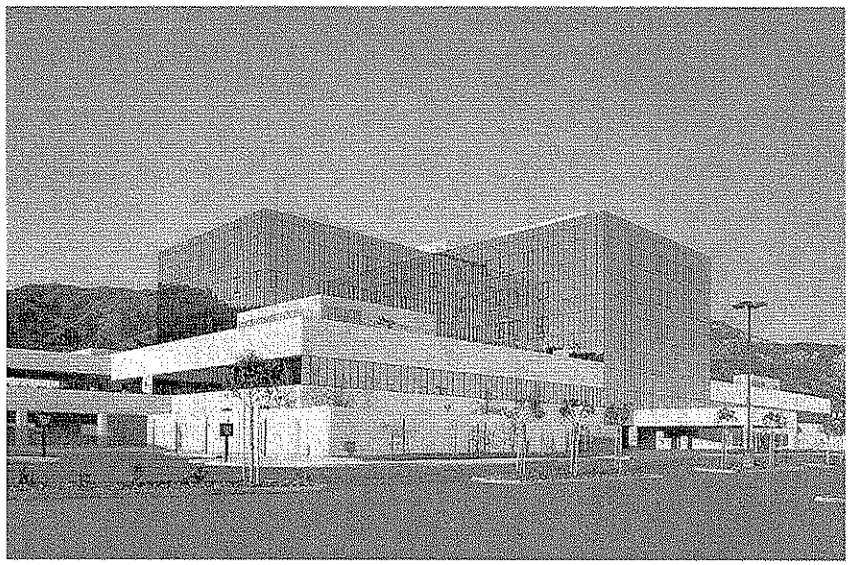
The OVMC Infectious Disease Manual

Basic ID management for the houseofficer



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Infectious Disease Manual—Introduction

Welcome to the infectious disease service. Hopefully in the next two weeks you will learn all the infectious disease you need to know for your medical career (just kidding!). In this brief booklet I've tried to assemble many of the "handouts" that we've developed over the years. While not comprehensive, they will give you an insight into some of the "basics" of ID— stuff every doctor should be familiar with. Upon seeing the ID service evolve over the years, I think there are several basic "truths" or observations that we need to come to terms with…

- **Explosion of ID knowledge:** The first edition of Mandell's Principles and Practice of Infectious Disease (the "Bible" of ID) had less than 1700 pages—the most current version (7th edition) weighs in at 4320 pages! (and this doesn't even include the on-line resources). Like many fields in medicine, ID has experienced an explosion in knowledge that is hard to keep up with, even for the attending "expert".
- **Limited time on the ID service:** With increasing demands on outpatient medicine, the amount of time available for education on subspecialty services has decreased. Many rotations are relatively brief and the houseofficer is constantly pulled away to other responsibilities.
- **The reality of constant change:** Bacteria evolve, resistance emerges and new diseases arise—constant change is a byword in infectious disease and the "clinical presentation" today may be different than the classic "textbook" description.

To help surmount these difficulties, the handouts were designed to teach an "approach" to evaluating infectious disease conditions, beginning with basic fever evaluation and moving on to individual clinical conditions. Hopefully, by reviewing them you will have an idea on "how an ID specialist thinks" and will be able to take the next step in any specific case. The checklists are designed with several features in mind:

√ **History and physical is still #1:** Despite the advent of sophisticated scanning and laboratory technology, a careful history and physical examination still goes a long way in patient evaluation and management. Pay special attention to epidemiological clues and make sure you perform careful and thorough physical examinations.

√ **Know the numbers:** Medicine (especially infectious disease) is often a game of probability—whenever possible, we've tried to include the basic stats with reference to clinical presentation (e.g. symptoms; signs) and epidemiology.

√ **What to do next:** Often absent from infectious disease texts, this may be the most important feature—in the following "checklists", we try to give you a list of things to do right now, as you are seeing the patient.

√ **Great expectations:** Many infectious disease texts don't tell you much about the expected time course. In addition to the diagnostic and treatment recommendations, the checklists try to give a sense of time course and the most common complications for some conditions.

The handouts are designed to "stand alone" and give you an insight into how an ID attending thinks—at the very least the checklist format will give you simple instructions on "what to do now" as you see the patient on the ward or in the clinic.

Note: *These handouts have been accumulated over years and may contain typographic or informational errors. When administering antibiotics, it's always wise to check a second source to ensure that drug dosing is correct. Nothing in medicine is static—any suggestions (or corrections) about the content of this this booklet is very much welcome!*

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The Olive View Infectious Disease Manual

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Antibiotic Therapy

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Urinary Tract Infection

Intraabdominal Infection

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ID Basics

The Fundamentals of Fever Evaluation

How to Think Like an ID Specialist

A 7-Step Approach to Diagnosis and Therapy

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. The late 19th century saw the first attempts by police to categorize crimes and keep files on criminals and their methods. Such early attempts at "criminal profiling" greatly tipped the odds in favor of the police in their day-to-day battle with criminals. 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 (abrupt 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, we have a responsibility to prevent additional cases—whenever possible. 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 other patients!

Fever evaluation and therapy

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. What follows is a practical approach to "fever" including standard definitions, methods of measurement and the pros/cons of symptomatic therapy.

What is the difference between fever and hyperthermia?

KNOW THE JARGON

When talking about body temperature, always 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 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.

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 °C 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.

What constitutes "normal" temperature?

In 1868, 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 98.6°F (37°C). 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.

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

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

Early morning: 37.2°C (98.9°F)
Evening: 37.7°C (99.9°F)

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. Patients with certain conditions (congestive heart failure; chronic liver or renal disease; hypothyroidism) tend to run lower temperatures—a temperature of 37.6°C may constitute a significant fever if the individual's normal temperature is closer to 36°C.

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 studies suggest an *improved survival* in infected animals able to mount a febrile response. Several studies suggest that aggressive treatment of fever may actually *decrease* symptom resolution following common conditions such as chickenpox. While extremely high temperatures (> 40°C) may be harmful in selected patients, most patients tolerate fever without significant complications or discomfort.

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. While many patients do not need aggressive treatment of fever—aside from efforts to treat the underlying cause of the fever— 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.
- **Stroke:** Studies suggest that high temperatures may lead to poorer outcomes in stroke patients.

- **Extremely high fever (> 40°C):** Although fevers are generally well tolerated, extremely high fever—especially temperatures in the 41 °C and above—can lead to CNS damage and should be treated aggressively.
- **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!).

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.

Although often used, the value of **external measures** (cooling blankets; sponging with alcohol or water) are very unclear; in many situations these efforts lead to shivering, skin vasoconstriction and increased oxygen consumption—responses that could prove harmful. What follows are recommendations for use of these two modalities…

- **Antipyretics:** The main agents available are acetaminophen, aspirin, and non-steroidal anti-inflammatory agents. While there is some evidence that NSAIDS produce a more prolonged response, they all appear therapeutically equivalent although differing in potential toxicities.

Drug	Dose	Comments
Acetaminophen (Tylenol)	650 mg PO Q 4hr (10-15 mg/kg/dose) 325 mg Rectal sup. (2 supp. Q 4-6 hr)	Avoid use of > 4 gm total per day because of risk of hepatotoxicity Antipyretic action lasts between 4-6 hours Do not exceed 12 suppositories in 24 hour period
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)	Caution in patients with history of GI bleed or underlying renal dysfunction Antipyretic action lasts 6-8 hours
Naproxen (Aleve)	500 mg BID	Caution in patients with history of GI bleed or underlying renal dysfunction

- **External measures:** In general, avoid use of external measures in patients with infection-induced fever. Studies of cooling blanket use in the intensive care patient show no benefit over administration of antipyretic agents. Aggressive external measures *are* appropriate in patients with extreme hyperthermia due to heat stroke, drug toxicity and other conditions interfering with body heat dissipation. Because of the high likelihood of inducing shivering—a response leading to considerable patient discomfort as well as *increased* metabolic demands—heavy sedation with paralysis (eg. pancuronium) is sometimes used when aggressive external measures are employed.

Additional 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 and lead 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).

When evaluating and treating fever, keep in mind the following...

- ❑ **Ensure accuracy:** If you are unsure about the reliability of a specific temperature (e.g. oral, axillary temps), obtain a rectal temperature.
- ❑ **Look for fever patterns:** Although often not diagnostic, a specific pattern (hectic, remittent, intermittent) might suggest a particular diagnosis
- ❑ **? Need for immediate lowering:** Weight the pros and cons in an individual case. Immediate lowering is probably not necessary in patients with milder temperatures (< 102° F; 38.7 °C), especially in those who are otherwise non-compromised. Be aggressive about temperature lowering in patients with extreme hyperthermia (>40 °C) and those with underlying conditions such as myocardial infarction or stroke.
- ❑ **Start an antipyretic** in patients requiring temperature reduction. Consider using round-the-clock acetaminophen or NSAID. In general, avoid external measures (e.g. sponge bath; cooling blanket) except in patients with severe hyperthermia requiring immediate temperature reduction.

Acetaminophen	Aspirin	Ibuprofen
650 mg PO Q 4-6 hr (10-15 mg/kg/dose) OR 325 mg Rectal sup. (2 supp. Q 4-6 hr)	650 mg PO Q 6 hr	400-800 mg Q 6-8 hr (5-10 mg/kg/dose)

- ❑ **Avoid external cooling measures** (e.g. cooling blankets) except in patients with extreme hyperthermia associated with heat illness and drug associated fever .
- ❑ **Treat underlying condition:** The best treatment for infection related fever is a diagnosis and specific therapy.

"Saturday Night Fever"—the ten minute "nosocomial" fever workup

It's 3:00 AM in the morning and you are the "on-call" intern. You've completed your work and just managed to get back to the on-call room, hoping to catch a few hours of shuteye before morning. Suddenly, the phone rings—it's a nurse from the medicine ward informing you that a previously afebrile patient just spiked a fever of 38.9°C. Shaking your head, you realize that—at least at the moment—your hope for sleep is not in the cards. In honor of this all-to-frequent situation, this handout examines the following:

- The most common causes and definition of "hospital-acquired" fever.
- Expeditious evaluation (that's the "ten minute" part!) for the harried houseofficer.
- Initial patient management pending cultures and laboratory results.

1. "Hospital-acquired" fever—definition

Most of us are used to the "workup" of a newly admitted patient with fever—it's a pretty well-established routine looking for the common causes of "community-acquired" fever. Although the initial evaluation may be similar, "hospital-acquired"—or nosocomial— fever remains a less defined entity with a different set of etiologies and outcomes.

KNOW THE JARGON

Hospital-acquired (nosocomial) fever: While there is no generally accepted standard, one review has suggested the following definition[i]:

- A single oral temperature ≥ 38.3 °C (101° F) or a temperature ≥ 38.0 °C (100.4 °F) for ≥ 1 hour.
- 5-day afebrile period before admission
- At least 48 hours of hospitalization before occurrence of fever

Although somewhat arbitrary, this definition does capture the essence of this problem—a new onset fever in a previously afebrile, hospitalized patient.

Fever—*in the eye of the beholder*

Although we have established a "standard" definition of fever, keep in mind that definition of fever is somewhat elastic—one patient's fever may be another patient's "normal" temperature. When called to evaluate a patient, keep in mind the following caveats:

- **Unreliable oral temperatures:** Because of tachypnea, oral temperatures can be unreliable (even with modern electronic thermometers) and fail to reflect core temperature. When in doubt, obtain at least one rectal temperature to confirm the accuracy of concomitant oral temperatures.
- **The older the colder**: Older patients and those with underlying disease (CHF, cirrhosis, renal failure) tend to run lower baseline temperatures. In an unstable patient, don't be fooled by a "normal" temperature—look at readings for the previous few days to establish a baseline. A "normal" temperature of 37.8° C may turn out to be a fever spike in a CHF patient with a baseline of 36°C.
- **Hypothermia alert:** A low temperature--hypothermia (Temp < 36° C) may also be a sign of sepsis—in some situations it may be a bad sign since septic, hypothermic patients tend to have a poorer survival.

Remember: If the patient is "afebrile" and you suspect infection, obtain a rectal reading to make sure you have the most accurate representation of "core" body temperature.

2. Hospital-acquired fever—sorting out the causes

There are few systematic studies of "hospital-acquired" fever in the generalized hospital patient population. Among these studies there is variability, depending upon the hospital and patient population. A 1993 study looked at 100 previously afebrile patients who developed fever while hospitalized on a general medicine ward (Table 1). Although this study may not apply to all situations, it does give a nice overview of the types of problems likely to be encountered.

