellent" oral availability, GI side effects (nausea, vomiting, diarrhea) limit dosing and prevent the much higher levels (5-10 x PO levels) attained following parenteral administration. In seriously ill patients, administer β-lactam agents via a parenteral route until you are sure the patient is clinically stable.

Go with what you know: There are so many oral agents that keeping track of the complexities (e.g. dosing; bioavailability; drug interactions etc.) can sometimes be daunting. In order to minimize confusion, try to get comfortable with an agent from each class so that you are fully familiar with the complexities of a specific drug. While newer agents sometimes seem more "attractive", older ones are likely to be cheaper and have a longer track record of safety.

ID History: The initial form of penicillin—penicillin G—was hampered by poor oral absorption. In an effort to improve acid-stability (a must for any agent that has to pass through the stomach), chemists altered the initial fermentation brew, leading to the production of phenoxymethyl penicillin (Pen VK)—an oral penicillin with over 50% absorption following oral administration.

2. To "feed or fast"—understand antibiotic-food interactions

Depending upon the agent, intestinal absorption of drugs can be tremendously affected by the presence of food or other medications in the intestinal tract (see Appendix 3). The effect of food on absorption (and side effects) can generally be broken down into one of three categories…

- **Food increases absorption:** With drugs such as atovaquone (PCP and malaria prophylaxis), cefuroxime, intraconazole (tablets) and nitrofurantoin, food has a positive effect and *increases* drug absorption.
- **Food decreases absorption:** Food interferes or delays absorption of ampicillin, azithromycin, dicloxacillin, ciprofloxacin, sulfonamides and tetracyclines—whenever possible, take these drugs on an "empty" stomach and try to avoid administration at mealtimes.
- **Food improves GI tolerance:** Gastrointestinal side effects are common with many antibiotics—in some cases (amoxicillin, erythromycin, metronidazole), administration with a meal or snack may decrease GI upset.

In most situations, pharmacists will be aware of the requirements and the precautions will be listed on the bottle. Unfortunately, time is at a premium and patients may not always be aware of the correct way to take meds. Learn the food "requirements" for the handful of agents that you prescribe. Whenever possible, inform the patient at the time you write the prescription or provide a handout outlining the appropriate precautions.

WATCH OUT! Adverse Effects

GI side effects—a potent pitfall: Do not underestimate the potential gastrointestinal side effects of oral antibiotics—significant nausea and vomiting will hamper the patient's ability to take the prescribed drug, leading to non-compliance and drug "failure". Such side effects are not always predictable—one patient will complain of severe GI side effects while another will appear to have an "iron stomach" and be able to take just about anything with impunity. Only a relatively small number of medications *require* food—in most instances, antibiotic absorption and peak levels are better on an empty stomach. Nevertheless, offering the drug with food—or a snack— may help some patients, so consider this an option, but be wary of of the potential for food to adversely impact drug absorption.

3. Down on the "FARM"—antibiotic-warfarin interactions

Many of your patients will be on warfarin (coumadin) for various conditions—when starting an oral antibiotic, be mindful of antibiotic-warfarin interactions and try to choose agents that are less likely to have an effect. Remember the names of antibiotics most likely to have an adverse interaction with warfarin using the mnemonic **FARMS**:

Table 3: Antibiotic-warfarin interactions (the "dirty five")

Drug	Outcome	Comments
Fluoroquinolones	Increased INR	
Azoles	Increased INR	
Rifampin	Decreased INR	
Metronidazole	Increased INR	
Sulfa (TMP/SMX)	Increased INR	

* Azithromycin has less drug interactions than other macrolides

Try to avoid the above antibiotics in patients receiving warfarin—if an antibiotic is necessary, monitor the INR closely (every other day) and adjust the anticoagulant dose as needed.

When combining antibiotics with warfarin, keep in mind the following:

√ **Rifampin** is an especially problematic drug because of its' ability to enhance CYP450 metabolism—in most cases INR will *decrease* following concomitant administration with warfarin.

√ **"Dirty five":** The rest of the "dirty five" (fluoroquinolones, azoles, metronidazole, sulfa drugs) *increase* the INR when given to a patient already receiving warfarin.

√ **B-lactam agents (**penicillins; cephalosporins) are less likely to have an effect on warfarin; however, however both **nafcillin** and **dicloxacillin** may lead to *reduced* INR by accelerating warfarin metabolism..

√ **"No interactions":** Studies in "normal" individuals (demonstrating "no interaction") don't necessarily reflect outcomes in patients with an acute illness—in patients receiving concomitant warfarin, always have a low threshold for checking a prothrombin time, even in those patients where a drug interaction is said to be "uncommon".

Word of Warning

Warning: Whenever you add a new drug to a patient on warfarin, warn the patient about the potential for bleeding and consider checking an INR (in a few days) to make sure no major alterations have occurred.

4. Pulmonary "pearls"—using respiratory quinolones

A major advance in management of respiratory infections has been the advent of the "respiratory quinolones"—quinolone drugs with special activity against respiratory pathogens such as *Streptococcus pneumoniae* and the "atypical organisms" (e.g. *Mycoplasma, Chlamydophila, Legionella*).

The "**respiratory quinolones**" include agents such as levofloxacin (2nd generation quinolone) and moxifloxacin and gatifloxacin (3rd generation quinolones). These drugs have very good oral absorption (90% +), convenient dosing (once daily) and—in the United States—excellent activity against *Streptococcus pneumoniae* (including penicillin resistant strains) and "atypical" respiratory pathogens..

Table 3: Antimicrobial activity of respiratory quinolones

Quinolones	Ciprofloxacin 1st generation	Levofloxacin 2nd generation	Moxifloxacin 3rd generation
Pneumococcus	Fair-poor	Good	Excellent
Atypicals*	Good	Good	Good
Gram negative bacilli			
E. coli	Good	Good	Good
P.. aeruginosa	Good-excellent	Good-excellent	Poor
Anaerobes	Poor	Fair-poor	Good-fair

* *Mycoplasma pneumoniae, Chlamydiophilia pneumoniae, Legionella* species

When using respiratory quinolones, keep the following in mind…

√ **Head-to-head comparisons:** Compared to levofloxacin, the "third" generation respiratory quinolones (moxifloxacin; gatifloxacin) have "two step" inhibition of bacterial DNA gyrase—although this leads to better *in vitro* "test tube" activity against *Streptococcus pneumonia*, it's not clear that this leads to better outcomes.

√ **Ciprofloxacin failures:** *Do not* use ciprofloxacin for respiratory infection where "gram positives" are a possibility—*Strep. pneumoniae* may be resistant to this drug, leading to antibiotic failure.

√ **Moxifloxacin** is eliminated via biliary secretion—*do not* rely on this drug for management of gram negative urinary tract infection.

WATCH OUT! Adverse Effects

Quinolone quirks—side effects associated with quinolones

In addition to the standard side effects associated with quinolones (drug allergy; nausea/vomiting), be aware of the following quinolone side effects:

QT prolongation: Although a class effect of quinolones, laboratory studies suggest it may be more common with selected agents (Moxifloxacin > levofloxacin > ciprofloxacin). The most dangerous outcome might be an unexpected bout of ventricular tachycardia (*torsades de pointes*), especially in those with underlying electrolyte abnormalities ((e.g. Lo K^+ or Mg^+) or patients receiving other QT-prolonging drugs (e.g. tricyclics; azoles; macrolides). When in doubt, check a baseline (and followup) EKG (to measure QT interval) while the patient is on therapy.

Tendon rupture: Quinolones interfere with cartilage formation and can have adverse effects on tendons. There have been cases of tendon rupture in patients taking these drugs, especially in those with underlying rheumatic diseases or individuals participating in vigorous physical exertion. In a patient taking a quinolone, counsel against vigorous exercise—avoid marathons while taking these drugs!

Absorption problems: Divalent ions (Mg+2; Ca+2) interfere with quinolone bioavailability—absorption is decreased if administered with multivitamins, milk and selected agents (e.g. sucralfate). In general, take quinolones on an empty stomach and avoid concomitant vitamins and milk products.

5. Battling bladder infections—outpatient management of UTIs

Standard oral agents for urinary tract infection (Table 4) include ampicillin, sulfa drugs (trimethoprim/sulfamethoxazole), cephalosporins (cephalexin) and quinolones (ciprofloxacin). Unfortunately, increasing antimicrobial resistance among outpatient *E. coli* isolates suggest that some of these drugs may be less-than-effective for empiric treatment of UTI.

Ampicillin—once a "mainstay" of outpatient antimicrobial therapy for UTIs—has become less effective with time (now less than 50% of outpatient *E. coli* isolates are susceptible) and is *not recommended* for empiric therapy of cystitis. Although ciprofloxacin remains a good choice for empiric therapy of cystitis, increasing resistance (now close to 20% of outpatient *E. coli* isolates are resistant) leads to occasional failures.

Table 4: Outpatient *E. coli* susceptibilities*

Antimicrobial	% susceptible
Ampicillin	40
Cephalexin	80
Ceftriaxone	95
TMP/SMX	60
Ciprofloxacin	80
Nitrofurantoin	95

* Based on 1316 isolates from Los Angeles, Ca.--2011

Table 5: Agents for treatment of cystitis

Antibiotic	Dose
Ampicillin	500 mg PO QID x 5 days
Cephalexin	500 mg PO QID x 5 days
Ciprofloxacin	500 mg PO BID x 3 days
Fosfomycin	3 gm PO x single dose
Methenamine	1 gm PO Q 6hr x 7-10 days
Nitrofurantoin	100 mg PO BID x 5 days
Trimethoprim-Sulfa	1 DS tab (160 mg/320 mg) BID x 5 days

While you are likely familiar with the most of the above "UTI" agents, there are also a few other drugs that might come in handy in selected situations. Use of these agents is limited to "non-toxic" patients with simple cystitis or urinary tract colonization:

- **Nitrofurantoin:** An old standby for UTI, this drug still maintains good activity against most strains of *E. coli* (90%+ for community strains!) and is commonly used in obstetrics because of lack of fetal toxicity (Class A drug). Nitrofurantoin (Macrodantin) attains good urine levels but has poor tissue penetration—it can't be relied on in patients with serious invasive infection (e.g. pyelonephritis) and is best for non-toxic patients with simple cystitis.
- **Fosfomycin:** A "new" antimicrobial agent, this drug impairs bacterial cell wall formation in both gram positive (enterococcus) and gram negative (*E. coli*) bacteria. Again, it's use is limited to "non-toxic" patients with lower urinary tract infection, particularly women with cystitis .Avoid this drug in patients with suspected pyelonephritis. The drug comes in powdered (sachet) form and is usually give as a single 3 gram dose; however, in selected patients (ESBL *E. coli.*) it may be given for a longer course.
- **Methenamine mandelate:** A urinary "antiseptic", this drug is also limited to non-toxic individuals with lower urinary tract/bladder infection. It has activity against *all* clinically significant bacteria (including *Pseudomonas aeruginosa*) and has the advantage that resistance *will not* develop despite repeated use. Taken by mouth, methenamine is converted into the active form (formaldehyde) in the bladder. This process requires "time in the bladder"—conversion will not occur in patients with an indwelling Foley catheter unless the catheter is clamped for a period of 1-2 hours.

When treating urinary tract infection, keep the following in mind…

√ **Rising resistance:** There has been increasing antimicrobial resistance to "standard" agents such as ampicillin or TMP/SMX—be careful with empiric use of these agents in "sicker" patients.

√ **A quinolone quandary:** Although *E coli* susceptibility to ciprofloxacin still remains good (~ 80 % of strains susceptible), rising community resistance may also render these agents less effective in the seriously ill patient.