Table 1: Causes of hospital-acquired fever in 100 patients on general medicine war

Condition	# Patients	Condition	# Patients
Infection	56	Non-infectious etiology	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	2	Pulmonary embolism	2
Other infections*	6	Malignancy	2
		Neuroleptic malignant syndrome	1
		Subarachnoid hemorrhage	1
		Connective tissue disease	1
		Acute gouty arthritis	1
		No Apparent Source	19

* Includes 3 abdominal infections, 1 tracheobronchitis, 1 soft tissue infection, 1 aseptic meningitis
† Includes 3 transfusions, 1 bronchoscopy, 1 therapeutic arterial embolization

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

- **Infection:** The first thing to note is the relative frequency of infection—in this study, approximately 50% of cases were associated with an underlying infectious condition. The most common causes (accounting for two thirds of cases) were urinary tract infection, blood stream infection, phlebitis and pneumonia. Less common causes include upper respiratory infection, AIDS (fever apparently not noticed prior to admission) and assorted other conditions.

- **Non-infectious:** Almost 25% of fevers were due to "non-infectious" causes such as post-procedure (transfusion, endoscopy), drug fever, vascular episodes (pulmonary embolism, stroke, myocardial infarction) and miscellaneous causes (underlying malignancy. Drug withdrawal, gout).

- **Unexplained:** Another 20% of fevers were "unexplained" spite relatively thorough evaluaton. Most of these fevers appeared relatively benign and often disappeared within a short time.

3. Playing the detective—Clues on history and physical examination:

As with most conditions, the diagnosis is usually suggested following a careful history and bedside examination. A complete history and physical exam may not be necessary—pay special attention to the following exam findings:

√ **Examine IV sites:** IV site infections or phlebitis are one of the most common causes of in-hospital fevers. Even if the catheter appears "normal", most peripheral IV catheters are infected within 72 hrs of placement, and if possible, should be pulled or changed.

Remember: " If in doubt, pull it out"—remove and culture any IV catheter that appears infected or has been in longer than 72 hr.

√ **Rule out pneumonia:** Question the patient about pulmonary symptoms and look for findings (tachypnea; rales) on examination. In-hospital aspiration is a common problem, especially in patients who have altered mental status or are overly sedated. In patients with suspect pneumonia, obtain a chest radiograph and try to obtain a sputum specimen; however, don't let this delay timely institution of antibiotics in a "septic" patient.

Remember: If you suspect pneumonia, try to obtain a good, deep-cough sputum specimen prior to antibiotics. An adequate specimen (as defined by the laboratory) usually has a predominant organism and ≥ 25 polys/HPF.

√ **Examine the back:** Don't rely on a "one-position" physical examination—roll the patient over an examine the back looking for spinal tenderness (vertebral osteomyelitis) or a new decubitus ulcer. While you are at it, examine the rectum for evidence of a perirectal abscess—an "occult" abscess may be overlooked if a careful rectal exam is not performed.

Remember: Don't be fooled by a "hidden" infection—turn the patient over and examine the back and make sure the patient does have a decubitus ulcer. !

√ **Check the scrotum and rectum:** In hospitalized patients, urinary tract infections are one of the most common causes of fever—look for a presence of a urethral discharge, epididymal welling/tenderness (epididymitis), perirectal tenderness (perirectal abscess) and prostatic enlargement/tenderness (prostatic abscess). UTIs are common in hospitalized patients, especially in those with Foley catheters or those with previous urinary tract instrumentation.

Remember: Occult prostatitis or perirectal abscess may be a cause of fever/sepsis in the hospitalized patient—don't forget to do a careful genital/perineal examination.

Should you do a lumbar puncture?

When to do a lumbar puncture: Hospital-acquired bacterial meningitis is uncommon except in post-neurosurgery patients. In the febrile patient, obtain an LP in the following situations:

- Patient has rigid neck or severe headache
- Confusion + documented bacteremia (ex. Confused patient with pneumococcal bacteremia)
- Post-neurosurgery patient with fever (Consult neurosurgeon about safety of LP)
- Patient confused and no other obvious sources of fever

Remember: In-hospital bacterial meningitis is uncommon; obtain a CT prior to LP in any patient with "red flag" signs for a mass lesion— papilledema on ocular examination, focal neurological findings or stupor/obtundation.

4. Non-infectious causes of fever

As noted above (Table 1), at least 25% of in-hospital fevers are due to "non-infectious" causes. When evaluating your patient, always keep the following in mind:

- **"Clots":** Pulmonary embolism, DVT, phlebitis and myocardial infarction
- **Drug fever:** especially B-lactam antibiotics (B-lactam agents; sulfa drugs, amphotericin B), cardiovascular agents (hydralazine, amiodarone, procaineamide, quinidine), selected chemotherapy regimens and anti-seizure medications (phenytoin, carbemazepine).
- **Blood products:** platelet and RBC transfusions

- **Post-procedure fever:** Fever after endoscopy, catheterization, and surgery (atelectasis)
- **Underlying disease:** Metastatic cancer, vasculitis
- **Drug/alcohol withdrawal:** Delirium tremens often begin during hospitalization. If family is available, ask about the possibility of heavy alcohol or sedative use.

Remember: Not all fever is due to infection—always consider "non-infectious" causes of fever such as drug reactions, phlebitis (DVT/pulmonary embolism) and the patient's underlying disease.

5. Empiric antibiotics—making the decision

After you've evaluated the patient, the final decision revolves around antibiotic therapy—is it safe to "watch" patient, or should they receive empiric therapy? Patients who are "septic" should probably receive immediate therapy—waiting till they develop signs of septic shock (hypotension) could prove fatal in individuals with life threatening bacterial infection.

Unfortunately, the decision is not always so easy—patients with fever may not necessarily be infected and might tolerate it just fine. The following factors are helpful in predicting which individuals are more likely to need immediate therapy:

- **Significant underlying conditions: Diabetes, neutropenia, cirrhosis**
- **Shaking chills:** *Severe* shaking chills—true "rigors", not mild "chilliness"
- **Vital signs:** Patient is hypotensive, confused and appears "toxic"
- **Leukocytosis:** While not always predictive, marked leukocytosis (> 15K) suggests possibility of bacteremia
- **Acidosis:** In patients with suspected sepsis, lactic acidosis ([lactic acid] > 2.ommol/l) is a marker for increased mortality and suggests the need for aggressive antibiotic and fluid therapy[1].

While there is no "magic" formula, we generally consider empiric therapy in the following situations:

√ **Infectious source** indentied (e.g. pneumonia, UTI, IV infection)
√ **Neutropenic patients** (neutrophil count < 1000)
√ **The patient appears septic** (high fever, hypotension, "looks toxic")
√ **Presence of leukocytosis** (WBC > 15K)
√ **Acidosis (check lactic acid levels)**

Unacceptable delays may occur if the ordered antibiotic doesn't get to the ward for several hours; in critical cases, contact the nurse and make sure the antibiotic is given immediately (within 30-60 minutes).

[1] Bakker J, Jansen TC. Don'take vitals, take a lactate. Intensive Care Med. 2007; 33:1863-65.

ID Checklist: Hospital-acquired (Nosocomial) fever

While there is no magic "cookbook" for evaluating in-hospital fever, a simple, methodical approach can often lead to the likely cause. When confronted by the febrile patient, follow this checklist…

- ❑ **Confirm presence of temperature.** If the patient is unstable but "afebrile", if necessary, check a rectal temperature.
- ❑ **Perform a careful physical examination** with special attention to the following areas:
  - √ Examine all IV sites
  - √ Look for sinusitis in patient with NG tube
  - √ Listen to the lungs for evidence of pneumonia
  - √ Genito-rectal exam for presence of Foley, epidiymitis and rectal tenderness
  - √ Rule out a decubitus ulcer (on head, back and heels)
  - √ Presence of diarrhea—consider C. difficile
- ❑ **Consider non-infectious causes** such as pulmonary embolism, myocardial infarction, intestinal ischemia, underlying malignancy and post-procedure fever (e.g. transfusion, endoscopy)
- ❑ **Examine the medication record** and consider drug fever. As part of this, keep in mind the possibility of alcohol or drug withdrawal
- ❑ **Review previous studies:** In addition to historical information, look for evidence of previous cultures that might give a clue to an underlying pathogen. If patient has received previous antibiotics, consider the possibility of a resistant pathogen.
- ❑ **Obtain simple laboratory tests** including blood cultures (2 sets), urinalysis, urine culture, complete blood count (? Leukocytosis) and serum lactate.
- ❑ **Order a chest radiograph** and O2 saturation in patients with pulmonary symptoms
- ❑ **Start empiric antimicrobial therapy** in patients with signs of sepsis, focal infection or febrile neutropenia.
- ❑ **Consider ICU transfer** or hemodymanic monitoring in unstable patients or those with suspected "sepsis".

Remember:

Your best chance to identify a pathogen is at fever onset—try to obtain appropriate cultures before giving parenteral antibiotics.

If you choose to start antibiotics—Don't delay! If you think the patient is "septic", start antibiotics as soon as possible!

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[i] Kaul DR, Flanders SA, Beck JM, Saint S. Brief Report: Incidence, Etiology Risk Factors and Outcome of Hospital-acquired Fever: A Systematic, Evidence-based Review. J gen Intern Med 2006; 21:1184-7.

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—the following piece offers a systematic approach to diagnosing ICU and post-operative fevers. In addition to the usual infectious sources (e.g. line infection, nosocomial pneumonia, UTI), keep in mind that ICU fever is often due to a non-infectious source—don't be too quick to change antibiotics unless the patient is actually septic.

Most cases of ICU/post-operative fever fall into one of several categories. In deference to previous similar mnemonics, I have called this expanded checklist the 8 "W"s of ICU fever:

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 102°F (38.3°C)—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 especially 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 much safer than in past years, consider the possibility of blood-borne pathogens in patients receiving 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 Optho to screen fundus) and erythematous skin nodules (Bx shows characteristic fungal elements). Rx c empiric fluconazole or echinocandin

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 liver tests and serum lipase/amylase.
- ❑ **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 cultures 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 the unrecognized alcoholic.
- ❑ **Consider antibiotic therapy:** While it's important to **Avoid "antibiotic roulette"**—frequent changes in antibiotics—consider addition (or change) in antibiotic therapy if you strongly suspect resistant organisms or an "uncovered" infection. Keep in mind; however, that ICU fever has many non-infectious causes.

Evaluation of FUO—Fever of Unknown Origin

ID specialists are "fever" doctors; evaluating—and diagnosing—a perplexing fever is one of the challenges of the specialty. What follows are some definitions as well as important principles on managing FUO:

1. **What is the definition of FUO?** Be careful in using the term "FUO"—specific criteria limit the number of patients and help narrow the diagnostic categories. By definition, "Classic" FUO requires that the following criteria be met:

Criteria-Classic FUO	Common causes
Temperature >38.3°C (100.9°F) Duration of >3 weeks Evaluation of at least 3 outpatient visits or 3 days in hospital	Infection, malignancy, collagen vascular disease See below

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—especially in immigrants from endemic regions—and is often difficult to diagnosis.
   - **Occult malignancy** is an important cause of FUO in the "developed" world—always keeps in mind the possibility of underlying hematological malignancy (especially occult lymphoma) 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:** Always consider the possibility of underlying AIDS —even in patients at "low risk" for HIV, request "routine" serological testing and look for clues that might suggest the condition (e.g. unexplained adenopathy; lymphopenia, oral hairy leukoplakia, previous zoster outbreak).
   - **Miscellaneous** conditions have been associated with prolonged fever (see Table) including drug fever (carefully review the patients medication lists), recurrent pulmonary emboli (especially in bed-ridden patients) and alcoholic hepatitis.

3. **Geographic variation in FUO:** 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. 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 less industrialized setting or countries with a large number of immigrants from the developing world.
- ✓ **TB/endocarditis:** 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:** Despite the availability of more sophisticated serological screening, inflammatory disorders (e.g. collagen vascular, granulomatous diseases) appear to be of increasing in importance.
- ✓ **"Undiagnosed" FUO:** In modern, tertiary care referral centers, the incidence of "undiagnosed" FUO has increased—many of these cases appear to have a relatively benign course and eventually resolve.

4. FUO in special populations: The definition—and causes—of FUO is different in special patient populations such as immunocompromised individuals, travelers and elderly patients. Keep the following considerations in mind in patients that fall into these classifications:

Nosocomial fever: Fever in the hospitalized patient…

Criteria	Common causes
Temperature >38.3°C (100.9°F) x 3 days Not present or incubating on admission; Patient hospitalized ≥ 24 hrs. Evaluation of at least 3 days in hospital	*Clostridium difficile* enterocolitis, Drug-induced fever, Pulmonary embolism, Septic thrombophlebitis, Sinusitis

Immune-deficient (Neutropenic) FUO: Fever in the neutropenic patient…

Criteria	Common causes
> 38 °C, > 3 days; Negative c/s after 48 hr Neutrophil count ≤ 500 cells mm^3 Evaluation of at least 3 days	Opportunistic bacterial infections, Aspergillosis, Candidiasis, Herpes virus

HIV-related FUO: Fever in the HIV patient…

Criteria	Common causes
> 38 °C, > 3 weeks (inpts or outpts); HIV confirmed; Duration of >4 weeks for outpatients, >3 days for inpatients	Cytomegalovirus, *Mycobacterium avium-intracellulare* complex, *Pneumocystis carinii* pneumonia, Drug-induced, Kaposi's sarcoma, Lymphoma

Tables adapted from Durack DT, Street AC. Fever of unknown origin—reexamined and redefined. Curr Clin Top Infect Dis 1991;11:37.

5. **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. 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 important epidemiological clues. Specifically ask about travel history, animal/pet exposure, unusual food ingestion, employment history, recreation/hobbies, sexual activity and illnesses in close family or friends.
- **Talk to patient 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 especially careful attention to the following findings:
  - **HEENT:** Look for sinus tenderness (sinusitis) and dental disease (occult dental abscess). Always perform a fundiscopic examination—look especially for choroids tubercles (miliary TB), "wax droppings" (sarcoidosis) and retinal hemorrhage (Roth spot in SBE). Examine the neck for thyroid tenderness/enlargement (thyroiditis may be a cause of FUO)
  - **Lymphadenopathy:** Carefully examine patient for adenopathy that might suggest granulomatous disease, occult HIV and/ or malignancy.
  - **Lung:** Look for pleural friction rubs (pulmonary embolism; SLE or inflammatory conditions)
  - **Heart:** Listen carefully for presence of new or changing heart murmur (SBE; atrial myxoma)
  - **Abdomen:** Check for presence of hepatosplenomegaly
  - **Genital examination:** In males look for epididymoorchitis (TB, brucellosis, polyarteritis nodosa); in females, look for evidence of pelvic tenderness (pelvic thrombophlebitis; PID; ovarian tumor)
  - **Rectum:** Always perform a rectal examination looking for occult perirectal abscess, prostate enlargement/tenderness (prostatitis in males) or the presence of a "rectal shelf" (peritoneal tumor).
  - **Joints:** Look for evidence of joint swelling/warmth—this may be the first sign of a rheumatologic condition (SLE, RA, Still's disease, JRA) or chronic infection (tuberculosis, fungal disease).
  - **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.
- **Radiology/scanning:** Following routine x-rays (e.g. chest radiographs), the next level of testing includes CT scans, cardiac echocardiography and nuclear medicine scans (e.g. leukocyte scan, Gallium scan). Again, these are likely to have a higher yield if ordered in a "targeted" fashion depending upon previous clinical and laboratory findings. Although sometimes indicated, in general avoid "blind" scanning without a clear reason.
- **Biopsy:** The fourth level of testing requires tissue biopsy and includes studies such as lymph node, liver and bone marrow biopsy. Again, these are more likely to yield useful information in patients with findings that point to these organ systems.

6. **Putting the case together:** Take the time to think the about the case and generate a differential diagnosis based on the initial findings. Don't be afraid to ask colleagues for suggestions and involve consultants at an early stage if the fever has no readily apparent cause.
   - ✓ **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:** All FUO patients should have a thorough eye examination by an ophthalmologist—a careful exam with sophisticated instruments may pick up clues missed by others. Likewise, don't be afraid to get other specialists involved when clinical findings bear upon their area of expertise—medical knowledge is constantly accumulating and your colleague may have just the piece of information to solve the case.
   - ✓ **Counsel patience:** 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 itself is rarely life-threatening and only a sign of an underlying disease process waiting to be diagnosed.

7. **? 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 these patients to already have received a course of therapy. This may provide additional clues—a clinical response—or non-response—to an antibiotic may help suggest a specific disease condition.

What to do when things go wrong...persistent fever

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—we are often wrong since disease presents with a multitude of sometimes downright misleading symptoms. 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 intial empiric therapy covers all the likely pathogens at the site in question. Remember also the importance of the infection "site" and pharmacokinetics—make sure your antibiotic choice has adequate penetration to the site of the suspected pathogens. This is especially important with central nervous system infections such as meningitis—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 choice of antibiotic, identity of the infection 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 a full response may be delayed by a few days, even if they are receiving the appropriate therapy.
- **"Medically impaired"** patients including individuals with underlying renal failure, chronic cardio-pulmonary disease and connective tissue disorders—despite appropriate therapy, a full clinical response may be delayed in these patient populations.
- **Specific infections:** 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. Different sometimes have a different response to therapy and one can't automatically assume that the treatment is a failure. 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—in this situation, some type of drainage is almost always necessary—either with an open surgical procedure or radiographic guided 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 may require immediate drainage—involve a surgeon early and don't expect antibiotics to always clear the infection.
- **Pneumonia:** Look for evidence of pleural effusion—significant pleural fluid should be tapped to rule out an underlying empyema.
- **Intraabdominal infection:** Although there is no specific size "cutoff", patients with pyogenic liver abscess often respond more rapidly following catheter-based drainage—this also helps confirm the microbiology in patients where blood cultures are "negative".
- **Pyelonephritis:** In patients with persistent fever, consider the possibility of an underlying peri-nephric abscess or pyohydronephrosis (renal pelvis/ureteral obstruction with renal abscess). Remember that diabetics are at risk for emphysematous pyelonephritis—these patients often require nephrectomy for definitive cure!
- **Soft tissue infection:** In patients with a poorly responding cellulitis, consider the possibility of an underlying fluid collection (e.g pyomyositis; soft tissue abscess); patients with severe toxicity and persistent pain (out of proportion to findings on physical examination) might have an underlying necrotizing fasciitis, a condition that almost always requires aggressive surgical debridement.

5. "Bugs in the blood"...persistent bacteremia

The patient has documented bacteremia and has been placed on "appropriate" antibiotics—unfortunately, he 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 with certain antibiotics (e.g. aminoglycosides) or in those receiving oral therapy—if in doubt, convert the patient to parenteral therapy and—with selected agents— obtain blood levels when available.
- **Vascular infection:** Persistent bacteremia is a hallmark of "vascular infections" such as infective endocarditis. In such situations, bactericidal therapy or surgical intervention (e.g. valve excision; drainage/debridement of perivalvular abscess) may be required for cure of the infection. Don't forget that vascular infection may be extracardiac—keep in mind the possibility of an infected aneurysm or suppurative thrombophlebitis.
- **"Pus under pressure":** Patients with underlying abscess, especially if related to an obstruction (e.g. stone, catheter, tumor, prosthetic device) or splenic abscess often have persistent bacteremia—image the patient and consider surgical drainage if appropriate(see above).

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, keep in mind the following conditions that often require specialized agents:

- **Viral infection:** Common viral infections (e.g. influenza, EBV, CMV, HIV) are not likely to respond to routine antibacterial antibiotics.

- **Fungal infection:** In certain regions, keep in mind the possibility of the "endemic" or geographic fungi (e.g. histoplasmosis, blastomycosis, coccidioidomycosis). Likewise, hospitalized or immuncompromised patients are at risk for nosocomial fungal infection (e.g. *Candida* species, aspergillosis, mucormycosis.).
- **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:** Consider checking the blood smear (e.g. rule out malaria) and question the patient carefully about previous travel.

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

8. Pharmaceutical pyrexia...Drug fever

Drug fever is a common cause of "persistent" fever in the hospitalized patient. Although just about any drug can be responsible for drug fever, some agents are more commonly associated with the condition—among antibiotics, B-lactam agents and sulfa drugs are particularly frequent offenders. When evaluating a patient with an unexplained, persistent fever, keep in mind the following clues to drug fever:

√ **Patient looks "good":** Although drug reactions can cause severe toxicity, most patients with drug fever "look good" and appear surprisingly well despite the fever.

√ **"Goal post" fever:** A clue to the possibility of drug fever is the so-called "goal post" fever—the patient becomes afebrile following initial antibiotic therapy (a response to antibiotic) but then develops subsequent fever several days later (patient has become sensitized to the drug). In football parlance, this resembles a "goal post" (I guess you have to use your imagination for this one!).

√ **Presence of rash:** Although often absent, a new onset "maculopapular" rash is a clue to an underlying drug allergy

√ **Relative bradycardia:** This is another potential clue to drug fever in the febrile—but non-toxic—patient. (Note: You can't really rely on this in patients on B-blockers)

√ **Laboratory findings:** Although there are no strict laboratory tests for drug fever, presence of eosinophilia and abnormal liver tests might be a clue.

Drug fever...what to do: If the above clues suggest drug fever, consider switching out the offending agent to a different class. In a patient on multiple agents, it may not always be clear which is the culprit; however, selected drugs are more common offenders (see table in following section) as well as "newer" drugs more recently introduced (But don't let length of therapy fool you—drug fever can sometimes develop in a patient who has been on an agent for a long time). In most cases, fever will disappear within 48-72 hours once you have eliminated the offending agent.

What to do with persistent fever—a simple checklist

In most cases, with a logical approach, you should be able to home in on the likely causes for a delayed response. 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. 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.

"Pharmaceutical pyrexia"—Drug fever

1. What are the most common mechanisms of drug fever?

√ **Immune-mediated/hypersensitivity reaction:** This is the most common cause of drug fever is due to any one of a number of reactions including IgE mediated antibody production (anaphylaxis), serum sickness (immune complex) and cell-mediated immune reactions.

√ **Altered thermoregulatory mechanisms:** Drugs may alter body temperature due to increased metabolic heat production; this is associated with agents that increase catecholamine production such as epinephrine, cocaine, amphetamines and MAO inhibitors. Drugs with significant anticholinergic activity (e.g. atropine, antihistamines, tricyclic antidepressants, phenothiazines and haloperidol) impair sweating and lead to elevated body temperatures.

√ **Drug administration:** Drug fever may be due to impurities introduced at the time of manufacture (e.g. endotoxin) or contamination occurring when the drug is prepared for administration. In these situations, the drug fever is usually closely associated with drug administration and in severe cases is associated with sepsis syndrome.

√ **Pharmacologic effects:** This category includes fever associated with the pharmacologic or therapeutic effects of the drug such as pyrogen release by antibacterial agents (e.g. Jarisch-Herxheimer reaction seen with treatment of syphilis, borreliosis, brucellosis and trypanosomiasis), a reaction that is not likely to persist beyond the initial phase of treatment. Cancer chemotherapy may be associated with fever due to tumor lysis and cytokine release.

√ **Idiosyncratic reactions:** These reactions are associated with a host genetic predisposition that leads to altered drug metabolism with an unexpected febrile reaction. Although uncommon, these reactions may be life-threatening and encompass such conditions as malignant hyperthermia (reaction to inhaled anesthetic agents), neuroleptic malignant syndrome (hyperthermia associated with major anti-psychotic agents) and G6PD-associated hemolytic anemia.

2. What clinical clues suggest the possibility of drug fever?

Although patients with drug fever are sometimes quite toxic, an important clue to the possibility of drug fever is that the patient may look "inappropriately well" despite a significant fever. In addition this clue, look for the following signs on physical examination or laboratory studies:

- **Fever pattern:** Drug fever may be associated with any fever pattern (e.g. intermittent, remittent, episodic); however, in patients with infections, the presence of initial defervescence (due to response to the antibiotic) followed by a return of fever 7-10 days later (due to drug hypersensitivity) is known as a "goalpost" fever and is a specific clue to the possibility of underlying drug fever.
- **Fever height:** Drug fever can be associated with any level of fever, from mild, low grade temperature elevations to high (> 40°C) spiking fevers suggesting an underlying bacterial infection. **Relative bradycardia** is an important clue to the possibility of drug fever and is seen in over 30% of cases—in this situation, patients maintain a normal or only slightly elevated pulse despite despite a high fever (>38.3°C). This sign is invalid if the patient is taking a B-blocker.
- **Presence of rash:** Although most patients with drug fever do not have a rash, the presence of an associated erythematous,pruritic maculopapular rash is highly suggestive of drug fever due to a hypersensitivity reaction. Other reaction patterns such as hives (IgE-mediated), bullae (e.g. fixed drug eruption), toxic erythema (e.g. erythema multiforme, Stevens-Johnson) are also associated with fever and drug hypersensitivity.
- **Presence of eosinophilia:** Although the absence of esosinophils does not rule out drug fever, almost all patients have eosinophils on peripheral smear and up to 20% have overt eosinophilia.
- **Abnormal laboratory tests:** Abnormal liver tests with mild elevations in alkaline phosphatase or transaminases are seen in up to 90% of patients with drug fever. Specific involvement of other organ systems (e.g. elevated BUN/creatinine in patients with B-lactam induced interstitial nephritis) may be

seen in selected reactions. The erythrocyte sedimentation rate is often elevated in patients with drug fever and may reach levels over 60 mm/hour.

3. What drugs are commonly associated with drug fever?

The following table outlines the most common drugs associated with "drug fever".