√ **IV vs PO therapy?** Because of the rising resistance to standard agents, consider an initial parenteral dose (e.g. IM/IV ceftriaxone) in sicker patients pending culture and susceptibility results.

√ **Nitrofurantoin redux:** This "older" agent is safe in pregnancy and still retains pretty good activity against urinary tract *E. coli* isolates—consider its' use in non-toxic patients with "simple" cystitis.

Practice TIP

The ESBL Conundrum: Gram negative bacilli such as *E. coli* and *Klebsiella* species may be resistant to 3rd generation cephalosporins via a plasmid mediated B-lactamase enzyme (the so called "Extended spectrum B-lactamase" or ESBL enzyme). Oral therapy is problematic since ESBL isolates are often resistant to other classes of agents such as quinolones or nitrofurantoin. For patients with "simple" urinary tract infection (e.g. cystitis), one trick is to treat with a combination of amoxicillin/clavulanic acid and cephalexin—the clavulanic acid blocks the ESBL B-lactamase enzyme and permits cephalexin antibacterial activity. Another option is every other day fosfomycin (1 gm PO QOD x 7-10 days)—while these options are possible in the afebrile, "stable" patient (cystitis), seriously ill, "sick" patients (fever; sepsis) require parenteral agents such as carbapenems (e.g. meropenem; imipenem; doripenem; meropenem).

6. Macrolide mania—effective use of the "new" erythromycins

Macrolides have a deserved reputation as well-tolerated, "safe" drugs with an important role in managing less serious respiratory infections (e.g. bronchitis, sinusitis, "mild" pneumonia). When compared to the old standard of erythromycin, the newer agents (azithromycin; clarithromycin) have slightly broader antibacterial activity (+ *H. influenza* activity) and less GI upset associated with administration.

Drug absorption can be a problem—most of these agents have less than 50% absorption by oral route; however, they "concentrate" in macrophages, a feature that increases activity against intracellular organisms such as *Legionella pneumophila* .

When using these agents, pay attention to the following:

- **Azithromycin:** The ubiquitous "Z-Pack" (500 mg Day #1, then 250 mg Qday 2-5) has become one of the most commonly prescribed antibiotics in the United States. The drug can be given for "short course" therapy (5 days) since it is taken up by leukocytes and maintains intracellular levels for up to 10 days. The five day course is generally adequate for "milder" infections (e.g. pharyngitis, bronchitis); however, the company recommends higher dosing (500 mg PO Qday x 10 days) for patients with established pneumonia (see Table 4). When compared to clarithromycin, azithromycin has less interaction with the CYP450 enzyme system and less drug interactions with other agents.
- **Clarithromycin**: Clarithromycin has a antibacterial spectrum that is similar to azithromycin. The main difference between the two agents is dosing (Clarithromycin has to be given *twice* a day) and potential for drug interactions (Clarithromycin has much greater effect on the CYP450 enzyme system). The CYP450 effect leads to significant interactions with warfarin (increased warfarin effect), theophylline (potentially toxic theophylline levels) and prolongation of the QT interval. Clarithromycin has found a special niche in treatment of *H pylori* infection—"triple" regimens (clarithromycin; bismuth; metronidazole) are effective in treatment of duodenal ulcer due to *H. pylori*.
- **Erythromycin:** This is the "old standard" that remains in use because of its' reliability, cost profile and long track record of safe use. Despite these benefits, it generally requires more frequent dosing (3-4 x per day) and is more likely to cause GI side effects. In the United States, azithromycin and clarithromycin have generally replaced erythromycin for management of respiratory tract infection.

Table 5: Dosing of the "new" macrolides for respiratory infection

Condition	Azithromycin Dosing	Clarithromycin Dosing
Pharyngitis/tonsillitis (2nd line Rx) *Streptococcus pyogenes*	500 mg (Day1), followed by 250 mg daily (Day 2-5).	250 mg PO BID x 10 days
Community-acquired pneumonia (mild))	500 mg (Day1), followed by 250 mg daily (Day 2-5). or 2 mg ER (single dose)	250 mg PO BID x 7-14 days or 1000 mg (XR) q24 hrs x 7days
Community-acquired pneumonia (moderate-severe)	500 mg Qday x 10 days	500 mg PO BID x 7-14 days or 1000 mg (XR) q24 hrs x 7days
Bronchitis (AECB*) (mild to moderate)	500 mg QD x 3 days OR 500 mg (Day1), followed by 250 mg daily (Day 2-5).	500 mg Q12 hr x 7-14 days or 1000 mg (XR) q24 hrs x 7days
Acute bacterial sinusitis	500 mg QD x 3 days	500 mg PO BID x 14 days or 1000 mg (XR) q24 hrs x 7days
Skin/soft tissue (Uncomplicated due to *Staph aureus* or grp A strep)		250 mg Q12 hr x 7-14 days

**ACEB: Acute Exacerbation of chronic bronchitis: XR: Extended release*

A Z-pack "Zebra"— the QT interval and azithromycin safety

The US Food and Drug administration has recently warned about the possibility of developing fatal cardiac arrhythmias due to QT interval prolongation (Ventricular tachycardia or "*Torsades de pointes*") among patients taking the standard 5-day course of azithromycin (see FDA Advisory 3/12/13). These concerns were based on several sources, including retrospective, population-based clinical studies and case reports of patients developing ventricular arrhythmias while receiving azithromycin. Several points about this are worth noting. While the risk is relatively low, it is more likely in individuals with known risk factors for QT prolongation such as congenital QT prolongation, electrolyte disturbances (hypokalemia; hypomagnesemia), and those receiving other drugs known to prolong the QT interval (e.g. anti-arrhythmics). Furthermore, other agents used for respiratory infection (e.g. levofloxacin) are known to prolong the QT interval and have a similar risk. While such warnings don't necessarily preclude use of these agents, they do offer caution, especially in patients with underlying cardiovascular disease or those with known risk factors for QT prolongation. In these cases, therapy with alternate agents (e.g. amoxicillin; penicillin VK or tetracyclines) might be safer as initial therapy, especially for "simple" respiratory infection (e.g. sinusitis; bronchitis) where the likelihood of pneumonia is less.

See: Mosholder AD et.a. Cardiovascular risks with azithromycin and other antibacterial drugs. N Engl J Med. 2013 May 2;368(18):1665-8.

7. Tetracyclines—from ACNE to Lyme

Introduction of tetracycline in the 1950s led to widespread use (and overuse) of these relatively safe agents. Although resistance subsequently hampered their continued use, they have excellent activity against a number of less common pathogens including spirochetes (syphilis, Lyme disease, leptospirosis), zoonotic pathogens (Psittacosis, Q fever, tularemia, plague, rickettsia) and bacteria associated with "atypical pneumonia" (*Mycoplasma, Chlamydophilia*). More recently, the drug has seen additional use as an agent for management of less complicated MRSA infections.

Because of less convenient dosing, tetracycline (QID dosing) has for the most part been supplanted by doxycycline or minocycline (BID dosing). Keep in mind that absorption of these agents is often hindered by food, milk and other meds (vitamins, calcium)—take these drugs on an "empty" stomach and avoid concomitant food.

In your daily practice, be familiar with the use of the following agents. ..

- **Doxycycline:** Now commonly used for MRSA in a standard dose (100 PO BID). Patients should avoid direct sun exposure (eg where a hat or use sunscreen) since photosensitivity eruptions are a problem with this agent.
- **Minocycline:** More commonly used for treatment of acne, this drug has the best in vitro activity of all tetracyclines against MRSA and is probably the drug of choice among this class. Be careful with long term (> 2 weeks) minocycline therapy—the drug can have some odd "hypersensitivity-like" reactions that can lead to a lupus-like syndrome (pulmonary infiltrates).

.

Practice TIP

Doxycycline—The Drug in your "Back Pocket": Doxycycline has activity against a number of unusual pathogens including "zoonotic" bacteria (plague, tularemia, Q fever *Bartonella*), spirochetes (syphilis; Lyme, Leptospirosis, *Borrelia*) and rickettsial diseases (Rocky Mountain spotted fever; murine typhus). When you are not sure what is going on—and patients are unresponsive to the ER "standard" (Zosyn + Vanco)— consider the possibility of an exotic pathogen and add doxycycline till additional test results are available.

8. Breaking up an "anoxic" bugfest—treating anaerobic infection

Anaerobic bacteria play an important role in a number of "mixed" anaerobic/aerobic conditions including intraabdominal infection (diverticulitis), diabetic foot infection, lung abscess and head/neck infection (dental abscess). Whenever you have a foul smelling infection, keep in mind anaerobes and try to include one of these agents in the regimen:

- **Amoxcillin/clavulanic acid (Augmentin):** In addition to standard pathogens (streptococci, staphylococci, gram negative bacilli), this agent has excellent anti-anaerobic activity and is a good for outpatient management of diverticulitis, diabetic foot infection and lung abscess. Taking this agent with food may help to reduce some of the gastrointestinal upset.
- **Clindamycin:** In addition to it's streptococcal/staphylococcal activity, this drug has good activity against most anaerobes including gram negative anerobes such as *Bacteroides* and *Fusobacterium* species. Although it has activity against clostridia species, approximately 25% of *C. perfringens* may be resistant making it a less-than-reliable agent for serious, life threatening infections requiring hospitalization.
- **Metronidazole:** This drug remains quite potent against "strict" anaerobes such as *Bacteroides* and *Fusobacterium* species—there is little resistance despite years of use. Keep in mind; however, that some aerotolerant gram positive anaerobes (*Actinomyces* species, Lactobacillus, Bifidobacteria, streptococci) are typically resistant to metronidazole—an additional agent (e.g. amoxicillin, levofloxacin) is required when treating "mixed" aerobic/anaerobic infection with this drug. Metronidazole is rarely employed as a "single agent" except in *C. difficile* colitis or special situations (e.g. *Bacteroides* species endocarditis) where mono-infection with a strict anaerobe is present.

9. Taming a tiger—managing outpatient CA-MRSA infection

Approximately 50% of outpatient *Staphylococcus aureus* strains are deemed community-associated methicillin resistant (CA-MRSA) organisms—strains that are typically resistant to B-lactam agents such as oxacillin (and dicloxacillin) and cephalosporins. In addition to B-lactam resistance, these isolates are often resistant to quinolones. (see Table 6).

When treating a possible CA-MRSA infection, keep in mind the following:

√ **Clindamycin:** CA-MRSA strains that are resistant to erythromycin may develop inducible resistance to clindamycin—in this situation, the laboratory should perform a "D-test" to rule out this possibility.

√ **"Combo" treatment:** Although not proven, some experts recommend combination therapy (e.g. TMP/SMX + rifampin; minocycline + rifampin) in patients with more serious infection.

√ **Rifampin:** *Never* use rifampin as a single agent since resistance may develop on therapy. Also be cautious adding this agent because of potential interactions with other drugs the patient may be taking.

√ **Strep alert:** Group A streptococci is typically resistant to TMP/SMX—when treating suspected CA-MRSA soft tissue infections with this agent, add clindamycin, rifampin or a B-lactam agent (e.g. amoxicillin; cephalexin) if group A strep is a possibility.