Common	Less Common	Rare
Antisera (Tetanus; botulism) Atropine Amphotericin B Asparaginase Barbiturates Bleomycin Blood products (RBCs, platelets) Methyldopa Monoclonal antibody preparations Penicillins/Cephalosporins Phenytoin Procaineamide Quinidine Salicylates (high dose) Sulfonamides Interferon	Allopurinol Azathioprine Cimetadine Clindamycin Hydralazine Imipenem Iodides Isoniazid Metoclopramide Minocycline Nifedipine NSAIDs Rifampin Streptokinase Vancomycin	Aminoglycosides Benzodiazepines Chloramphenicol Corticosteroids Macrolides Salicylates (therapeutic doses) Tetracyclines (except minocycline) Vitamin preparations
Table modified from Cunha B. Drug Fever. Infect Dis Clin NA 1996;10:90.		

What to do if you suspect drug fever...

- **Have a high index of suspicion** for drug fever, especially in patients who appear "non-toxic" or those with clinical clues on physical examination or laboratory studies (see above).
- **Eliminate all non-essential medications:** Even seemingly "benign" medications (e.g. laxatives) are sometimes associated with drug fever; discontinue all unnecessary drugs and observe the patient to see if the fever continues.
- **Switch to a different class:** When a specific agent is highly suspect—and the patient requires continued therapy for an underlying condition—consider switching to another class of agent that has a low risk of cross reaction with the suspect drug.
- **Wait for a response:** When the suspect agent is discontinued, the fever should resolve within 72 hours; continued fever suggests that there is another cause (or drug) responsible for the reaction.
- **Continued therapy—is it safe?** When a patient will benefit from continued therapy, some clinicians recommend "treating through" a mild reaction with administration of agents such as antihistamines. While this is sometimes reasonable, an initial fever or rash may be a harbinger of a more serious reaction; whenever possible, discontinue the offending agent or switch to a alternate class.

Antibiotic Therapy

Antimicrobial use, selection and resistance

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—does the patient have a pneumonia, urinary tract infection or cellulitis? In most cases, a brief history, physical and simple laboratory studies 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 the following tables), you can choose the antibiotics most likely to cover the infection.

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" 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 hours of admission) is especially necessary in the following situations:

- **"Toxic", septic patients:** Patients that look "toxic"—or appear septic (see box)—generally merit empiric antibiotic therapy. Findings that should trigger 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 secondary to neutropenia, chemotherapy, corticosteroids and various forms of immunodeficiency (e.g. HIV/AIDS; hypogammaglobulinemia) have a higher mortality rate with "sepsis" and should have a lower threshold for treatment.
- **Complicated medical problems:** Those with complicated underlying medical problems (cancer, congestive heart failure, renal failure) demonstrate a lower tolerance for bacteremia/severe infection—have a lower threshold for immediate, empiric treatment of these individuals.

Non-infectious fever: Not 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 6 months—have they taken a course of antibiotics within the past three months? A "yes" answer to these questions increases the likelihood of an antibiotic-resistant pathogen. In these situations, "broader" antibiotic coverage—with a carbapenem, aminoglycoside or BL/BLI drug (piperacillin/tazobactam) may be appropriate until culture results are available.

ESBL alert: Although still quite uncommon in community-acquired infections, rare patients present with ESBL *E. coli* or *Klebsiella* infection—organisms that contain an extended spectrum B-lactamase with resistance to 3rd generation cephalosporins. These organisms are best treated with a carbapenem (e.g. etrapenem; doripenem), especially in critically ill ICU cases where there is little margin of error.

5. Does the patient have any drug allergies?

Ask the patient about previous drug allergy—especially to agents such as B-lactam antibiotics (e.g. penicillins and cephalosporins) and sulfa agents—the most common causes of antibiotic allergy. In a patient with a history of an "immediate" hypersensitivity reaction to penicillin (e.g. hives, difficulty breathing, hypotension), avoid *all* B-lactam agents unless you are willing to desensitize the patient in a monitored setting.

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.

Antibiotic Choices...empiric therapy using the "grid"

The above section gives you an idea of some of the considerations that come into play when choosing an antibiotic. The following section utilizes the antibiotic "grid" for empiric therapy and gives you some of the rationale behind the choices.

A. CNS infection

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, experts recommend addition of vancomycin (for "highly-resistant" strains) until susceptibilities are available.

√ **Meningococcal disease** (*Neisseria meningiditis*) is also a concern—especially among selected populations such as college students or military recruits (the crowding of dormitory situations increases the likelihood of 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 (individuals on corticosteroids), the extremes of age (neonates; patients older than age 50) and during the summer (Food-borne illness is more common during the summer). Other features suggesting *Listeria* meningitis include subacute presentation (sick for several days) and several associated physical findings including 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.

B. Pneumonia

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

√ **Severe CAP:** Patients admitted to the intensive care unit), *Mycoplasma* and *Chlamydia* are far less common but pneumococcus remains the primary pathogen. In this situation, *Staphylococcus aureus* (community-acquired MRSA), gram-negatives (*Klebsiella pneumoniae*) and *Legionella pneumophila* become increasingly important considerations.

√ **Other pathogens:** Specific risk factors raise the possibility of other pathogens. Patients with **lung abscess**—and foul smelling sputum—have a high incidence of anaerobic infection requiring antibiotic coverage. Individuals with a **history of aspiration** (loss of consciousness; history of seizure; alcohol or drug intoxication) also run the risk of infection with oral anaerobes. *Staphylococcus*

aureus 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.

√ **Healthcare-associated pneumonia:** Early on in admission (< 4 days) these are usually related to the "standard" CAP pathogens—later (≥ 4 days), patients have had a chance to be colonized by "hospital flora" and you are more likely to be dealing with gram negatives (*Enterobacteriaceae;Pseudomonas aeruginosa*) or *Staphylococcus aureus* (MSSA; MRSA).

Pneumonia		
Site	**Microbiology**	**Suggested antibiotics**
Community-acquired (Mild-moderate severity)	*Streptococcus pneumoniae, Mycoplasma pneumoniae Chlamydia pneumoniae*	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* Cefotetan 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 Gent if severe sepsis)
* If patient has methicillin susceptible *Staph aureus*, can switch to B-lactam agent (oxacillin nafcillin or 1st generation cephalosporin)		

C. Intraabdominal infection

Intraabdominal infection		
Site	**Microbiology**	**Suggested antibiotics**
Local GI infection (Appy/chole/divertic)	E. coli, strep, anaerobes	Cefotetan (2 gm IV q 12 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" sepsis**, including critically ill patients (e.g. ICU), severe peritonitis and intraabdominal infection in chronically ill, hospitalized patients generally requires "coverage" with activity against *Pseudmonas aeruginosa* and more resistant gram negatives.
- √ **Pancreatitis:** In general, "standard" cases of pancreatitis (mild-moderate illness) *do not* require antibiotic coverage—patients with "severe" pancreatitis (e.g. "septic"; + pancreatic necrosis on CT scan) do appear to benefit from broad-spectrum coverage with carbapenems (e.g. imipenem).
- √ **Diarrhea:** Patients admitted with enteric fever type syndromes (e.g. fever, diarrhea, abdominal pain/distension) are more likely to benefit from quinolone therapy, especially in patients with documented *Shigella, Salmonella* or *Campylobacter* infection. When in doubt, cover with ceftriaxone + metronidazole until stool cultures are available.

D. Urinary tract/GYN infection

Urinary tract Infections including PID		
Site	**Microbiology**	**Suggested antibiotics**
Pyelo (uncomplicated)	GNR (*E. coli*)	Ceftriaxone (1 gm IV Q day)
Pyelo (complicated–foley, instrument, under disease)	GNR + enterococci	Gent + amp
Prostatitis	GNR + enterococci	Gent 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.* In the OVMC population, 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

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

√ **Cellulitis and skin abscesses:** When you initially see the patient, try to determine whether they have a simple spreading cellulitis (usually due to Grp 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—an organism resistant to 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. In these situations, many specialists recommend addition of clindamycin since it has MRSA activity (over 80% of strains) and "turns off" production of toxins by grp A streptococci.

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

F. Endocarditis/vascular infection

Endocarditis and vascular infection		
Site	**Microbiology**	**Suggested antibiotics**
Endocarditis-IVDU*	*S. aureus*, GNR (rare)	Gentamicin + vancomycin
Endocarditis-post RHD	Viridans streptococci; HACEK	Gent + Ceftriaxone + vancomycin
IV site	*S. epidermidis*, *S. aureus*, rare GNR	Vancomycin (add AG or quinolone 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		

√ **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. On rare occasion, intravenous drug users will develop endocarditis due to gram negatives such as *Pseudomonas aeruginosa*—administer an aminoglycoside till cultures are available.

√ **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 such as those seen in patients with a history of rheumatic heart disease or congenital valve abnormalities (e.g. Bicuspid aortic valve; mitral valve prolapse). In these situations, a combination of gentamicin, ceftriaxone and vancomycin is appropriate till culture results are available.

G. Febrile neutropenia

Febrile neutropenia		
Site	**Microbiology**	**Suggested antibiotics**
Febrile neutropenia	GNR, viridans strep, staph sp.(IV site)	Cefepime (2 mg IV Q 8hr) (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. A broad spectrum B-lactam agent (e.g. cefepime; piperacillin/tazobactam or carbapenem) is appropriate therapy till cultures are available. 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.

H. Sepsis-Unknown source

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":** There will be occasions when you are unable to identify a potential source although the patient appears "septic" and requires immediate antibiotic therapy. 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.* 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 more expensive antibiotics (e.g. piperacillin/tazobactam; carbapenems) is appropriate until cultures are available.

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, although bacterial antibiotic susceptibilities change, the causative "bugs" stay 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). Parenteral therapy is almost always necessary in critically ill patients or those with significant nausea and vomiting.
- ❑ **Choose empiric antibiotics** based on the OVMC empiric antibiotic grid
- ❑ **Keep in mind** the following concerns...
  - √ **Allergy:** Always ask the patient (or the patient's family members) whether there is a history of drug allergy, especially to B-lactam agents or sulfa drugs.
  - √ **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 with your antibiotic choice.
  - √ **Cost/convenience considerations:** Once daily or BID administration is generally cheaper than Q 4-6 hour dosing. Whenever possible, try to avoid "expensive" parentereal agents (~ $75-$100 per day) that generall
- ❑ **Reevaluate the patient at 24-48 hours**—if cultures reveal a single pathogen, narrow therapy to a single, specific agent.

ID Checklist: OVMC empiric antibiotic therapy—2010/2011

Disease	Organisms	Empiric antibiotic therapy
Meningitis	*S. pneumoniae* (? PCN resistance[1]) *N. meningiditis* *Listeria monocytogenes* (age>50; steroids, subacute, summer)	Vancomycin + ceftriaxone (Add ampicillin if *Listeria* risk factors or immunocompromised)
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 (Add Gent if severe sepsis)
Intraabdominal		
Local GI infection (Appy/chole/divertic)	E. coli, strep, anaerobes	Cefotetan (2 gm IV q 12 hr) or Ceftriaxone + metronidazole
Abdominal sepsis (peritonitis;shock)	E. coli, enterococci, anaerobes	Gent + pip/taz or Gent + 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
Urinary tract Infection		
Pyelo (uncomplicated)	GNR	Ceftriaxone (1 gm IV Q day)
Pyelo (complicated: Foley, recent instrumentation, underlying disease; older male)	GNR + enterococci	Gent + amp
Prostatitis	GNR + enterococci	Gent OR cipro + ampicillin
OB-GYN		
PID	GC, *Chlamydia*, mixed infection	Cefotetan + doxycycline (IV/PO)
Soft tissue		
Cellulitis*	Grp A streptococci, *S. aureus*	Cefazolin (+clindamycin in nec fasc)
Cellulitis c skin abscess *	*S. aureus* (MRSA)	IV Vancomycin or Clinda 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-IVDU*	*S. aureus*, GNR (rare)	Gentamicin + vancomycin
Endocarditis-post RHD	Viridans streptococci; HACEK	Gent + Ceftriaxone + vancomycin
IV site	*S. epidermidis*, *S. aureus,* rare GNR	Vancomycin (add AG or quinolone in septic patients till cultures available)
Febrile neutropenia	GNR, viridans strep, staph sp.(IV site)	Cefepime (2 mg IV Q 8hr) (add vancomycin if line infection)
Sepsis—unknown source*	*E.coli, S. pneumo., S. aureus*, group A strep	Ceftriaxone + vancomycin + [gent or levofloxacin]

* MRSA risk factors (recent hospitalization or antibiotic Rx, IVDU, homosexual males)-add vanco in seriously ill patients
[1]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*