Table 6: *Staph aureus* susceptibilties*

Antibiotic	% Strains
Oxacillin	50
Cefazolin	50
Levofloxacin	50
TMP/SMX	98
Clindamycin	92
Rifampin	99
Vancomycin	100

* OVMC 422 community isolates—2003

Table 7: Oral antibiotics for CA-MRSA

Antibiotic	Dose
TMP/SMX (Bactrim)	1-2 DS tablet PO BID
Clindamycin	600 mg PO Q 6hr
Doxycycline	200 mg load; 100 mg BID
Minocycline	100 mg PO BID
Rifampin	600 mg PO daily
Linezolide (Zyvox)	600 mg PO Q 12 hr

Practice TIP

MRSA management tips: For patients with suspected focal MRSA infection (boils or carbuncles), surgical treatment (e.g. incision and drainage of the lesion) may be as important as antibiotic therapy. Although definitive studies are not yet completed, most ER docs will cover suspected MRSA infection with a course of oral trimethoprim-sulfamethoxazole (Bactrim DS: 1-2 tabs PO BID) or PO doxycycline (100 mg PO BID). If you are concerned about streptococcal infection, add cephalexin or use oral clindamycin until culture results are available (strep is often resistant to TMP/SMX or tetracyclines). Never underestimate the potential seriousness of cutaneous staphylococcal infection—even "simple" skin infections can sometimes lead to life-threatening bacteremia with all its' attendant complications (e.g. endocarditis; osteomyelitis; septic arthritis; pneumonia)

10. A word of warning…when oral antibiotics are "inappropriate"

While we've given you a lot of reasons to choose oral antibiotics (e.g. convenience; good absorption; outpatient therapy), there are some definite situations where oral antimicrobial therapy might be dangerous or downright contraindicated.

Before placing a patient on a regiment of oral antibiotics, keep in mind the following reservations or "contraindications"…

➢ **The "septic" patient:** Don't rely on initial oral therapy in the seriously ill, "septic" patient—most pharmacokinetic studies are in "healthy" patients and absorption parameters (e.g. bioavailability; serum levels) might be different in hypotensive or seriously ill individuals. For the critically ill patient, parenteral therapy is best until the patient is stabilized and culture results are available.

➢ **Gastrointestinal disease:** Although gastrointestinal disease doesn't necessarily preclude oral therapy, be cautious about relying on oral agents in seriously ill patients with serious underlying intestinal diseases such as malabsorption and ileus.

- **Nausea and vomiting:** If a patient vomits up the medication, it's not likely to be effective—poorly controlled nausea and vomiting is a contraindication to oral antibiotic therapy.
- **Patient compliance:** Some oral antibiotic regiments (e.g. B-lactams, clindamycin) require more complicated QID or TID dosing regimens. When prescribing an oral regimen, keep in mind the complexity of the regime and your patient's ability to comply—if doubtful of patient compliance, enlist a family member—or visiting nurse—to help with the regimen.

What you need to know about oral antibiotic therapy…

- Oral antibiotic therapy can be as effective as parenteral administration, provided that the patient 1) has minimal nausea/vomting, 2).receives an agent with good oral bioavailability (>90% of dose) and 3). Is compliant with the regimen.
- Avoid initial oral antimicrobial therapy in critically ill, septic patients, or those with significant gastrointestinal disease such as uncontrolled nausea/vomiting, ileus or malabsorption.
- Antimicrobial agents with especially *good* bioavailability (> 90% absorption) include quinolones, clindamycin, trimethoprim/sulfamethoxazole, metronidazole and selected B-lactam agents (amoxicillin; cephalexin).
- Food interactions are important in oral antibiotic therapy. Some agents are best taken on an empty stomach (e.g. quinolones, azithromycin, trimethoprim-sulfamethoxazole) whereas others have enhanced aborption when taken with food (atovaquone; cefuroxime, itraconazole, nitrofurantoin).
- Antibiotics that have adverse drug interactions with warfarin (Coumadin) can be remembered with the mnemonic "FARMS"—fluoroquinolones, azoles, rifampin, metronidazole and sulfa drugs. Rifampin *decreases* the INR, whereas the other four agents lead to an increase in INR when taken with warfarin.
- Respiratory quinolones (levofloxacin; moxifloxacin; gatifloxacin) have excellent activity in community acquired pneumonia because of their activity against *Streptococcus pneumonia* and "atypical" pathogens such as *Mycoplasma pneumonia*, *Legionella* species and *Chlamydophilia.*
- In addition to "standard" agents such as ciprofloxacin, amoxicillin and sulfa drugs (TMP-SMX), urinary antiseptics such as nitrofurantoin, fosfomycin and methenamine mandelamine have activity against simple cystitis and non-complicated lower urinary tract infection.
- Doxycycline and minocycline have activity against "atypical" pulmonary pathogens (e.g. *Mycoplasma pneumonia; Chlamydophilia*) as well as "uncommon" bacteria responsible for spirochetal (syphilis; Lyme; leptospirosis) and zoonotic inection (Q fever, tularemia, psittacosis, plague).
- Oral agents such as TMP-SMX (trimethoprim-sulfamethoxazole), clindamycin, doxycycline and linezolid are useful for management of less-severe MRSA infections, provided that susceptibility testing rules out drug resistance.

Chapter 13

Persistent fever?—what do when things go wrong

You've made your initial call on a likely diagnosis and started the patient on a regimen of empiric antibiotics—forty eight hours later, there has been no clinical response and the team—and patient's family—turn to you for an answer. This is a common scenario that requires you to review and reconsider the case. When you take a second look, broaden your differential and keep the following possibilities in mind:

1. Incorrect diagnosis!

Medicine can be a humbling experience— disease presents with a multitude of sometimes downright misleading symptoms and—despite our best efforts—our initial assumptions may be wrong. It's now 48 hours (or more) after the initial treatment and time to reexamine the patient. Check the initial laboratory data (including culture results) to see if your initial suspicions are reconfirmed. Is there new information or new findings? Could it be a non-infectious problem? Reconsider the case and if necessary, broaden your differential.

2. The wrong drug?

Did you give the right antibiotic? Now that culture results are available, make sure the organisms are susceptible and the patient is receiving appropriate therapy. Also keep in mind the possibility of "mixed" infection—make sure your initial empiric therapy covers all the likely pathogens at the site in question. Remember also the importance of the infection "site" and pharmacokinetics—is your patient receiving the correct drug at the proper dose? This is especially important with central nervous system infections—while a bug might be susceptible, poor CSF penetration will delay clinical response or doom the treatment to failure.

3. The power of patience…a "delayed" antibiotic response

Response to antibiotics varies depending upon the identity of the infection, choice of antibiotic and the nature of the underlying host. With appropriate antibiotic therapy, most standard bacterial infections generally respond within 48 to 72 hours; even if the patient is not completely afebrile, they should be clinically improving and feeling better. Keep in mind that the following patients might have a delayed response to antibiotic therapy:

- **Immunocompromised patients:** Neutropenic patients, patients on immunosuppressives (e.g. chemotherapy, corticosteroids) and those with impaired immune systems (e.g cancer patients, HIV) may have a delayed response to antibiotics. While these individuals should improve with appropriate antibiotic therapy, they don't "bounce back" as quickly and—even if they are receiving appropriate therapy—a full response may be delayed by a few days. In the patient with a "neutropenic" fever, a period of 5 days is usually used before the treatment is deemed a "failure".

- **"Medically impaired"** patients including individuals with underlying renal failure, chronic cardio-pulmonary disease and connective tissue disorders are also likely to have a slower response to appropriate antibiotic treatment.

- **Specific infections:** Different sometimes have a different response to therapy and one can't automatically assume that the treatment is a failure. The patient with uncomplicated pneumococcal pneumonia often responds promptly (within 24-48 hours) to appropriate antibiotic therapy; defervescence may be delayed in the patient with Legionnaire's disease—even if they are receiving the "right" antibiotic.

In these situations a steady hand is necessary—if you strongly suspect a specific diagnosis, don't be too quick to change therapy if the patient isn't automatically improved within 24-48 hours.

4. Saved by the scalpel…Surgical intervention

Modern antibiotics are wonderful but they won't necessarily cure an intraabdominal abscess unless the patient receives appropriate surgical or catheter drainage. In a patient with a well-documented infection site, keep the following in mind…

- **CNS infection:** Brain abscess, epidural abscess and subdural empyema—unless they are relatively small—generally respond faster following surgical drainage. A "wait and see" period may be appropriate if the abscess is relatively small and the patient remains neurologically stable (this decision needs to be made with the assistance of a neurosuregeon).

- **Pneumonia:** An underlying empyema may be one reason a patient with a bacterial pneumonia may not improve—if a patient has a significant pleural effusion, perform a thoracentesis to exclude an infected pleural space and consider chest tube drainage if an empyema is highly likely. In rare cases, patients with true "gangrene" of the lung—a focal necrotic abscess or lobe—may require lobectomy or surgical drainage.

- **Intraabdominal infection:** Most patients with a significant intraabdominal abscess will require surgical or catheter drainage in order to assure cure. Patients with pyogenic liver abscess and persistent fever will often respond rapidly following catheter drainage—in addition to the therapeutic effect, this will increase the chances of identifying a specific pathogen if initial blood cultures remain negative.

- **Pyelonephritis:** In patients with persistent fever, consider the possibility of an underlying peri-nephric abscess or pyohydronephrosis—ureteral obstruction with renal pelvic abscess. Remember that diabetics are at risk for emphysematous pyelonephritis—look for "gas" on the CT scan and consider the need for catheter drainage or outright nephrectomy.

- **Soft tissue infection:** In a patient with a "severe" cellulitis (severe pain, advancing infection; WBC > 20K) always keep in mind the possibility of an underlying necrotizing soft tissue infection or pyomyositis. In these cases, consider additional studies (e.g. CT scan, MRI, UTZ) and make sure that a surgeon is involved as early as possible. Do not rely completely on radiographic studies to rule out a "surgical infection"—despite "normal" studies, sometimes the only way to make a diagnosis of necrotizing fasciitis is by surgical exploration.

5. "Bugs in the blood"…persistent bacteremia

The patient has documented bacteremia and has been placed on "appropriate" antibiotics—unfortunately, he or she remains febrile and repeat blood cultures (48 hours later) remain positive. Here is a short list of possible explanations for this problem:

- **Resistant bacteria:** Check the susceptibilities and make sure the "bug" is susceptible to the "drug".

- **Inadequate blood levels:** This may be a problem in patients receiving oral antimicrobial therapy, or with certain antibiotics (e.g. aminoglycosides; vancomycin) where clinical response depends upon reaching adequate levels. Make sure the patient is receiving the prescribed drug (check the nursing record) and check blood levels where indicated.

- **Vascular infection:** Persistent bacteremia is a hallmark of patients with vascular infection such as endocarditis, infected aneurysm and septic thrombophlebitis. In addition to bactericidal therapy (a "must" for endocarditis), consider the need for valve excision and/or drainage/debridement of a perivalvular infection. Patients with an infected aneurysm frequently require surgical excision of the affected lesion; individuals with suppurative thrombophlebitis may need surgical extraction of the infected venous segment/clot.

- **"Pus under pressure":** Patients with underlying abscess, especially if related to an obstruction (e.g. stone, catheter, tumor, prosthetic device) often have persistent bacteremia—image the suspected site and consider surgical or catheter drainage if an abscess is found.