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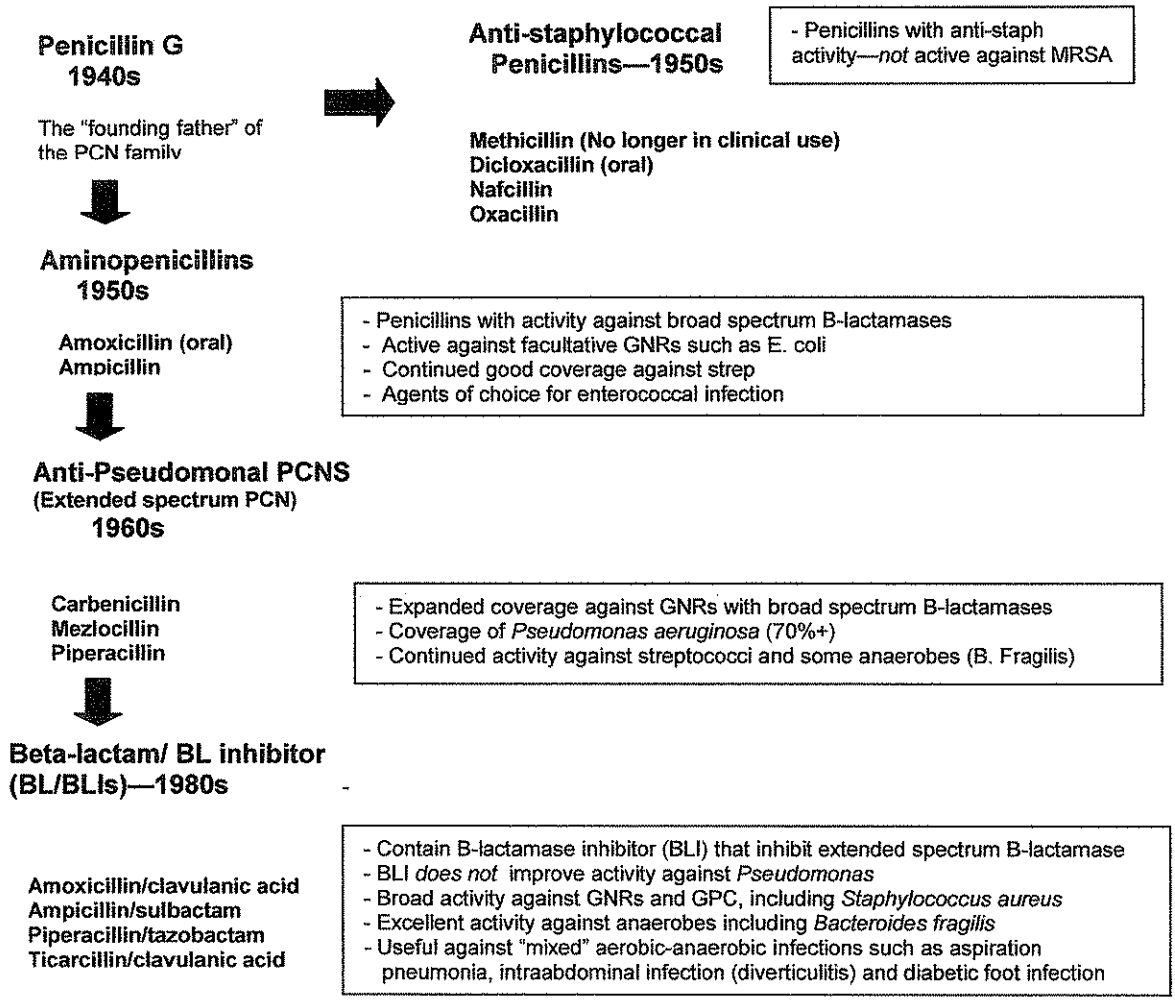
What every physician should know about antibiotics

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.

I. Penicillin—founding father of modern antimicrobial therapy

Despite the passage of time, the penicillin agents remain some of the most common antimicrobials prescribed by physicians. The following schema—outlining the historical development—should help you to remember the agents along with their antimicrobial spectrum:



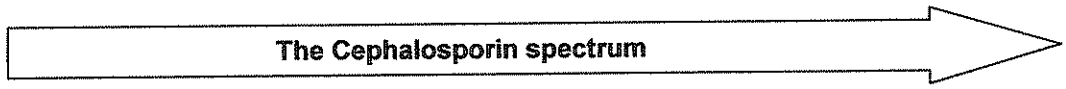
Remember...

- **Pneumococcus:** Increasing resistance to PCN G (Rx with 3rd generation Ceph or Vancomycin)
- **MSSA** (methicillin-sensitive *Staph aureus*): Use nafcillin, oxacillin or cefazolin
- **MRSA** (methicillin-*resistant Staph aureus*): Resistant to all B-lactams...use vancomycin.
- **E. coli:** Increasing resistance to ampicillin (40% sen); most still sensitive to ceftriaxone except for ESBL organisms (Rx with carbapenems)

- **BL/BLI:** Broadest coverage (GNR+staphy+ANO2)…but most expensive! ($50-$100 per day)

II. Cephalosporins…The next generation

Close cousins of penicillins, these B-lactam antibiotics are grouped according to "generations"—an old marketing term that still remains useful.



1st Generation	2nd Generation	3rd Generation	4th Generation	5th Generation
Cefazolin Cephalexin (PO) Cephradine (PO)	Cefuroxime: Cefotetan Cefoxitan	Cefotaxime Ceftriaxone Ceftazidime	Cefepime	Ceftbiprole
Good staphylococcal and streptococcal coverage, these agents also have good activity against *Klebsiella* and fair activity against *E. coli* .	Better GNR (+ H flu) coverage than 1st generation agents, the cephamycins (cefoxitan; cefotetan) also have excellent activity against anaerobes. activity (Cefotetan, cefoxitan) against anaerobes	These agents have improved GNR activity at the cost of slightly decreased strep and staph activity. Ceftazidime has activity against *Pseudomonas aeruginosa*	The newest agent in the class, cefepime has excellent GNR, staph ar strep coverage but poor anaerobe activity	This drug has activity against both MRSA and *Pseudomonas aeruginosa.*

Remember...

- **Cefazolin; cephalexin:** 1st generation cephalosporins with good staph/strep activity except MRSA
- **Cefotetan** and **cefoxitin** have excellent anaerobic activity—the best of cephalosporins
- **Ceftriaxone:** 3rd generation cephalosporin with improved GNR coverage, good CSF penetration and activity against *Streptococcus pneumoniae.*
- **Cefepime** good for nosocomial GNR infection (e.g. *Pseudomonas*) and staph/strep except MRSA
- **Ceftobiprole:** First cephalosporin with MRSA activity (also *Pseudomonas*)

III. Carbapenems…the "Terminators"

I call these drugs the "terminators" since they seem to kill everything in their path—they have an extremely broad spectrum and are useful for serious, hospital-acquired nosocomial infections. Aside from their expense ($50-100 per day), they wipe out normal flora and can lead to overgrowth of resistant organisms such as *Candida* species.

Imipenem: Extremely broad coverage (ESBL GNR, SPICE bugs) but $$$ and neurotoxicity
Meropenem: Spectrum similar to imipenem…but lower neurotoxicity
Doripenem: Similar to impenem and meropenem

Ertapenem: Once daily cephalosporin (good for home antibiotics) similar spectrum to other carbapenems but no *Pseudomonas* or *Acinetobacter* coverage

- The top 3 agents (imipenem, meropenem, doripenem) have a pretty similar spectrum and only minimal differences in toxicity and pharmacokinetics.
- Try to avoid imipenem for CNS infection since it appears to have a higher incidence of neurotoxicity.
- These drugs are the agents of choice for ESBL organisms (*E. coli*; *Klebsiella* species) resistant to 3rd generation cephalosporins.

- Overuse of these drugs has led to the emergence of carbapenem resistant GNRs (The "KPC" bugs—*Klebsiella pneumoniae* carbapenemases) that require treatment with such agents as colistin and tigecycline.

IV. Anaerobe agents:

Anti-anaerobe agents are necessary for "mixed" infections (Intraabdominal abscess; head/neck infection; diabetic foot infection) that contain both aerobes and anaerobes. *Bacteroides fragilis*—an important pathogen in intraabdominal infection—is the "poster bug" for any anti-anaerobe agent. The following drugs have activity against anaerobes and can often be used in "mixed" aerobic-anaerobic infection:

BL/BLI agents (Piperacillin/taxozobactam; ampicillin/sulbactam; amoxicillin/clavulanic acid)
Cefotetan/Cefoxitan: Both these agents have broad activity against anaerobes (the best of the cephalosporins) and can be used against mixed aerobic-anaerobic infection.
Clindamycin: Broad anaerobe coverage with *Staph* and strep activity; causes *C. difficile* colitis
Metronidazole: This agent has excellent bactericidal activity against strict anaerobes. It has relatively poor activity against microaerophilic organisms (e.g. streptococci) or "aerotolerant" bacteria (e.g. actinomycosis); in most situations, the drug requires addition of an agent with activity against strep (e.g. cephalosporin; penicillin; vancomycin).

V. Aminoglycosides...

- The aminoglycosides are drugs with excellent activity against facultative gram-negative rods
- They have poor activity against GPC and *no* activity against anaerobes
- Concentration dependent killing... dose once a day for best results and lower toxicity
- Once daily dosing has pretty much minimized the toxicity of these agents; however, √ trough levels after the third dose to minimize adverse reactions.
- When using these agents, ask the patient about tinnitus, "stuffed ears" or hearing loss—signs of early ototoxicity.
- Don't use these agents for long-term treatment (> 10-14 days) without supervision from an ID specialist
- Amikacin most active followed by tobramycin and gentamicin

VI. Quinolones...Attack of the clones

A godsend for treating gram-negative infection, their convenience (QD or BID dosing), excellent oral absorption and broad antibacterial spectrum make them the subject of intense pharmaceutical marketing!

1st Generation	2nd Generation	3rd Generation
Ciprofloxacin	Levofloxacin	Moxifloxacin/Gatifloxacin
Mainly GNR (includes Pseudomonas) 50% staph Poor S. pneumo	Respiratory quinolone Good S. pneumoniae + *Pseudomonas aeruginosa* Fair staph/strep	Respiratory quinolones Excellent S. pneumoniae Good GNR (No *Pseudomonas*) Fair anaerobe

Ciprofloxacin: Excellent GNR coverage; poor coverage of respiratory pathogens (pneumococcus)
"Respiratory quinolones": These drugs have excellent activity against resistant *S. pneumoniae* and "atypical" pulmonary pathogens (*M. pneumoniae, Legionella, C. pneumoniae*)

Levofloxacin
Moxifloxacin
Gatifloxacin

These drugs are three tough competitors for the "pneumonia" market. Should probably be reserved for sicker patients with higher likelihood of resistant pneumococcus. Watch out for **QT prolongation**—especially in patients receiving drugs with similar effects.

Warning: Overuse of these drugs is leading to increased GNR and GPC resistance!

VII. Macrolides

These agents have a long history of safety and tolerability making them excellent drugs for outpatient therapy. Their absorption is 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: Like ERY + *H.flu* coverage…Watch out for QT prolongation and drug interactions
Azithromycin: Similar to Clarithromycin but easier dosing (QD), better H.flu coverage and fewer drug interactions

- Erythromycin is still a good (and cheap) agent although it is less commonly prescribed since the newer agents seem to have better tolerability.
- Whenever using clarithromycin, be especially careful about QT interactions since these may lead to ventricular arrhythmias
- There is increasing resistance to macrolides among pneumococcus and Group A streptococci (about 20%); be cautious about relying on these agents solely in patients with life-threatening infections.

VIII. Tetracyclines

Reliable drugs (**doxycycline**) for treating atypical pulmonary pathogens (*M.pneumoniae, C. pneumoniae*) and an assortment of rare—but life-threatening—infections (plague, tularemia, Q fever, psittacosis, typhus).

Tigecycline: This is a new, parenteral "super" tetracycline (related to minocycline) with broad activity against GPC, GNR and anaerobes, including resistant bugs such as MRSA, VRE and KPC organisms. It is touted as an agent for mixed aerobic-anaerobic intraabdominal infection (diverticulitis, intraabdominal abscess) and "mixed" soft tissue infection (diabetic foot infections). The drug is "bacteriostatic" (rather than cidal) and there have been some drug failures in patients with bacteremia—avoid using this drug in critically ill patients unless it is needed for some of the more highly resistant organisms.

IX. New Entries in the Gram positive battle

Linezolide: Oral agent for MRSA and VRE; outpatient Rx costs $70 a pill!
Synercid (quinupristin/dalfupristin): IV Rx for VRE (*E.faecium*) and MRSA
Daptomycin: "Lipopeptide" drug active against GPC including MRSA, VRE

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 intern started oral medications (oral 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 patients with possible septic syndrome, do not allow supportive measures (e.g. intravenous fluids, vasopressors) or administrative problems (e.g clerk, nursing and pharmacy delays) to delay appropriate antibiotic therapy. In sepsis, there is a "golden" period—probably only a few*

hours—where appropriate antibiotic therapy can prevent the development of irreversible septic shock. In the above case, more immediate antibiotic treatment might have prevented the patient's death.

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.

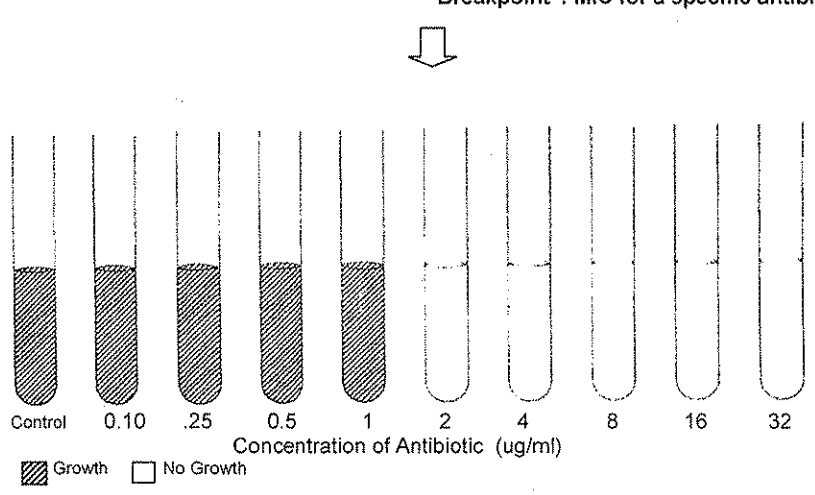
Warning: *Avoid cephalosporins in patients with a history of anaphylactic reaction to penicillin.*

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

If cultures are positive for a specific organism, its' critical to know whether they are 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.

The laboratory report below is an example of standard reporting procedures for antibiotic susceptibility. For this isolate of *E. coli*, the second column reports the MICs for various antibiotics tested. The designations in the third column (e.g. sensitive, intermediate, resistant) denote susceptibility of the organism to antibiotic concentrations attainable in the serum following a standard dose of a specific agent.

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 intrauteral 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 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 respiratory quinolones (e.g. levofloxacin-750 mg QD x 5 days) may well be adequate for patients with community-acquired pneumonia.

√ **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

The standard recommendation for a "10-day" course of antibiotics is in part based on large trials studying the utility of penicillin in preventing post-streptococcal rheumatic fever. In this research, optimal eradication of pharyngeal streptococcus carriage generally required a full 10-day course of therapy; shorter treatment courses led to a greater antibiotic failure rate with a higher risk of rheumatic fever.

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, 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.
- **Can the patient take oral medications?** With most common bacterial infections, a switch to oral therapy may be possible as soon as the patient is able to eat. On the other hand, oral therapy may be a bad idea if the patient has continued nausea/vomiting, or has some underlying gastrointestinal condition (e.g. ileus, malabsorption) that impairs drug absorption. Before switching to PO antibiotic, make sure the patient is clinically improving and able to tolerate oral medication.
- **Which antibiotics have the best oral absorption?** Not all oral antibiotics are created equal—the following table outlines some of the available oral agents along with useful dosing and bioavailability data (e.g. % absorption, serum levels).
- **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!

Table 3: Oral bioavailability of common antimicrobials

Antibiotic	Dose	Absorption (%)	C_{peak} (ug/ml)	Note
Penicillins				
Amoxicillin	500 q 8hr	90	7.5	Less diarrhea than ampicillin
Amox/clav acid (Augmentin)	875/125 q 12hr	90/60	15/2	Broader coverage including anaerobes
Ampicillin	500 q 6hr	40	3.5	
PCN VK	500 q 6hr	60	5	
Dicloxacillin	500 q 6hr	50	15	Anti-staphylococcal pcn
Cephalosporins				
Cephalexin	500 q 6hr	99	18	
Cefaclor	500 q 8hr	93	9.3	
Cefuroxime	500 q12hr	52		Gm Pos + H flu coverage
Cefixime	400 q12hr	50	3.7	Oral 3rd generation cephalosporin
Quinolones				
Ciprofloxacin	500-750 q 12 hr	70	2.8	Levofloxacin gati,floxacin and moxifloxacin are "respiratory quinolones" with good activity against S. pneumo; Ciprofloxacin ia unreliable against pneumococcus
Gatifloxacin	400 q 24hr	96	3.8	
Levofloxacin	500 q 24hr	99	5.7	
	750 q 24 hr	99	8.6	
Moxifloxacin	400 q 24 hr	90	4.5	
Macrolides				
Azithromycin	500 load then 250 qd x 4 days	35	0.3	Attains highest intracellular levels
Clarithromycin	500 q 12 hr	50	3	
Erythromycin	500 q 6hr	50	1.2	

Tetracyclines				
Doxycycline	200 load; 100 q 12	93	4	
Minocycline				
Tetracycline	500 q 6hr	60	1.5	
Miscellaneous				
Clindamycin	300 q 8 hr	90	10	Unreliable against enterococcus
Metronidazole	500 q 12hr	90	26	Strict anaerobes only
TMP/SMX	160/800 q 12 hr	98	3.4/	
Rifampin	600 q 24 hr	95	7	Rapid resistance when used as monotherapy for Staph aureus
Linezolide	600 q 12 hr	100	16	Active against MRSA and VRE

Table based on material from Cunha BA, Antibiotic Essentials, Physicians Press 2002.
* Cost data based on Tarascon Pocket Pharmacopoeia—2001 edition. Tarascon Pub. Loma Linda, Ca.; $<$25; $$-$25-49; $$$-$50-99; $$$$-$100-199; $$$$$-≥$200 for 10 day course of drug
Bold: Denotes "best buy" agents: good absorption; relatively inexpensive

As you can see from the table, even within specific classes of antibiotics, there are pharmacokinetic differences that might favor one antibiotic over another. When choosing oral agents, remember the following caveats…

√ **B-lactam agents:** 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-suceptible Staph aureus (MSSA), dicloxacillin has excellent activity and is usually the drug of choice. 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 (e.g. cefpodoxime or cefixime).

√ **Quinolones:** Ciprofloxacin is generally the recommended agent for most gram-negative infections since it is well absorbed and quite inexpensive. 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.

√ **Anaerobe agents:** For patients with anaerobic or "mixed" aerobic/anaerobic infection, there are several possible agents that can be used. Metronidazole has the best activity against strict anaerobes but, for mixed infections, usually requires addition of an agent active against streptococci or microaerophilic bacteria. For patients able to tolerate a penicillin antibiotic, amoxicillin/clavulanic acid has excellent anti-anaerobic activity and a good choice for patients with "mixed" infection such as diabetic foot ulcer or diverticulitis. Of the quinolone class, although resistance appears to be increasing, moxifloxacin has the best anti-anaerobic activity and can be used for "mixed" aerobic/anaerobic infection.

A Rogue's Gallery of Resistant Bacteria

On ward rotations and in daily discussions with colleagues, you're bound to hear more about the following "antibiotic-resistant" organisms. They represent the price we pay for the widespread overuse of antibiotics and increasing complexity of medical care.

1. DRSP (Drug-resistant *Streptococcus pneumonia*):

First isolated in South Africa during the 1970s, DRSP isolates have spread to many parts of the world and now account for up to 50% of invasive pneumococcal infections in some cities. The overuse of oral amoxicillin—especially for treatment of otitis media in the pediatric population—is a key factor in the emergence of this organism. There is an increasing incidence of this organism in older adults, especially patients with a history of recent antibiotic therapy.

Mechanism: The mechanism of resistance is due to decreased binding of penicillin to target molecules—penicillin binding proteins (PBPs)—in *Streptococcus pneumoniae*. As a consequence, penicillin is unable to interfere with cell wall synthesis except in high concentrations. The origin of the original resistance mutation is unclear but may be due to pneumococcal uptake of DNA material from penicillin-resistant viridans streptococci found in the oral cavity.

Diagnosis: PRSP should be suspected in patients at the extremes of age (infants, > age 50), immunocompromised patients (HIV, cancer) and those who have recently received antimicrobial therapy. Laboratory identification of the organism depends on MIC determination via an E-test—a simple susceptibility test available in most clinical laboratories.

Treatment: Treatment of infection with DRSP depends upon susceptibility of the organism (intermediate vs. resistant) as well as the location of the infection (CNS vs non-CNS). CNS infections such as bacterial meningitis are the most challenging to treat because of the relatively poor penetration of B-lactam agents into the central nervous system.

Susceptibility	MIC	Antibiotic therapy
Penicillin		
Susceptible	MIC < 0.1 mg/L	Penicillin G
Intermediate	MIC 0.1 – 1.0 mg/L	Ceftriaxone or cefotaxime
Resistant	MIC ≥ 2.0 mg/L	Ceftriaxone or cefotaxime
Ceftriaxone/cefotaxime		
Susceptible	MIC ≤ 0.5 mg/L	Ceftriaxone or cefotaxime
Resistant	MIC > 0.5 mg/L	Ceftriaxone or cefotaxime plus vancomycin or rifampin

2. MRSA (Methicillin-resistant *Staphylococcus aureus*):

MRSA isolates were recognized almost immediately after the introduction of anti-staphylococcal penicillins such as methicillin and oxacillin in the late 1950s. Resistance remained relatively low until the late 1970s and early 1980s when MRSA emerged as a significant nosocomial pathogen in hospitalized patients. The organism is a particular problem in large hospitals (>500 beds) where hospital-wide outbreaks amy be difficult to contain. A worrisome trend is the increase in community-acquired MRSA—individuals at risk for this problem include intravenous drug users and patients with serious underlying illness who have been recently hospitalized or received antibiotics[1]. In some parts of the United States, there are now reports of community-acquired MRSA in children with no previous predisposing risk factors[2].

Mechanism: B-lactam resistance in most isolates of *Staphylococcus aureus* is mediated by production of a B-lactamase enzyme excreted by the organism—anti-staphylococcal penicillins are typically unaffected by this

enzyme. The mechanism of resistance in MRSA is entirely different—alteration of penicillin-binding proteins (PBPs) leads to decreased antibiotic binding and continued bacterial growth. The altered PBP—PBP2a—is produced by a novel gene (*mecA*) present on the MRSA chromosome that confers broad resistance to both penicillins and cephalosporins[3]

Diagnosis: Think about the possibility of MRSA in patients with the following risk factors: intravenous drug use, previous antimicrobial therapy, recent hospitalization (especially in nursing homes or facilities with a high incidence of MRSA) and patients with serious underlying illness.

Treatment: Vancomycin is the drug of choice for treatment of serious MRSA infections. Although MRSA isolates may show *in vitro* susceptibility to other cephalosporins and carbapenems, these agents *should not* be used as MRSA isolates are broadly resistant to B-lactam agents and laboratory testing misleading. Clinical isolates may be sensitive to other antibiotic classes (tetracyclines (e.g. minocycline), trimethoprim-sulfamethoxazole, rifampin or quinolones); however, resistance can develop quickly to these agents and they are typically reserved for patients with milder illness who are able to take oral therapy. New antibiotics with activity against resistant gram-positive pathogens—linezolid (oral or parenteral formulations) and dalpristin/quinopristin (parenteral formulation)—offer additional options for treatment of serious MRSA infections

3. VRE (Vancomycin-resistant enterococci):

Another highly resistant organism, vancomycin resistance among nosocomial enterococcal infection has increased 20-fold between 1989 and 1995[4]. This increase is in part due to the widespread empiric use of vancomycin for suspected gram-positive infection as well as the use of the drug for treatment of *C. difficile* enterocolitis. The addition of glycopeptides to animal feeds may also have played a role in this increase. Enterococci are already "intrinsically" resistant to certain antibiotics (cephaloporins, penicillinase-resistant penicillins, clindamycin, fluoroquinolones, trimethoprim-sulfamethoxazole, low concentrations of aminoglycosides)—the development of acquired, "high-level" resistance to vancomycin and other antibiotics is truly a disturbing trend. Studies suggest that VRE infections lead to an attributable mortality approaching 50%[5].

Mechanism: VRE are classified as one of several phenotypes depending upon a number of characteristics including sensitivity to vancomyin/teicoplanin, species and the nature of the genetic determinant. Vancomycin normally works by binding to peptidoglycan—a cell wall component—and interfering with subsequent cell wall construction. In VRE strains, alteration of the cell wall target leads to reduced binding of vancomycin and continued wall construction. Production of this "less avid" peptidoglycan target is under the control of a complex suite of genes; the source of this genetic material is unclear although bacteria likely acquire from other bacteria with similar resistance patterns.

Diagnosis: The laboratory plays an important role in the detection of VRE infection. Automated laboratory testing systems may sometimes underestimate the degree of resistance of specific isolates. Most laboratories have additional systems in place (E-test, broth dilution) to confirm resistance in specific strains.