6. Search for "zebras"…"non-bacterial" infections

Of course, you wouldn't expect a viral infection to respond to pencillin unless there was the possibility of a bacterial superinfection. In a patient who fails to respond to antibiotics, if the standard cultures are "negative", think outside the box and consider the following "non-bacterial" infections:

- **Viral infection:** Common viral infections (e.g. influenza, EBV, CMV, HIV) are not likely to respond to routine antibacterial antibiotics.
- **Fungal infection:** Keep in mind the possibility of "endemic" fungus (e.g. histoplasmosis, blastomycosis, coccidioidomycosis) in patients with residence in or travel to the appropriate region. Hospitalized patients on broad spectrum antibiotics may be at risk for nosocomial candidiasis— check for fungal colonization, obtain fungal blood cultures and consider a trial of an azole for echinocandin. Febrile neutropenic patients are especially at risk for invasive fungal infection—with persistent fever, look for nodules/infiltrates on chest CT scan and consider a trial of voriconazole or amphotericin B.
- **Mycobacteria:** Tuberculosis can be a great mimic—check a PPD on your patient and consider additional testing (e.g. sputum AFB, biopsy) to clinch the diagnosis.
- **Parasitic infection:** Question the patient about previous travel (or transfusions) and check a peripheral blood smear for malaria or babesiosis.
- **"Atypical" bacterial infection:** Remember that not all infections respond to "Zosyn + vanco"—keep in mind the possibility of rickettsial infection (RMSF; murine typhus; erhrlichiosis), zoonoses (Psittacosis; tularemia; plague) and consider adding doxycycline if these are a possibility.

7. Wolves in sheep's clothing…fever due to non-infectious conditions

Not all patients with fever have infection—consider the possibility that he patient has one of the following "non-infectious" conditions (this is the short list!):

- **Pulmonary embolism** is notorious for mimicking pulmonary infection, especially in the bed bound, hospitalized patient. The PIOPED study on the clinical presentation of pulmonary embolism, suggested that up to 40% of patients developed fever as part of the clinical presentation. Although the fever is typically "low-grade" (less than 102 °F; 38.7 °C), patients may occasionally develop high-grade fevers accompanied by shaking chills or rigors.

- **Underlying malignancy:** A number of malignancies are associated with fever, especially underlying lymphoma and disseminated adenocarcinoma (with liver metastasis).

- **Endocrine conditions** such as hyperthyroidism and pheochromocytoma may present with persistent unexplained fever. Keep in mind the possibility of adrenal insufficiency in "septic" patients with fever and persistent hypotension.
- **Rheumatological disease** such as SLE and various forms of vasculitis commonly associated with fever (e.g. Wegener's granulomatosis; polyarteritis nodosa). Still's disease—a form of juvenile rheumatoid arthritis seen in adults—is notorious for high, spiking fevers and persistent leukocytosis.
- **Alcoholic hepatitis**: In the alcoholic with persistent fever, elevated liver tests and leukocytosis (sometimes to extreme levels of close to 100K) keep in mind the possibility of underlying alcoholic hepatitis; these patients may be febrile for weeks despite antibiotic therapy.

In a patient with unexplained fever, don't automatically assume "infection"—numerous non-infectious conditions can present with fever and chills.

8. Pharmaceutical pyrexia…Drug fever

In the hospitalized patient, drug fever—fever secondary to the any of the myriad number of drugs that the patient is taking—is an important cause of persistent fever. Although any drug can potentially cause drug fever, certain agents are more commonly associated with the condition (Table 1).

Table 1: Common causes of drug fever

Agent class	Drugs
Antibiotics	B-lactam agents (penicillins; cephalosporins), sulfa drugs, amphotericin B
Cardiovascular agents	Quinidine, procainamide, hydralazine, amiodarone
Antineoplastic drug	Bleomycin, daunarubicin, cytarabine, monoclonal Antibodies
CNS drugs	Phenytoin; carbamazepine; anti-psychotic agents

In the "world" of infectious disease, B-lactam agents (penicillins; cephalosporins) and sulfa drugs are notorious causes of drug fever. In an infected patient who appears to have clinically responded to treatment—but develops persistent or new-onset fever—keep in mind the possibility of drug fever and consider stopping the suspect agent or switching the drug to a new antibiotic class—defervescence within 48-72 hours will confirm the presence of drug fever.

In patients with fever, the following clues suggest the possibility of drug fever…

- **"Patient looks "well":** Although fever is present, the patient "looks well" despite persistent pyrexia.
- **Physical exam clues:** The following clues on physical examination suggests drug fever..
  - ✓ **Inappropriate bradycardia (10%):** Patients may not have an elevated pulse associated with the fever. Normally, patients with a fever of 102° F (38.7 °C) will have a pulse of approximately 110 beats per minute; with higher temperatures, the pulse will rise an addition 10 bpm for every additional degree in Fahrenheit (e.g. pulse of 130 bpm in patient with temperature of 104 ° F).
  - ✓ **Rash (25%):** Although often absent, presence of a maculopapular rash with accompanying pruritus is an important clue to the possibility of drug fever.
- **Laboratory clues:** Look for the following clues on laboratory testing…

- ✓ **Eosinophilia (25%):** While absolute eosinophilia (> 400 cells/mm3) is uncommon, patients with drug fever almost always has some eosinophils on peripheral smear.
- ✓ **Abnormal liver tests:** A mild elevation in liver tests (e.g. elevated AST, ALT, alkaline phosphatase) is common in drug fever.

When considering the possibility of drug fever, keep in mind the following…

- ✓ **"New drug" fever:** Although patients may develop fever secondary to a drug they have been receiving for some time, drug fever is more likely to be secondary to a newly introduced agent.
- ✓ **"Goal post fever"** In those receiving antibiotics, a clinical clue may be the presence of "goal post" fever—the infection initially responds to the antibiotic (with defervescence), but the patient's temperature returns 5-10 days later as they develop hypersensitivity to the agent.
- ✓ **Antibiotic "switch-out":** If you suspect antibiotic induced drug fever (often due to B-lactam agents or sulfa drugs), try to "switch out" the agent to a completely different class—if a drug fever is present, it usually disappears with 48 to 72 hours.

What to do with persistent fever—a simple checklist

When evaluating the patient with a persistent fever, keep the following checklist in mind…

- **Reexamine the patient** looking for clues on examination that you might have missed the first time around. Don't be afraid to repeat the history—especially if you encounter family or friends that might have additional information about the patient's condition.
- **Review the laboratory data** including any culture results and antibiotic susceptibility testing. See if the cultures confirm your initial diagnosis. If cultures are positive, review the antibiotic susceptibilities to make sure the patient is receiving antibiotics active against the infection.
- **Check antibiotic dosing:** On rare occasions (not all that infrequent!) the patient is not receiving the antibiotic that you ordered—review the medication list and make sure the patient is on the right agents at the appropriate dose. Specifically review the nursing "med sheets"—this is the official record of medication administration and ensures that the patient has received the antibiotics that you have ordered.
- **Consider the possibility of a "surgical" infection:** If there is a possibility of an abscess or "surgical" infection, don't be afraid to call your surgical colleagues. In some cases, a timely surgical intervention—or catheter drainage—will remove the cause of a persistent fever.
- **Repeat the blood cultures:** While we don't recommend blindly ordering repeated sets of blood cultures, a single set of repeat blood cultures might be helpful, especially in patients with already-documented bacteremia. As stated earlier, persistent bacteremia (while on appropriate antibiotics) raises the question of underlying vascular infection or an undrained abscess.
- **Suspect a non-infectious condition:** Don't automatically assume that all fever equals infection—remember the "non-infectious" conditions (see above) that may be associated with persistent fever.
- **Remember drug fever**, especially in patients receiving B-lactam antibiotics or sulfa drugs. The patient with drug fever will often look quite good despite the persistent fever. Don't forget the non-antibiotic agents—review the med list and always keep in mind the possibility of a drug-induced fever.
- **Be patient** and remember that a delayed response is sometimes par for the course in immuncompromised patients or those with underlying medical conditions. While a repeat evaluation may be appropriate, avoid frequent antibiotic changes unless you have a clear rationale.

Don't forget! Persistent fever requires a reassessment of a case to make sure that your initial evaluation and management were appropriate. In most cases, a thoughtful approach will allow you to generate a list of possibilities as to why your patient has not "responded" to the initial therapy. No doubt there will be pressure to "change" or add antibiotics—whenever possible, resist this unless there is a clear rationale for adding a new drug. If you choose to add a new agent, make sure you are clear about the reasons why and discuss your thinking with the patient's physicians. Nothing is worse—and more confusing—than a form of "antibiotic roulette" where antibiotics are changed on a daily basis because of a persistent fever or poor clinical response.

What you need to know about patients with persistent fever…

- If a patient does not respond to antibiotic therapy, consider the possibility your diagnosis is "incorrect"—reevaluate the case and consider the possibility of an alternative infectious—or non-infectious—diagnosis.
- If you believe your diagnosis is "correct", make sure the patient is receiving an appropriate antibiotic—and dosing—for the suspected condition. Check the nursing records to make sure the drug is actually be administered as prescribed.
- Consider the possibility that the patient has an abscess that requires surgical drainage—inadequate drainage of an intraabdominal abscess often leads to persistent fever.
- If patients have persistent bacteremia, consider the possibility of 1). Pathogen resistant to the chosen antibiotic, 2). Inadequate dosage of the appropriate antibiotic, 3). An abscess that requires surgical drainage or, 4). Intravascular infection such as endocarditis, an infected aneurysm or septic thrombophlebitis.
- If patient has a persistent fever (and cultures are "negative") consider the possibility of alternative agents such as fungi, mycobacteria and viral infection.
- Keep in mind that a number of "non-infectious" conditions may present with persistent fever including pulmonary embolism (and deep venous thrombosis), alcoholic hepatitis, rheumatologic conditions (SLE; vasculitis, Still's disease), malignancy and endocrine conditions (e.g. hyperthyroidism).
- Drug fever is an important cause of persistent fever. An important clue is that the patient "looks good" despite the persistence of fever. Other clues to the possibility of drug fever include inappropriate bradycardia (high fever without accompanying tachycardia), skin rash, eosinophilia and abnormal liver tests. If drug fever is a possibility, consider switching the patient to an alternative agent from a different class.
- Be patient—immunocompromised patients—and those with other chronic conditions (e.g. congestive heart failure, renal or pulmonary disease) may have a "delayed" response to therapy compared to individuals with otherwise "normal" immune systems.

Chapter 14

Aspirin and acetaminophen—a practical guide to fever Rx

The infectious disease specialty is about being a "fever" doctor—you're called when someone has a fever and you tend to leave the scene when the infection is treated and the fever goes away. While most of us focused on the "antibiotic" component of fever treatment, we often forget (or are not told) some of the practical issues regarding measurement and lowering of fever. What follows is a practical approach to "fever" including standard definitions, methods of measurement and the pros/cons of symptomatic therapy.

1. What is the difference between fever and hyperthermia?

When discussing body temperature, be careful to make a distinction between ***fever*** and ***hyperthermia***…

Fever: Elevated core temperature due to an underlying infection or inflammatory reaction to some noxious process (e.g. tumor, toxin). This rise in temperature is due to the *febrile response*—a complex pathophysiological reaction that includes internal secretion of cytokines, acute phase reactants and hormones.

Hyperthermia: Temperature elevation secondary to environmental influences (e.g. heat stroke), increased metabolism (e.g. malignant hyperthermia) or inability to dissipate body heat (e.g. peripheral vasoconstriction secondary to medications). Patients with hyperthermia lack the typical cytokine response and "reset" hypothalamic temperature center seen in the febrile response.

The differences in pathophysiology between fever and hyperthermia are especially important when treating these conditions…

- √ **Fever:** Patients with fever respond to antipyretic agents (e.g. aspirin, acetominophen, NSAIDS) that block the febrile response through action on the hypothalamic fever centers.
- √ **Hyperthermia:** Patients with hyperthermia *do not* respond to aspirin or related agents and require vigorous external cooling measures.

A "porcine" pyrexia—malignant hyperthermia

Malignant hyperthermia is a rare form of drug-induced hyperthermia associated with anesthetic agents such as succinylcholine, halothane and related agents. A genetic defect in the muscle leads to excessive intracellular calcium release with associated muscle contraction and severe hyperthermia (Temperatures may exceed 106ºF!). Researchers have described a similar condition—porcine stress syndrome (PSS)—in pigs undergoing the stress of crowding in large-scale pig farms. These animals develop visible muscle changes ("muscling") that reduce the quality and value of the meat. Farmers now perform a simple "pen-side" test (administering a whiff of anesthetic to all piglets), in order to screen out susceptible animals. In human malignant hyperthermia, mortality (previously 80%) has been dramatically reduced with prompt recognition and treatment with dantrolene, a muscle relaxant that decreases free intracellular calcium.

Source: http://en.wikipedia.org/wiki/Malignant_hyperthermia accessed: 8/04/13

2. What is the best way to measure body temperature?

"Core" temperature is defined as the temperature measured at some internal site such as the right atrium—this is thought to represent the closest measurement of "true" body temperature. For practical purposes, temperature is measured at any one of a number of sites, each with their own advantages and disadvantages…

- **Oral:** Even when using an electronic thermometer, oral temperatures often run 0.5-1.0 ºC lower than a simultaneous rectal temperature. Request a rectal temperature in tachypneic or uncooperative patients where oral temperatures may be unreliable.
- **Rectal:** Although less convenient than oral readings, rectal temperatures provide the closest estimate of "core" temperature short of the use of more invasive procedures such as central venous catheter thermistors.
- **Tympanic membrane:** A popular option in the emergency room and urgent care settings, such thermometers measure tympanic membrane temperature using infrared sensing technology. While convenient, such measurements may be unreliable in patients with high fever—be cautious about readings in patients who "look" febrile but have a normal or low reading.
- **Axillary:** Although one study suggests that axillary temperatures are accurate in neonates, they are unreliable in adults and should be avoided if possible. When taken, axillary temperatures are generally 1-2 degrees lower than oral or rectal temperature.

Wunderlich and the rise of modern thermometry

Modern clinicians owe a debt of gratitude to Carl Reinhold August Wunderlich (1815-1877), the German physician most responsible for establishing "temperature" as a modern vital sign. As medical director of the Leipzig clinic, Wunderlich used a foot-long mercury thermometer to measure axillary temperatures in close to 25,000 patients (over one million separate observations!) over a 14 year period. In addition to his establishment of a mean "normal" temperature of 98.6 °F, he noted slightly higher temperatures in females and a lower mean temperature in elderly patients. Wunderlich believed that variations from "normal" and height of the temperature had clinical significance—patients with "higher" temperatures appeared sicker and more likely to have adverse outcomes. Wunderlich's rigorous investigations placed medical thermometry on solid ground as a diagnostic tool in clinical medicine and confirmed the importance of temperature measurement as a routine "vital" sign.

Source: Mackowiak PA and Worden G. Carl Reinhold August Wunderlich and the Evolution of Clinical Thermometry. Clinical Infectious Diseases; 18(3):Vol. 18(3): 458-467. 1994.

3. What constitutes "normal" temperature?

As noted above , the German physician Carl Reinhold August Wunderlich measured axillary temperatures in over 25,000 healthy individuals (over 1,000,000 observations!) and concluded that the "normal" mean body temperature was 98.6ºF (37ºC). While Wunderlich's work represents a milestone in clinical medicine, problems with calibration of thermometers may have allowed the introduction of some error into the measurements.

A "modern" study… Using electronic thermometry, Mackowiak in 1992 analyzed 700 oral temperatures in 148 apparently healthy male and female volunteers. These investigators found a range of "normal" between 35.6ºC (96ºF) and 38.2ºC (100.8ºF) with an overall mean of 36.8ºC ± 0.4ºCº (98.2ºF ± 0.7ºF). Several other important findings of this study include…

- **Diurnal variation:** There is a diurnal variation in temperature with a lower mean temperature (36.4ºC; 97.6ºF) in the morning (6:00 AM) versus readings taken (mean = 36.9ºC; 98.5ºF) later in the day (6:00 PM).
- **Male vs female:** Although this barely clinically discernable, women have slightly higher mean temperatures than men (36.9ºC versus 36.7ºC).
- **Cutoffs:** When measuring temperature in an adult population, the study's authors recommended the following "cutoffs" for the morning and evening **upper limits of normal**…

37.2ºC (98.9ºF)	**36.8ºC (98.2ºF)**	**37.7 ºC (99.9ºF)**
Early AM "cutoff"	**"Normal" mean temp**	**PM "cutoff"**

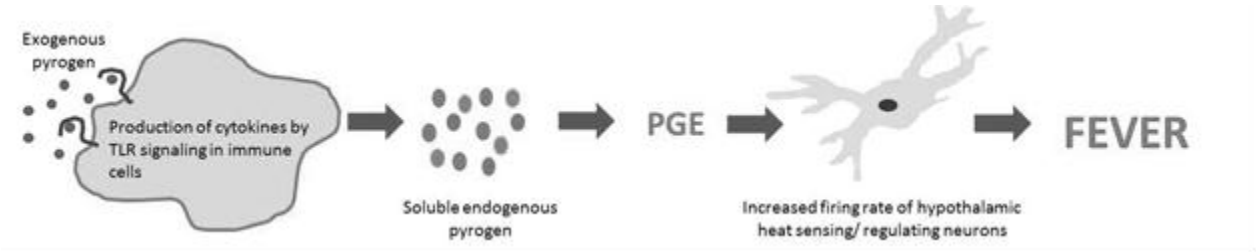
Temperatures above the early AM and PM "cutoffs" are usually "abnormal"

Caveats…

- ✓ **"Normal" variability:** These recommendations are based on a relatively small number of patients—in selected individuals, "normal" temperature may sometimes lie above this "cutoff" and temperature must always be evaluated in light of the patient's normal baseline.
- ✓ **Chronic conditions:** Patients with certain conditions (congestive heart failure; chronic liver or renal disease; hypothyroidism) tend to run lower temperatures—a temperature of 37.6ºC may constitute a significant fever if the individual's normal temperature is closer to 36ºC.

Pathophysiology of Fever

The pathway to infection-related fever begins with attachment of microbial products (lipopolysacharides; exogenous pyrogen) to toll-like receptors (TLR) on macrophages and immune cerlls. This leads to production of "endogenous pyrogens" or cytokines (IL-2; TNF) which act on the brain to increase production of selected prostaglandins (PGE). The increased prostaglandins serve to disinhibit temperature regulating neurons in the hypothalamus, leading to peripheral actions to increase body temperature (e.g. shivering; increased metabolism in brown fat stores; actions to alter external temperatures).

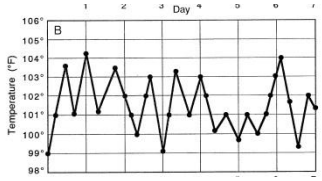
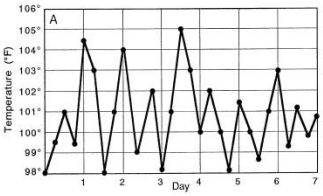
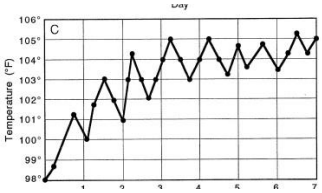
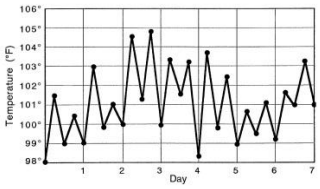
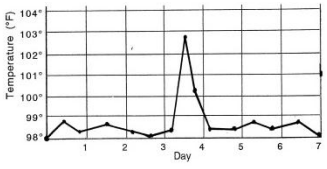


Source:http://www.bio.davidson.edu/people/midorcas/animalphysiology/websites/2011/Clemens/cascade.jpg

4. Fever patterns…what's the significance?

In the pre-antibiotic era, clinicians spent a lot of time observing patients throughout the course of their disease—this led to the description of the fever curves associated with the "classic" infectious diseases such as malaria, typhoid and tuberculosis. In managing the FUO patient, such fever patterns (see table 1) may still have value and provide important clues to the underlying diagnosis; however, the utility of fever pattern is far less in patients with nosocomial fever or individuals who have received antibiotic treatment.

Table 1: Fever patterns and their significance

Fever pattern	Graphic	Underlying conditions
Remittent: Fever with marked daily variation (usually > 1 °C), but not usually reaching normal		Viral URI Plasmodium falciparum malaria Legionella Mycoplasma Tuberculosis SBE (viridans streptococci)
Intermittent: Marked fever, usually for several hours but reaching normal within 24 hour period		Gram-negative/positive sepsis Abscesses (renal, abdominal, pelvic) Acute bacterial endocarditis Kawasaki disease Malaria Miliary tuberculosis Peritonitis Toxic shock syndrome Antipyretic use
Continuous fever: Fever c minimal variation (< 1 °C)		Central fever Roseola infantum (HHV-6) Brucellosis Kawasaki disease Psittacosis Rocky Mountain Spotted fever Scarlet fever Enterococcal SBE Typhoid fever/tularemia Drug fever
Double Quotidian: Two fever spikes per day—originally described in malaria		Still's disease (Adult JRA) Gonococcal endocarditis Visceral leishmaniasis Tuberculosis
Single fever spike:		Manipulation of colonized/infected mucosal surface. Blood/blood products transfusion Infusion related sepsis (Contamination) Temperature error

Source: modified from Cunha B. The clinical Significance of Fever Patterns. Infectious Disease Clinics of North America. editor. Cunha B. WB Saunders. Philadelphia. March 1996.

Keep in mind these additional fever "patterns" that may have significance….

- **Biphasic fever (Cameback or Saddleback fever):**

Patients develop fever followed by a brief (2-7 day) afebrile period with return of the pyrexia (Figure 1). Dengue fever is the classic illness where this phenomenon is seen—in patients with severe dengue, the return of fever is often accompanied by hemorrhage and shock. Other conditions that manifest a "biphasic" fever (Table 2) include arthropod-borne viral diseases (Chikungunya fever, Colorado tick fever), hemorrhagic fevers (Ebola, Marburg, Lassa) and a number of bacteria illnesses (leptospirosis, brucellosis and rat-bite fever).

Presence of biphasic fever in a patient recovering from influenza suggests development of a secondary bacterial pneumonia. Antibiotic drug fever may have also have this pattern (known as "goal post" fever)—following initial defervescence (with antibiotic treatment) fever may recur due to drug allergy.

Figure 1: Biphasic fever

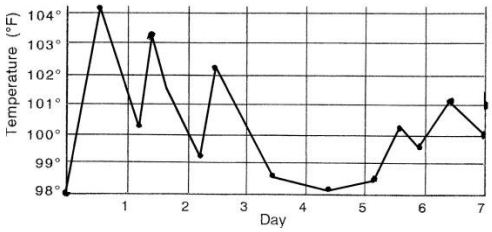


Table 2: Causes of biphasic fever

Viral disease	Bacterial disease
Colorado tick fever	Leptospirosis
Dengue fever	Brucellosis
LCM*	Rat-bite fever (*Spirillum minus*)
Poliomyelitis	Bacterial complications of influenza
Smallpox	
Chikungunya fever	
Rift Valley fever	Non-infectious
African hemorrhagic fever (Marburg, Ebola, Lassa)	Drug fever

* LCM: Lymphocytic choriomeningitis

Modified from Fever; Infectious Disease Clinics of NA; 1996

- **Relapsing fever:**

Relapsing fever implies recurrent temperature elevations (and symptoms) days to weeks following the initial illness—there may be more than one fever recurrence occurring after the the initial illness.