Treatment: Until recently, treatment of these infections was highly problematic. Teicoplanin—a glycopeptide not currently licensed in the United States—may be used for treatment of Van B and Van C phenotypes. Individual isolates may be susceptible to chloramphenicol, fluoroquinolones, tetracycline or rifampin; however, resistance may develop quickly and these agents are not bactericidal—a serious drawback in the treatment of deep-seated enterococcal infections. Two new agents—linezolid and quinupristin/dalfupristin—have activity against *Enterococcus faecium* and are useful in the treatment of the majority of hospital-acquired VRE infection[6].

4. VISA (Vancomycin intermediate-susceptible *Staphylococcus aureus*)

In 1997, an MRSA with intermediate sensitivity to vancomycin (MIC= 8 ug/ml) was isolated from a dialysis patient in Japan—the patient failed to respond to vancomycin and had to be treated with a combination of arbekacin (an aminoglycoside not yet available in the United States) and ampicillin-sulbactam[7]. The widespread problem with MRSA—and frequent empiric use of vancomycin—has raised concerns that these organisms may become more prevalent.

Mechanism: The mechanism of resistance in VISA organisms is still uncertain—isolates demonstrate increased production of PBPs, altered PBPs, decreased bacterial autolytic activity and increases in cell thickness and size (3 maranan).

Diagnosis: These organisms are still quite uncommon; however, the increasing use of vancomycin for MRSA infection is likely to lead to more widespread vancomycin resistance. Keep in mind the possibility of VISA infection in patients who have received multiple courses of vancomycin—especially in dialysis patients where the drug is commonly used for empiric treatment of fever.

Treatment: Optimal therapy of infections with VISA isolates is still uncertain; however, agents such as linezolid and daptomycin seem to have *in vitro* activity.

5. ESBL (Extended-spectrum B-lactamase) producing organisms:

ESBL refers to an extended-spectrum B-lactamase produced by a number of facultative anaerobic gram-negative bacteria—the enzyme confers resistance to broad-spectrum agents—especially 3rd generation cephalosporins—and related antibiotics[8]. It had become a problem among selected *Klebsiella* and *Escherichia coli* isolates. Risk factors for ESBL acquisition include prolonged hospital stays and a history of previous antibiotic administration. A specific ESBL type often predominates in a particular hospital and spread of the organism between patients likely to occur if hospital ignore proper infection control procedures.

Mechanism: The B-lactamase confers resistance to oxyimino-B-lactam antibiotics (cefotaxime, ceftriaxone, ceftazidime) and antibiotics with oxyimino side chains (aztreonam). Genetic determinants for these enzymes are carried on plasmids and transferred between cells. The B-lactamase is secreted into the periplasmic space (between the outer and inner membranes) of gram-negative organisms where it acts on antibiotics that manage to penetrate through the outer membrane via porons. B-lactamase inhibitors (clavulanic acid, sulbactam) have activity against ESBLs but may not be reliable.

Diagnosis: Clinical laboratories commonly overlook these organisms as they appear sensitive—or of intermediate sensitivity—to third-generation cephalosporins in standard automated susceptibility testing systems. This apparent sensitivity may be due to the "inoculum" effect—the false appearance of susceptibility when a small inoculum of organisms is used in the test well. "Intermediate" susceptibility to cefotaxime or ceftazidime is a clue to the possibility of an ESBL producer. Most clinical laboratories are aware of the problem and have improved procedures for identifying these organisms. If in doubt about the possibility of an ESBL organism—especially in patients with *Klebsiella* or *E.coli* infections— make sure the laboratory is aware of your concern and performs the appropriate testing.

Treatment: Serious infections related to ESBL producing gram-negative organisms respond poorly to 3rd generation cephalosporins; cephamycins (cefoxitan, cefotetan) are less affected by the enzyme but could be unreliable if membrane porons impede entry of the antibiotic into the cell. Some ESBL producers are sensitive to aminoglycosides and fluoroquinolones; however, many isolates carry plasmid-mediated resistance factors that render these antibiotics also ineffective. Although BL/BLI drugs (e.g. piperacillin/tazobactam) might be expected to be effective in ESBL infections—due to inhibition of the ESBL by the B-lactamase inhibitor—these drugs have proven less than effective because ESBL overproduction overwhelms the BLIs. Carbapenems (imipenem, meropenem) have the most consistent activity against ESBL strains and are now considered first-line agents for treatment of these infections.

6. SPACE bugs: AmpC B-lactamases

The term "SPACE" bugs is shorthand for several bacteria that are commonly resistant to 3rd generation cephalosporins by means of an inducible, chromosomal-mediated B-lactamase. Although occasionally seen in community-acquired infections, they are most common in the hospital setting as nosocomial pathogens. The acronym SPACE stands for the following organisms...

S *Serratia marcesens*
P *Pseudomonas aeruginosa*
A *Acinetobacter* sp.
C *Citrobacter* sp.
E *Enterobacter* sp.

(Some authorities add indole+ *Proteus* sp. to this list instead of *Acinetobacter* leading to the acronym "***SPICE***" bugs)

Mechanism: Antibiotic resistance in these organisms is coded by an inducible, chromosomal gene—AmpC—that produces a broad-spectrum B-lactamase capable of inactivating 3rd generation cephalosporins (cefotaxime, ceftizoxime, ceftriaxone, ceftazidime)[9]. Initial B-lactamase production is minimal—antibiotic exposure leads to "induction" and increased production of the enzyme with subsequent inactivation of the target compound. Within a few days, an apparent "sensitive" bacteria may turn "resistant" and lead to a clinical relapse of the infection.

Diagnosis: Again, a high index of clinical suspicion plays an important role in the detection of these organisms. SPACE bugs initially appear sensitive to third generation cephalosporins—their true nature is revealed following antibiotic exposure when the bug turns on production of the deadly B-lactamase. Using PCR technology or DNA probes, some research laboratories are capable of detecting the gene for an inducible B-lactamase. Unfortunately, these tests are not available in most clinical laboratories—when a "SPACE" bug is the pathogen, the clinician must identify a clinical relapse as soon as possible.

Treatment: Be wary of treating "SPACE" bugs with a single 3rd generation cephalosporins such as cefotaxime or ceftazidime. These organisms are best treated with other classes of antibiotics such as aminoglycosides or quinolones; some specialists recommend combination antibiotics (aminoglycoside + B-lactam; quinolone + B-lactam) for optimal therapy. Fortunately, carbapenems such as meropenem and imipenem retain activity against the B-lactamase and remain reliable agents for the treatment of these infections. The new "4th" generation cephalosporin—cefipime—also appears active against inducible B-lactamases associated with the AmpC gene. Whatever treatment you use, watch the patient carefully for signs of clinical failure suggesting emergence of a resistant organism.

7. Multidrug resistant Gram Negative Bacilli (MDR GNB)

"MDR" refer to gram-negative bacteria resistant to almost all commonly used antibiotics. These pathogens are most commonly seen in hospitalized ICU patients, individuals who have generally received heavy exposure to antibiotics. These pathogens are typically resistant to most agents including third generation cephalosporins, extended spectrum pencillins (e.g piperacillin/tazobactam), quinolones, aminoglycosides and carbapenems. Resistance to carbapenems is especially problematic—in ICU settings, we typically rely on this class of antibiotic for "resistant" pathogens.

Mechanism: In these organisms, antbiotic resistance is typically multifactorial including B-lactamases (including activity against carbapenems), altered porins (decreasing antibiotic penetration) and antibiotic resistance pumps (pump out antibiotics). *Pseudomonas aeruginosa* is the most common "MDR" organism; however, other gram negative bacillin, including *Acinetobacter* are also seen.

Diagnosis: Think of these bugs in hospitalized individuals who have been heavily treated with antibiotics. In these patients, you shouldn't be surprised if the laboratory report documents extensive resistance, including resistance to carbapenems and aminoglycosides.

Treatment: Treatment of infection with these bugs remains especially problematic. Although they are frequently resistant to B-lactam antibiotics, laboratory studies suggest that combination therapy (using two to three antibiotics) may lead to effective synergistic activity. This often includes using *two* B-lactams (e.g. piperacillin + cefepime) with

an aminoglycoside or quinolone. Another approach relies on use of older agents such as colistin that typically have significant side effects such as nephrotoxicity.

8. "KPC"s—*Klebsiella pneumonia* carbapenemases

We have traditionally relied on carbapenems (e.g. imipenem; doripenem; meropenem) for treatment of highly resistant gram negative bacilli, however emergence of bugs that produce carbapenemases—B-lactamases with activity against carbapenems has threatened this approach. Although they may be seen in any of the *Enterobacteriaceae* (*E. coli*) this has been especially common in *Klebsiella* species, leading to the designation as KPCs (*Klebsiella pneumonia* carbapenemases) or CRKP (Carbapenem resistant *Klebsiella pneumonia*) bugs.

Mechanism: KPC bugs have carbapenemases (B-lactamases) with specific activity against carbapenems such as imipenem, doripenem, meropenem or ertapenem. These enzymes are frequently carried on plasmids, so they may spread rapidly between patients (via phages) leading to hospital or ICU outbreaks.

Diagnosis: Again, think of these bugs in patients who have been hospitalized, especially in patients who have previously received carbapenems. Although uncommon, patients without a history of antibiotic therapy may occasionally acquire these organisms in the community. More recently, publicity about the NDM-1 bugs, first described in a Swedish patient who likely acquired the bug in India (the NDM designation refers to New Delhi metallo-carbapenemase that has activity against carbapenems).

Treatment: Treatment of KPC (CRKP) bugs is difficult and depends upon laboratory determined susceptibilities. Since the resistance gene is often found on plasmids, there are usually additional resistance elements to antibiotics such as quinolones, aminoglycosides and broad spectrum penicillins. Agents such as colistin and tigecycline may have activity against these pathogens—talk to the laboratory and test for these agents.

9. MDR tuberculosis (Multidrug-resistant *Mycobacterium tuberculosis*[10]):

Thought to be a "dying" disease in many parts of the developed world, the reemergence of tuberculosis in the late 1980s proved that this organism remains a potent threat. MDR or multidrug-resistant tuberculosis—defined as *Mycobacterium tuberculosis* resistant to *both* isoniazid and rifampin—played an important role in this reemergence. The resurgence of tuberculosis due to AIDS—combined with the breakdown of public health control measures—led to a worrisome increase in infections with this organism. In many countries in the developing world, the absence of effective TB control programs—leading to poor patient compliance with intermittent, substandard treatment—served to label these regions as "breeding grounds" for MDR tuberculosis.

Mechanism: Spontaneous genetic mutations lead to alterations in "target" proteins and bacterial resistance to antibiotic action. There is no evidence of that these resistance factors are passed between bacteria via transmissible agents (plasmids, transposons) or sexual conjugation (Mycobacteria don't have sex!). Mutations are most likely to occur in infections with large numbers of organisms—cavitary pulmonary tuberculosis may contain up to 10^{11} bacteria—where there is ample opportunity for multiple resistance mutations. Patients with poor, intermittent compliance are at great risk for developing MDR-TB with subsequent relapse. Other risk factors include AIDS, homelessness and recent travel to—or from—a country with a high incidence of MDR-TB.

Diagnosis: While DNA probes are available for detection of some resistant genes, diagnosis of MDR resistance in the clinical laboratory relies on growing the bacteria and testing them against concentrations of the various anti-mycobacterial antibiotics. Once TB is grown from a patient, modern broth susceptibility techniques permit determination of antibiotic susceptibility within 2 weeks.

Treatment: In regions with a high incidence (>5%) of MDR-TB, patients with documented or suspected tuberculosis should receive a 4-drug regimen—isoniazid, rifampin, pyrazinamide and ethambutol—until antibiotic susceptibility results are available. The choice of therapy in those with a tuberculosis relapse relies upon a cardinal rule of tuberculosis therapy—"Never add one drug to a failing regimen". The addition of a single "new" drug may quickly lead to resistance to that agent and limit future options for successful therapy. Once drug susceptibilities are available, a regimen—often consisting of 4-5 drugs—can be chosen; successful cure usually requires that these

agents be administered for 18 to 24 months. Taking some of these agents can be a daunting task—the "second-line" antibiotics (ethionamide, cycloserine, PAS, capreomycin) are often less active against *Mycobacterium tuberculosis* and have significant side effects. In rare cases, patients may require surgical excision of infected organs in order to reduce the load of bacteria. The presence of resistance to both isoniazid and rifampin makes MDR-TB particularly difficult to treat—some studies have shown that cure rates drop to about 50% in cases with multi-resistant organisms.