Table 2: Causes of relapsing (recurrent) fever

Relapsing fever (*Borreliia recurrentis*)	Fungal	Non-infectious conditions
Ascending cholangitis	Blastomycosis	Behcet's disease
Bartonellosis	Coccidioidomycosis	Crohn's disease
Brucellosis	Histoplasmosis	Weber Christian disease
Chronic meningococcemia		Leukocytoclastic angiitis
Leptospirosis	Parasitic	Sweet's syndrome
Lyme disease	Malaria	Familial Mediterranean fever
Rat-bite fever (S. moniliformis)	Visceral leishmaniasis	FAPA syndrome
Rheumatic fever	Viral	(Fever, adenitis, pharyngitis, apthous ulcer)
Tuberculosis	Cytomegalovirus	Systemic lupus erythematosus
Typhoid fever	Epstein-Barr virus	Hyper IgD syndrome
Syphilis	HIV	Lymphoma and malignancies

Modified from Fever; Infectious Disease Clinics of NA; 1996

- **"Relative bradycardia"—Fever with inappropriate bradycardia:**

Patients with fever usually develop an associated tachycardia, with the degree of tachycardia correlating with the height of the fever an (add 10 beats per minute for every ºF above 102 °F). Those with "**relative bradycardia**" fail to develop the "appropriate" rise in pulse rate with the associated temperature increase. Such a finding suggests a specific set of diseases, especially pathogens associated with "intracellular"

infection such as *Legionella*, salmonellosis and *Brucella* (Table 4). In addition to infection, relative bradycardia may also suggest non-infectious conditions such as drug fever and neoplasms (lymphoma).

Know the criteria… The following criteria must be met before you can accurately evaluate a patient for "relative bradycardia":

1. **Age** of patient ≥ 13 years
2. **Temperature** ≥ 102 °F (38.9 °C) and ≤ 106 °F (41.1 °C)
3. **Pulse:** The pulse is taken simultaneously with the temperature,
4. **Rhythm:** Normal sinus rhythm with no arrhythmias, 2nd or 3rd degree heart block or pacemaker
5. **Medications:** The patient is not taking a medication (e.g. ß-blockers) that causes bradycardia

Table 3: Relative bradycardia*

Temperature	Beats/min
41.1 °C (106 °F)	150
40.6 °C (105 F)	140
40.7 °C (104 F)	130
39.4 °C (103 F)	120
38.9 °C (102 F)	110
38.3 °C (101 F)	100

*Appropriate temperature -pulse relationship

Table 4: Causes of relative bradycardia

Infectious		Noninfectious
Legionella	Malaria	B-blockers
Psittacosis	Leptospirosis	CNS lesions
Q fever	Yellow fever	Lymphomas
Typhoid fever	Dengue fever	Factitious fever
Babesiosis	Viral hemorrhagic fever	Drug fever
	RMSF*	

* RMSF: Rocky Mountain Spotted Fever
Source: Cunha BA. Diagnostic significance of relative bradycardia. Infect Dis Pract. 1997;21:38-40.

5. Is there any benefit to treating fever?

Despite a long tradition of aggressive efforts to treat fever, the benefit of lowering temperature remains unclear. Fever is an adaptive mechanism that may help to fight infection—animal and human studies (see below) suggest *improved survival* in infected animals able to mount a febrile response. Likewise, suppression of fever (with anti-pyretics) might have ***adverse effects*** in selected situations…

- ✓ **Spontaneous bacterial peritonitis:** In patients with spontaneous bacterial peritonitis, the presence of fever is associated with improved survival (Hoefs JC et al.. Hepatology 1982;2:399-407.)
- ✓ **Chickenpox:** Children treated with acetaminophen had delayed scabbing and more prolonged viral excretion (Doran TF. Et al. Journal of Pediatrics 1989;114:1045-8.)
- ✓ **Malaria:** Antipyretic treatment (acetaminophen) *prolonged* parasitemia in at least one clinical trial from Africa (Brandts CH et al. Lancet. 1997 Sep 6;350(9079):704-9.)

Even the desire to treat patients in order "make them more comfortable" may be in error—a recent study failed to demonstrate a clinical or "comfort" benefit from treating fever in elderly patients.

But wait! … Despite these reservations, there may be benefit to treating fever in selected situations:

- ✓ **Gram negative sepsis:** Early use of antipyretics did not appears to increase mortality in the patient with gram negative sepsis (Mohr N et al. Intern Emerg Med. 2012)
- ✓ **Fever control in septic shock:** In an ICU setting, efforts to control fever in septic shock patients led to lower use of vasoconstrictor therapy and improved short-term survival. (Schortgen F et al. Am J Respir Crit Care Med. 2012 May 15;185(10):1088-95.)

What to do… While extremely high temperatures (> 40ºC) increase the risk of adverse consequences such as seizure and CNS damage, most patients tolerate fever without significant complications or discomfort. Although the benefits of fever treatment are not always clear, most experts recommend attempts to lower fever in the following situations:

- **Cardiopulmonary disease:** Fever leads to increased metabolic demands—an outcome that might prove adverse in patients with limitations due to underlying cardiopulmonary disease. Although treatment of fever in such a situation might prove helpful, there are no studies that show a clear benefit..
- **Extremely high fever (> 40ºC):** Although fevers are generally well tolerated, hyperpyerexia (temperatures ≥ 41 ºC) can have adverse consequences (CNS damage, cardiac arrest; circulatory collapse) and merit aggressive treatment with cooling measures.
- **Children:** Kids seem to have higher temperatures and appear to be at greater risk for adverse effects associated with fever, especially the "febrile seizure". Although confirmatory data may be lacking, pediatricians tend to be more aggressive about lowering temperature in infants (part of this is no doubt due to parental pressure!).

"Leaping Lizards!"—the benefits of fever

While it might seem counterintuitive (it certainly goes against your mothers' teachings!) fever may actually have a survival benefit in patients with infection; however, harm could arise from overly aggressive temperature control. A 1981 study (Kluger) examined the effects of temperature in lizards deliberately infected with *Salmonella.*—animals able to increase their body temperature (by moving to a warmer part of the cage) had a much higher survival rate compared to those kept in a cooler environment. Subsequent experiments demonstrated a *decreased survival* when infected animals were given antipyretics! Studies of other animal models (honeybees, roundworms, scorpions) demonstrate similar results—mounting a fever may well be an evolutionary mechanism to help combat the ill effects of infection. Such findings suggest caution in overly aggressive attempts to "reduce fever" in infected patients—in many cases, "a little fever" may actually be a good thing!

6. What is the best approach to lowering fever?

There are two main approaches to lowering body temperature—antipyretics and external cooling measures. As already mentioned, **antipyretics** are the drugs of choice for lowering temperature in patients with a febrile response due to underlying infection or inflammation. These drugs act centrally to block prostaglandin production and dampen the metabolic cascade responsible for fever.

In patients with infection, the value of **external measures** (cooling blankets; sponging with alcohol or water) is very unclear; in many situations these efforts lead to shivering, skin vasoconstriction with increased oxygen consumption—responses that could prove harmful in a tenuous patient. While external cooling is appropriate in patients with hyperthermia due to heat stroke or drug toxicity, such measures are best avoided in infected patients with fever unless they have extreme hyperthermia (Temp > 40° C) and and appear "at-risk" for CNS toxicities (e.g. altered mental status; seizures).

What follows are recommendations for use of these two modalities…

- **External measures:** In general, avoid cooling blankets in moderately ill patients with infection-induced fever since antipyretics are just as effective and do not cause the discomfort associated with shivering. For ICU patients with septic shock, aggressive external measures may improve survival, but make sure measures are taken to reduce likelihood of shivering (e.g. patient sedation; paralysis). Aggressive external measures *are especially* appropriate in patients with extreme hyperthermia due to heat stroke, drug toxicity and other conditions interfering with body heat dissipation.

- **Antipyretics:** The main agents available are acetaminophen, aspirin, and non-steroidal anti-inflammatory agents. While NSAIDS produce a more prolonged response, they all appear therapeutically equivalent, although with slightly different toxicities.

Drug	*Dose*	*Comments*
Acetaminophen (Tylenol)	650 mg PO Q 4hr (10-15 mg/kg/dose) 1000 mg IV Q 6hr	Antipyretic action lasts between 4-6 hours. Avoid use of > 4 gm total per day because of risk of hepatotoxicity. New IV formulation available for patients unable to take PO.
Aspirin	650 mg PO Q 6 hr	Avoid in patients with a bleeding diathesis or history of GI bleed. Do not use in children with viral infection because of risk of Reyes syndrome
Ibuprofen (Advil)	400-800 mg Q 6-8 hr (5-10 mg/kg/dose) 400-800 mg IV Q 6-8 hr	Antipyretic action lasts 6-8 hours. Caution in patients with history of GI bleed or underlying renal dysfunction. New IV formulation available for patients unable to take PO
Naproxen (Aleve)	500 mg PO BID	Caution in patients with history of GI bleed or underlying renal dysfunction

Additional fever caveats…

√ **"Roller coaster" fever:** "Intermittent" dosing may lead to a "roller coaster" fever pattern—dramatic ups and downs that occur when the medication wears off or takes effect. In patients, with persistently high fever, round-the-clock dosing may prevent this effect, leading to better patient comfort.

√ **Rectal temperatures are more reliable** than oral or tympanic membrane measurements—if in doubt about the reliability of an oral temperature (hyperventilation; poor patient cooperation),obtain a rectal temperature to ensure accuracy.

√ **Fever is rarely dangerous:** Most patients tolerate fever without any adverse consequences. Numerous studies suggest that fever has beneficial effects and little data exists to support aggressive suppression of fever for patients with infectious disease conditions.

√ **Antipyretic agents are usually safe:** In generally, there is little harm from brief courses of antipyretic agents such as acetominophen, aspirin or ibuprofen—choose the drug keeping in mind the patient's underlying pre-existing conditions and avoid agents that might produce a specific adverse side effects in an individual patient.

√ **Avoid use of cooling blankets** in patients with infection or inflammation-induced fever—such aggressive measures provoke considerable patient discomfort (e.g. shivering) and are no more effective than traditional antipyretic agents. External measures to reduce body temperature *are* appropriate in patients with hyperthermia—pyrexia due to heat stroke, over-exercise and drug-induced hyperpyrexia (e.g. malignant hyperthermia).

ID Checklist: When managing fever, keep in mind the following…

- **Consider a rectal temperature:** If you are unsure about the reliability of a specific temperature (e.g. oral, axillary temps), measure the rectal temperature to obtain the most accurate estimate of "core" body temperature. Remember that a rectal temperature is most likely to give you an accurate assessment of "core" body temperature.
- **Look for fever patterns:** Although often not diagnostic, a specific pattern (remittent, intermittent, continuous) might suggest a particular diagnosis, especially in individuals presenting with fever of unknown origin (FUO).
- **? Need for immediate lowering:** Weigh the pros and cons in an individual case…
  - ✓ **Mild temperatures** (< 102° F; 38.7 °C): Immediate lowering is probably not necessary in patients with milder temperatures.
  - ✓ **Moderate temperatures** (102°--104°F; 38.7 °-- 40°C): Rapid temperature lowering usually not necessary but consider in patients with stroke, CHF or myocardial infarct.
  - ✓ **Hyperthermia** (> 104°F or > 40°C): Be aggressive about temperature lowering in patients with hyperthermia (> 40 °C), especially in those with underlying conditions such as myocardial infarction or stroke.
- **Start an antipyretic** in patients requiring temperature reduction. Once you make the decision, consider using round-the-clock acetaminophen or NSAID in patients.
- **Watch out for toxicities:** When using aspirin, acetaminophen or NSAIDs, watch out for toxicities such as gastrointestinal bleeding (aspirin; NSAIDS), nephrotoxicity (NSAIDS) and hepatitis (acetaminophen).
- **Avoid a "cooling blanket"** in patients with infection-related fever. In general, external measures (e.g. sponge bath; cooling blanket) are more effective (and indicated) in patients with severe hyperthermia due to external factors such as heat stroke or drug toxicity (e.g. malignant hyperthermia; serotonin syndrome).
- **Treat underlying condition:** The best treatment for infection-related fever is a diagnosis and specific therapy—when bacterial infection is a consideration, start antibiotics as soon as possible.

What the physician needs to know about fever management…

- "Fever" is defined as an elevated core temperature due to reset of central temperature regulation "thermostat" in the hypothalamus; it is a consequence of cytokine response associated with an underlying infection or inflammatory reaction. .
- "Hyperthermia" is an elevated temperature elevation secondary to extra-CNS processes such as environmental stress (e.g. heat stroke), increased metabolism (e.g. malignant hyperthermia) or inability to dissipate body heat (e.g. peripheral vasoconstriction secondary to medications). Patients with hyperthermia lack the typical cytokine response seen in patients with the infection (or inflammation) associated fever.
- "Normal" body temperature varies throughout the day and between individuals—it is lower in the morning and is typically slightly reduced in older patients. Recent studies using electronic thermometers in "normal" individuals suggest that "normal" core body temperature is between 35.6ºC (96ºF) and 38.2ºC (100.8ºF) with an overall mean of 36.8ºC ± 0.4ºCº (98.2ºF ± 0.7ºF).
- Fever patterns may be helpful in determining the cause of fever; however, their utility in the modern era is less since rapid treatment frequently reduces the chance that a specific pattern will develop.
- Specific fever patterns that might be seen include "remittent" fever (temperature decreases but does not return to normal), "intermittent" fever (temperature returns to normal on a daily basis) and "continuous" fever (fever remains elevated with less than 1 ºC variation).
- "Biphasic" fever implies a decrease in temperature (for a few days) followed by a recrudescence lasting several days. Although classically a sign of dengue fever and a number of similar viral infections (Colorado tick fever; hemorrhagic fevers), it can also be a sign of drug fever or a secondary complication (e.g. bacterial pneumonia) in a patient with influenza.
- Patients with **"**relapsing" or recurrent fever have intermittent fever (lasting from days to weeks) accompanied by periodic afebrile periods. This pattern can be seen with a number of chronic infections (e.g. tuberculosis, typhoid fever, brucellosis, fungal diseases) as well as rheumatological conditions or fever associated with occult malignancy (e.g. Pel-Ebstein fever in lymphoma).
- Patients with "relative bradycardia" fail to have an accompanying rise in heart rate when they develop fever. This may be seen with selected "intracellular" pathogens such as *Legionella, Salmonella* and tuberculosis. In patients with relative bradycardia examine the medication record—patients receiving β-blocker agents have a lower heart rate that can mimic relative bradycardia in the febrile patient.
- Because of differences in pathophysiology,"fever" and "hyperthermia" are not managed in the same manner. Fever is treated with anti-pyretic agents (aspirin; acetaminophen) that "reset" the hypothalamic temperature control center in order to reduce core temperature.
- Hyperthermia is managed with aggressive external measures (e.g. cooling blanket; immersion in ice; external alcohol rubs) designed to increase the rate of heat loss.
- In most cases, fever is a survival mechanism that helps body combat infection. The benefit of lowering fever in most patients is unclear; however, situations where fever reduction may prove beneficial include: 1).Extremely high fever (> 40 °C [104°F]), 2). Fever in a patient with stroke, 3). Fever in patients with cardiopulmonary disease, and 4). Fever in septic ICU patient.
- Once a decision is made to lower fever, it may be best to give "around-the-clock" antipyretics (e.g. Q 4-8 hr acetaminophen) in order to minimize the extreme variations in temperature that lead to patient discomfort.

Fever and Empiric Antibiotic Therapy

Appendix

The Ten Commandments of being an Infectious Disease consultant

Unless you are an infectious disease fellow, you're probably on the ID service for a relatively short period and will have limited time to learn the "art" of ID. What follows is a summary of some of the unwritten rules of being an ID consultant—they are practical recommendations that will help speed rounds and put you on a path to becoming ID "savvy":

1. **Play the detective:** In no other medical specialty is the history and physical so important. Asking the right question can unlock a case and provide the key to a puzzling fever. When reviewing a case, I've found the following to be especially helpful:

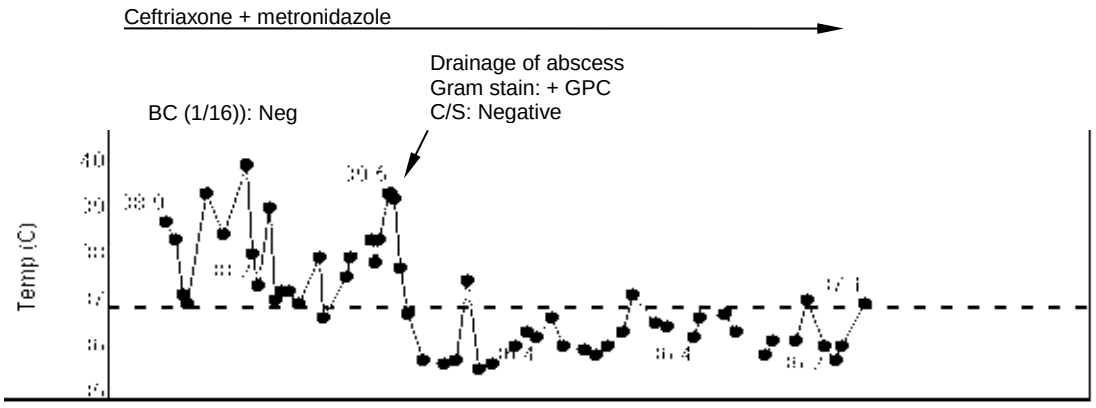
   √ **Date the "true" onset of the fever/disease:** While a patient may have come to medical attention recently, try to date the real onset of the disease. If it was six months ago, try to focus your exposure questions (travel, animals, food) around this period of time.

   √ **Review the ER record:** Nurses are specifically instructed to keep a careful record (with date/time) of ER interventions. Look specifically at the timing of cultures and antibiotics—a "negative" blood culture is to be expected if cultures were drawn *after* an antibiotic dose was given.

   √ **Talk with the patient's family/friends:** Without compromising patient confidentiality, try to obtain information from other sources such as the patient's family or close friends—they may remember details (or have their own theories) that help shed new light on the case.

   √ **Obtain old records:** Go out of your way to obtain old records or notes from previous physicians or hospitals—you'll gain new insights to the case and may discover key test results that arrived late or were overlooked.

2. **Make a chart of the illness:** Modern in-hospital cases can be complicated with multiple interventions and a variable clinical course. In more complicated cases (and even some of the "simple" ones), make a chart that includes basic information such as the fever curve, cultures (with results) and antibiotics (include start/stop points). Here's an example of a 49 yr old male who presented with one month history of fever and RUQ pain due to a liver abscess—note the persistent fever (despite antibiotics) until the abscess was drained on 1/19.



Date	1/16		1/19		1/26
WBC	17.7		18.9	15.9	13.9
H/H	31/10				
B/Cr	6/.58				

3. **Know thy "MICs"—talk to the laboratory:** As an infectious disease consultant, you are expected to know the culture results and antibiotic susceptibility data. Try to get the most up-to-date data—if results are "pending", call the laboratory and obtain "preliminary" information if available. The MIC (minimal inhibitory concentration) is the concentration of antibiotic required to inhibit growth of the organism—the laboratory report usually shows the MIC (a "number") and an interpretation (sensitive-intermediate-resistant) based on the MIC and achievable drug level. To speed rounding, try to have a printout of the key lab reports which show culture results and susceptibilities.

4. **Avoid "scattershot" testing:** Think of your tests as darts trying to hit a bull's-eye—be able to justify each test and avoid "scattershot" testing with multiple expensive (and frequently negative) lab tests. The same goes for X-rays—review the ones you already have before ordering more complicated tests that will require additional radiation exposure. Develop a reputation for thoughtful, judicious testing.

5. **Know your antibiotics!** As an infectious disease consultant, you're expected to be an expert on antibiotic therapy. Obtain an antibiotic manual (e.g. "The Sanford Guide to Antibiotics"; "Antibiotic Essentials" by Burke Cunha) and make sure your dose recommendations are appropriate.

   This expertise should focus on at least four areas:

   √ **Avoid allergy/anaphylaxis:** Don't completely rely on what's written in the chart, before you give an antibiotic, ask the patient (or family members) if the patient is allergic to the drug you plan to give. If there is any question about potential allergy, carefully document the need for the drug make sure the drug is administered in some type of monitored environment.

   √ **Appropriate dosing:** Using appropriate guidelines, make sure the dose is appropriate and take into account renal and liver function.

   √ **Drug interactions:** Review the patient's medication list, looking for potential drug interactions.

   √ **Anticipate adverse reactions:** Know the side effect profile of the planned antibiotic and anticipate any adverse reactions.

6. **The power of "patience"—remember the "48 hour" rule:** With persistent fever, clinicians sometimes practice a form of "antibiotic roulette"—they change (or add) antibiotics on a daily basis, hoping to hit on the "right" combination by chance. This rarely works and usually complicates the situation, putting the patient at greater risk for side effects and increased antimicrobial resistance.

   When an antibiotic change is made, be "patient" and try to give the patient 48-72 hours to respond—antibiotics rarely work immediately and most maneuvers require a reasonable period of time to demonstrate response. With today's broad-spectrum antimicrobial therapy, failure to respond often means a wrong diagnosis or some complication (e.g. Undrained abscess) requiring a different intervention.

7. **Don't forget drug fever:** If you're called to see a patient that has persistent fever—or develops a "new" fever while on antibiotics—think about the possibility of "drug fever". Keep in mind the following "clues" to drug fever:

   √ **Fever/clinical appearance disconnect:** The patient "looks good" despite the fever—this is one of the most important clues to the presence of drug fever.

   √ **Pulse-temperature differential:** In about 30% of patients with drug fever, you'll see a "pulse-temperature" differential with a high fever and relatively low pulse. [Note: Not surprisingly, concurrent treatment with a B-blocker will obviate this rule.]

- √ **Presence of rash:** Although not always seen, the new onset of a maculopapular rash or pruritus is an additional clue to drug fever/allergy.
- √ **Eosinophilia:** Check the CBC, sometimes the new presence of eosinophils (even if it is below the standard cutoff of 400 cells/mm3) may be a clue to drug fever

If you suspect drug fever (although any drug can do this, the B-lactam and sulfa drugs are an especially common cause of drug fever), drop the suspected agent or switch the patient to a different class. Most patients with drug fevers will defervesce within 48-72 hours.

8. **Remember the "Big Three"—TB, HIV and infective endocarditis:** These conditions present with multisystem involvement and should always be considered in patients with atypical or unusual presentations. When dealing with unexplained illnesses, make it a habit to routinely obtain a PPD, HIV test, a RF (rheumatoid factor)—and (in selected cases)—an echocardiogram.

9. **Become a better communicator:** As a consultant, it's your job to make sure patients, family and fellow MDs know what you are thinking—it's the right thing to do and will reduce the risk of an unhappy patient or adverse medical-legal outcome. When consulting on the case, pay attention to the following:

   - √ **Patients:** Take time to introduce yourself, explain your role ("fever" or "antibiotic" doctor) and make sure the patient has an idea of what you have found and what you plan to do.
   - √ **Families:** Whenever possible (and within HIPPA rules) introduce yourself to family members and explain your role. With persistent, unexplained fever, the concern is "Is this dangerous—is our family member dying?" Reassure patients and family members that while fever may be a sign of an underlying problem, it is rarely life-threatening in and of itself.
   - √ **Nurses:** They spend far more time with the patient than you do—in difficult cases, make an effort to get their insights and make sure they know your thoughts and plans.
   - √ **Doctors:** Don't just leave a note—whenever possible, talk directly to fellow housestaff (or attendings) about what you've found and the logic behind any recommendations—it's a chance to make sure everyone is on the same "wavelength" and will increase the chances that your recommendations are followed.

10. **Listen to your legal voice:** We live in litigious times—while it should not be paramount, always consider the legal ramifications of your recommendations. A few simple precautions should help minimize the risk of an adverse "legal" outcome:

    - √ **Anticipate antibiotic side effects:** Consider potential antimicrobial side effects, discuss them with patients and staff, and briefly document your conversations in the chart. In selected situations where there is a high risk of adverse effects (e.g. long-term aminoglycoside therapy), consider obtaining written patient consent (with the risks clearly outlined) prior to treatment.
    - √ **Avoid "chart wars":** In your routine notes, be cautious about injudicious or adversarial comments—such statements could be used against you (or another physician) in some future legal battle. Medicine is a "humbling" experience—while a course of action may seem patently wrong to you, it's possible that you might not have all the information and could be proved wrong in the future.
    - √ **Document patient (and family) conversations:** Memories can be short and altered by the passage of time. In difficult, complicated cases, document patient (and family) conversations at critical junctures to show that you have done your best to keep everyone informed.

ID Checklist: Empiric antibiotic therapy—2016/17

Disease	Organisms	Empiric antibiotic therapy
Meningitis	*S. pneumoniae* (? PCN resistance†) *N. meningiditis* *Listeria monocytogenes* (age>50; steroids, subacute, summer)	Vancomycin + ceftriaxone (Add ampicillin for *Listeria if* elderly,pregnant, immunocompromised or during summer)
Brain abscess	Streptococci + anaerobes	Ceftriaxone + metronidazole
Pneumonia		
Community-acquired (CAP) (mild-moderate)	*S. pneumoniae,* *Mycoplasma pneumoniae* *Chlamydia pneumoniae*	Ceftriaxone (1 gm IV) + [doxycycline (PO/IV) or macrolide (PO)] OR Levofloxacin 750 PO Qday
(severe-ICU)	Above pathogens + CA-MRSA *Legionella pneumophila*	Ceftriaxone (2 gm) + azithromycin (IV) + vancomycin (IV levofloxacin + vanco also option)
Aspiration/ANO_2	Oral anaerobes	Ceftriaxone + metronidazole
IVDU	*Staphylococcus aureus*	Ceftriaxone + vancomycin
Hospital-acquired (Note: Rx nursing home acquired pneumonia as hospital-acquired pneumonia)		
< 4 days hosp. ≥ 4 days hosp.	CAP pathogens + GNR Resistant GNR + *S. aureus*	Piperacillin/tazobactam + vancomycin (Consider carbapenem or add amikacin if severe sepsis/shock)
Intraabdominal		
Local GI infection (Appy/chole/divertic)	*E. coli*, strep, anaerobes	Cefoxitin (2 gm IV q 6 hr) or Ceftriaxone + metronidazole
Abdominal sepsis (peritonitis;shock)	*E. coli*, enterococci, anaerobes	Piperacillin/tazobactam (Add amikacin if septic shock)
SBP (peritonitis)	GNR, *S. pneumoniae*	Ceftriaxone (2 gm IV Q 24 hr)
Diarrhea	*Salmonella, Shigella, Campylobacter*	Ciprofloxacin PO or IV
Urinary tract Infection		
Pyelo (uncomplicated)	GNR	Ceftriaxone (1 gm IV Q day (Add amikacin or meropenem if previous UTI, hx of ESBL, nursing home or ICU/septic shock)
Pyelo (complicated: Foley, recent instrumentation, underlying disease; older male)	GNR + enterococci	Piperacillin/tazobactam
OB-GYN		
PID	GC, *Chlamydia*, mixed infection	Cefoxitin + doxycycline (IV/PO)
Soft tissue		
Cellulitis*	Group A streptococci, *S. aureus*	Cefazolin (+clindamycin in nec fasc)
Cellulitis c skin abscess *	*S. aureus* (MRSA)	IV Vancomycin or Clindamycin Outpt: TMP/SMX (2 DS BID) ± rifampin
Diabetic foot infection	Mixed bacteria (GNR, staph/strep, ANO_2)	Ceftriaxone + Metronidazole (PO)
Diabetic foot infection (Severe illness or sepsis)	Mixed bacteria (GNR, staph/strep, ANO_2)	Piperacillin/tazobactam + vancomycin
Vascular infection		
Endocarditis-native valve	*S. aureus*, step viridans, HACEK	Ceftriaxone + vancomycin + rifampin
Endocarditis-prosthetic	*S. aureus*, CNS, step viridans	Gent + Ceftriaxone + vancomycin
IV site	*S. epidermidis*, *S. aureus,* rare GNR	Vancomycin (Add cefepime in septic patients)

Febrile neutropenia	GNR, viridans strep, staph sp.(IV site)	Cefepime (2 mg IV Q 8hr) (add vancomycin if line infection; add amikacin or use carbapenem in severe sepsis/shock)
Sepsis—unknown source*	*E.coli, S. pneumo., S. aureus*, group A strep	Ceftriaxone + vancomycin ± metronidazole [Add amikacin or consider carbapenem in severe sepsis/septic shock]

* MRSA risk factors (recent hospitalization or antibiotic Rx, IVDU, homosexual males)-add vanco in seriously ill patients
†Drug-resistant *S. pneumoniae* (hx daycare, recent B-lactam use)-add vancomycin in seriously ill patients
Abbreviations: AG: aminoglycoside; CAP: community-acquired pneumonia; GC: *Neisseria gonorrhea*; GNR: gram negative rods; MRSA: methicillin-resistant *Staphylococcus aureus;* HACEK: Hemophilus; Actinobacter; Cardiobacerium; Eikenella; Kingella

Olive View-UCLA Antibiotic Susceptibility Patterns*

Streptococcus pneumoniae
(OVMC:13 outpatient isolates 2011)

Antibiotic	% Susceptibility	
Penicillin G*	78	*MIC ≤ 0.12
Erythromycin	75	
Levofloxacin	100	
Vancomycin	100	
Cefotaxime	92	MIC ≤ 0.5
Doxycycline	100	

- About 25% of pneumococcal isolates at OVMC are resistant to penicillin G
- These isolates have "intermediate" resistance to penicillin—they are often susceptible to 3rd generation cephalosporins (e.g. ceftriaxone)
- OVMC pneumococcal isolates remain susceptible to a respiratory quinolone (e.g. levofloxaxin; moxifloxacin)
- Doxycycline is a reasonable choice for outpatient management of bronchitis and "mild-moderate" bacterial respiratory infection.

Staphylococcus aureus
(OVMC: 476 outpatient isolates 2011)

Antibiotic	% Susceptibility
Oxacillin	50
Cefazolin	50
Levofloxacin	50
Vancomycin	100
TMP/SMX	95
Rifampin	95
Clindamycin	80
Tetracycline	95

- 50% of outpatient staphylococcal isolates are MRSA (resistant to oxacillin and cephalosporins)
- All isolates remain susceptible to vancomycin
- TMP/SMX (Bactrim) remains a good choice for outpatient management of MRSA infection
- There is a significant resistance (~20%) to clindamycin—be cautious about empiric use of this drug in critically ill patients.
- Doxycycline remains a good choice for outpatient Rx of MRSA

Escherichia coli
(OVMC: 1316 outpatient isolates—2011)

Antibiotic	% Susceptible	
Ampicillin	44	
TMP/SMX	68	
Ceftriaxone	94	
Gentamicin	92	
Ciprofloxacin	79	88% in 2003
Nitrofurantoin	94	

- Outpatient *E. coli* isolates have a high rate of resistance to ampicillin—this drug is a poor choice for "empiric" coverage of UTI.
- Approximately 70% of outpatient isolates are susceptible to TMP/SMX (Bactrim)
- There is a gradual increased resistance to quinolones in the community (~80% susceptible)—be cautious about empiric use of ciprofloxacin in critically ill patients.
- Almost all (95%) of community acquired *E. coli* isolates remain susceptible to ceftriaxone.
- Consider use of a carbopenem in patients with severe sepsis/septic shock to cover rare ESBL GNR community islates

Pseudomonas aeruginosa
(OVMC: 71 Inpatient isolates—2011)

Antibiotic	% Susceptible
Gentamicin	74
Tobramycin	90
Pip/taz	83
Cefepime	79
Ciprofloxacin	58
Imipenem	74

- Approximately 75% of inpatient *Pseudomonas* isolates are susceptible to gentamicin; rates are higher (90%) with tobramycin or amikacin.
- 80% of strains are "susceptible" to piperacillin/tazobactam by current testing criteria—be cautious about empiric use of this drug in critically ill, septic patients.
- There is significant resistance to quinolones (close to 50%) among hospital acquired *Pseudomonas* isolates.
- Carbapenems (e.g. meropenem) have resistance patterns similar to aminoglycosides and 3rd generation cepahlosporins (about 75% susceptible).

*Note: 2013 findings similar to 2011 data

Oral antibiotics—PO absorption and food requirements

You may have already looked at chapter 12 on oral antibiotics, but here is some additional information about bioavailability and food requirements for these drugs

Table 1: Oral bioavailability of common antimicrobials

Excellent (>90%)	%	Good (30-80 %)	%	Inadequate Poor oral absorption	%
Amoxicillin	90	Cephalosporins		Aminoglycosides	<10
Amoxicillin/clavulanate	90/60	Cefaclor	80	Vancomycin	<10
Cephalexin	99	Ceftibuten	80		
Chloramphenicol	90	Cefuroxime	50		
Clindamycin	90	Cefpodoxime	50		
Dicloxacillin	xx	Ciprofloxacin	70		
Doxycycline	90	Macrolides			
Gatifloxacin	96	Azithromycin	35		
Levofloxacin	99	Clarithromycin	50		
Linezolid	100	Erythromycin	50		
Metronidazole	100	Nitrofurantoin	80		
Minocycline	95	Penicillins			
Moxifloxacin	90	Ampicillin	50		
Rifampin	95	Penicillin V	60		
TMP/SMX	98	Telithromycin	55		
		Tetracycline	60		

Source: Cunha B. Antibiotic Essentials. Physicians' Press. New York 2005.

Table 2: Effect of food on antibiotic absorption

Take with food Food may reduce GI upset	Take with food Food increases absorption/bioavailability	Take on empty stomach Food decreases or delays absorption
Amoxicillin	Atovaquone (Mepron)	Ampicillin
Amox./clavulanic acid	Atovaquone/proguanil	Azithromycin
Erythromycin	Cefuroxime (Ceftin)	Ciprofloxacin
Ethambutol	Cefpodoxime (Vantin)	Dicloxacillin
Ketoconazole	Itraconazole	Isoniazid [2]
Methenamine	Mefloquine [1]	Rifampin
Metronidazole	Nitrofurantoin	Sulfonamides [3]
Rifabutin		Tetracyclines [4]
Sulfasalazine		

1. Take with food and full glass of water
2. Can take with food if stomach upset occurs
3. Take with a full glass of water
4. No food or milk within 3 hours