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ID Checklist: Antibiotic resistant organisms

Organism	Mechanism	Clinical	Treatment
PRSP Penicillin-resistant *Streptococcus pneumoniae* Penicillin susceptibilities: Sensitive MIC≤ 0.1 ug/ml Intermediate MIC=0.1-1.0 ug/ml Resistant MIC ≥ 2.0 ug/ml	Altered Penicillin-binding proteins (PBPs) with decreased pencillin binding	Most common at in infants (day-care), older patients, immunocompromised patients (HIV) and those recently treated with B-lactam agents.	Vancomycin Ceftriaxone or cefotaxime usually effective in non-CNS infection Newer agents—linezolide or quinupristin/dalfopristin—may be alternatives
VRE Vancomycin-resistant Enterococcus	Altered peptidoglycan with decreased vancomycin binding	Nosocomial pathogen in environments with overuse of vancomycin and 3rd generation cephalosporins	Daptomycin Linezolide Quinupristin/dalfopristin
MRSA Methicillin-resistant *Staphylococcus aureus*	Altered PBPs	Resistant to methicillin *and* cephalosporins; usually nosocomial pathogen but increasing incidence in community-acquired infection—especially diabetics and IVDUs	Vancomycin Linezolide, daptomycin are alternatives in patients failing or intolerant to vancomycin
VISA (VRSA) Vancomycin-intermediate *Staphylococcus aureus*	Mechanism uncertain ? Thickened wall ? Altered PBPs	Most cases in dialysis patients receiving frequent doses of vancomycin	Linezolide Daptomycin
"SPACE" Bugs *Serratia* *Pseudomonas* *Acinetobacter* *Citrobacter* *Enterobacter*	Associated with inducible, chromosomal mediated AmpC B-lactamase—exposure to antibiotic leads to increased enzyme production.	On initial isolation, organisms may appear sensitive to 3rd generation cephalosporins—with continued antibiotic therapy, organisms develop resistance with subsequent clinical relapse.	Carbapenems (imipenem, meropenem) Drugs with variable activity: Aminoglycosides Cefepime Piperacillin/tazobactam Quinolones
ESBL Extended-spectrum B-lactamase	BLE with activity against monobactams (aztreonam) and 3rd generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime) Resistance gene for ESBL B-lactamase carried on transmissible plasmid.	Most commonly seen in *E. coli* and *Klebsiella* isolates—these organisms may appear falsely sensitive to 3rd generation cephalosporins. Usually a nosocomial pathogen although occasional community-acquired case is reported. Clue: Borderline or intermediate susceptibility to3rd gen cephalosporins (e.g. ceftriaxone)	Carbapenems Cefepime Piperacillin/tazobactam, quinolones and aminoglycosides have variable activity—plasmid may carry other MDR genes
MDR GNB Multi-drug resistant gram-negative bacilli	Highly resistant organisms with combination of mechanisms including efflux pump, decreased membrane permeability and B-lactamases	MDR *Pseudomonas aeruginosa* is most common organism—generally seen as a nosocomial pathogen in ICU patients who have received multiple antibiotics	Difficult to treat; check azteonam, cefepime, colistin, tigecycline. Colistin may be beneficial in refractory cases although has high incidence of nephrotoxicity (40%)
KPC *Klebsiella pneumonia* carbapenemase	Highly resistant organism with enzyme activity against carbapenems. Often carries other resistance genes (ESBL; AmpC)	Most common among *K. pneumoniae* or *E. coli* isolates. Usually nosocomial pathogen but occasional from community. Clue: Look for borderline (or intermediate) susceptibilities to imipenem.	Resistant to carbapenems! Check susceptibilities Often resistant to AG, FQ Tigecycline Colistin; Polymyxin B

Abbreviations: AG: Aminoglycosides BLE: Beta-lactamase enzyme; FQ: Flouroquinolones; PBP: Penicillin-binding proteins

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Managing the emerging threat of MRSA

Puzzled when a "trivial" skin infection fails to respond to an oral antibiotic?

Keep in mind the possibility of infection with methicillin-resistant *Staphylococcus aureus* (MRSA)—staphylococci resistant to B-lactam agents such as anti-staphylococcal penicillins (nafcillin, oxacillin) and cephalosporins (cefazolin, cephalexin). Once almost exclusively confined to hospitalized patients, new strains of MRSA circulating in the community—community associated MRSA **(CA-MRSA)** have emerged as important and virulent pathogens in community-acquired skin and soft tissue infection.

Risk factors for MRSA infection include recent antibiotic therapy, intravenous drug use or close contact with an MRSA carrier. The emergence of MRSA infection in the community is particularly disturbing—many of these patients have no obvious risk factors and some develop life-threatening infections with bacteremia, endocarditis and pneumonia. What follows is an explanation of the importance of these pathogens as well as recommendations for therapy:

1. **What is community-associated MRSA?** The term methicillin-resistant *Staphylococcus aureus* (MRSA) refers to staphylococci resistant to the standard anti-staphylococcal agents such as oxacillin, nafcillin and cefazolin. Resistance is due to altered cell wall penicillin binding proteins (PBPs)—these enzymes (the main focus of B-lactam action) have reduced binding of penicillin and related agents. Previously a nosocomial problem (hospital-acquired MRSA or HA-MRSA), MRSA strains are now prevalent in the community (community associated MRSA or CA-MRSA) and are responsible for over 50% of community acquired staphylococcal infections (see table 1).
2. **Who is at risk for CA-MRSA?** In Los Angeles, the initial cases of CA-MRSA were seen in prisoners (there was an outbreak in the county jail), intravenous drug users and homosexual males (HIV patients were at particular risk). More recently, the outbreak has become widespread and is being seen in patients with no history of s"traditional" risk factors. Nevertheless, risk factors that should increase your suspicion for CA-MRSA are noted in Table 2.

Table 1: Antibiotic susceptibility—stapylococci*

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

* OVMC 422 community isolates—2003

Table 2: Risk factors for CA-MRSA

History of MRSA infection/colonization
intravenous drug use
MSM (men who have sex with men)
Incarceration
Crowded living conditions (e.g. homeless shelters)
Sports participants (skin contact, shared equipment)
Pts c recent antibiotic use or poor response to B-lactam
Recent hospitalization or exposure to pt c MRSA
Dialysis, diabetes, recent surgery, indwelling catheters

3. **An elusive "spider bite"—the clinical presentation of CA-MRSA.** The clinical presentation of CA-MRSA strains is sometimes very abrupt—patients complain of the sudden onset of a painful, erythematous skin lesion (boil) that suggests the possibility of a "spider" bite. Spider bites are actually quite uncommon in Southern California; the prime suspect in such cases—the brown recluse spider—is found in southeastern United States and is not native to Southern California. Most patients with CA-MRSA present with focal, localized skin/soft tissue infection (e.g. boils, carbuncles, impetigo, cellulitis); however, recent reports suggest the possibility of serious invasive infection including necrotizing soft tissue infection, bacteremia (endocarditis) and pneumonia.
4. **Why is CA-MRSA more virulent than "standard" staphylococcal strains?** Most CA-MRSA strains carry a gene (Pantone-Valentine gene) that codes for a leukocidin—a toxin that destroys leukocytes and thought responsible for the increased "necrosis" seen with CA-MRSA infection. Although standard methicillin-susceptible staphylococci (MSSA) may occasionally carry the "PV" gene, it appears more common in current circulating strains of CA-MRSA.
5. **What antibiotics are active against CA-MRSA?** Hospital-acquired MRSA strains are usually resistant to most antibiotics except vancomycin; however, CA-MRSA strains are often

susceptible to drugs such as trimethoprim/sulfamethoxazole (Bactrim), clindamycin, rifampin and tetracyclines (minocycline). Although the utility of such drugs in severe, life-threatening infection is not clear, they are often valuable for oral therapy of mild-moderate infection that does not require hospitalization. Intravenous vancomycin is the drug of choice for severe CA-MRSA infection; however, drugs such as linezolide, daptomycin and quinupristin/dalfupristin are alternative—but more expensive—agents.

6. In a patient with CA-MRSA, what other measures are important?

Incision and drainage of any suspected abscess is critical for management of these infections—this may be curative although patients should receive oral antimicrobial treatment active against MRSA. **Infection control measures** such as hand-washing and isolation procedures (for hospitalized patients) are critical to prevent spread to health care workers or close family members.

CA-MRSA and the deadly presence of the Pantone-Valentine gene

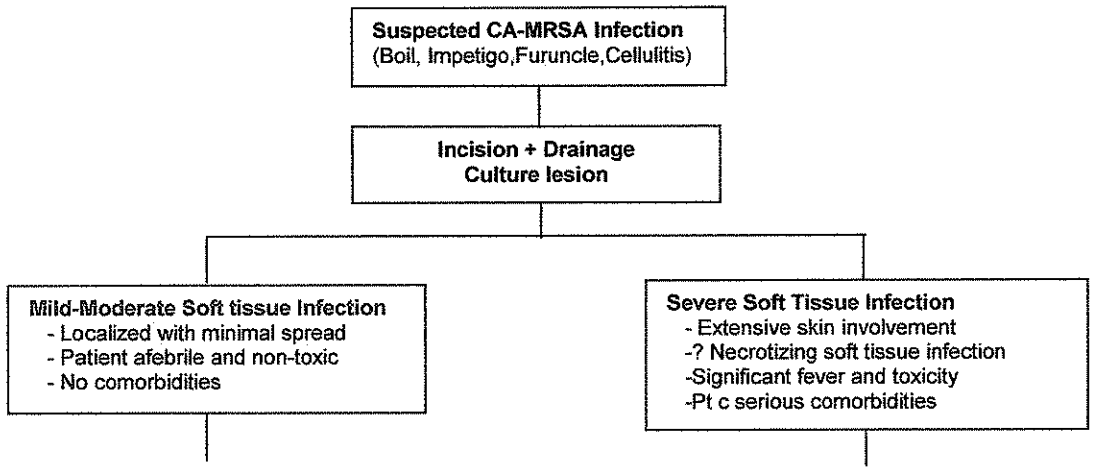
In the early days of antibiotic therapy, staphylococci quickly became resistant to pencillin due to the emergence of strains with a B-lactamase—an enzyme able to break the B-lactam bond and inactivate penicillin. The development of antistaphylococcal penicillins (methicillin, nafcillin,oxacillin) and cephalosporins circumvented this problem since these antibiotics are resistant to the standard staphylococci-associated B-lactamases (Note: Drugs containing a B-lactamase inhibitor such as piperacillin/tazobactam are also active against these 'standard" strains.) More recently, widespread overuse of antibiotics led the emergence of (MRSA) strains resistant to the newer B-lactam agents. These organisms have a *different* mechanism of resistance—a mutation in the cell wall enzymes (penicillin binding proteins—PBPs) reduces antibiotic binding and renders traditional antibiotics useless (B-lactamase inhibitors offer no benefit). These patients require treatment with vancomycin or other agents (see below). If the organisms are susceptible, less serious infections can be treated with oral antibiotics such as trimethoprim-sulfamethoxazole, clindamycin and minocycline; however, some isolates—especially hospital-acquired strains—now carry additional resistance determinants compromising the effectiveness of these agents. A particularly worrisome feature of CA-MRSA is the presence of the Pantone-Valentine gene in over 80% of isolates—this gene codes for a leukocidin (lyses WBCs) and appears responsible for the virulent nature of infection with select strains.

Recommendations for therapy in patients with suspected CA-MRSA infection:

- **Suspect the possibility of CA-MRSA infection:** Ask patients about risk factors for CA-MRSA, especially intravenous drug use, previous antibiotic use, sexual orientation and recent hospitalization. Even if these risk factors are "negative", consider the possibility of CA-MRSA in all patients with focal skin infection.
- **Drain the abscess:** Surgical drainage is as important now as it was in the pre-antibiotic era—many focal cutaneous infections (boils, carbuncles) will not heal unless the lance the abscess and allow it to drain. In hospitalized patients, remove any infected line or catheter as soon as possible.
- **Obtain a culture:** While empirical therapy has become commonplace, the possibility of increasing community antibiotic resistance emphasizes the importance of obtaining cultures in patients with skin infection. Swab the drainage, unroof the blister and needle the abscess; an initial culture with antibiotic susceptibilities may spare the patient days of ineffective therapy and avoid later, more serious complications.
- **Consider hospital admission** in patients with more extensive skin involvement or those with significant comorbidities (e.g. diabetes, renal failure, HIV, malignancy). Remember the CA-MRSA

organisms have been associated with necrotizing fasciitis and toxic shock syndrome—never underestimate the severity of these infections; mortality is significant in patients with bacteremia or other invasive infections.

- **Administer effective antibiotics:** Although resistant to penicillins and cephalosporins, CA-MRSA strains are often susceptible to TMP/SMX (Bactrim), rifampin, clindamycin and minocycline; see following treatment algorhythm. Patients requiring hospitalization should receive parenteral therapy such as IV vancomycin or clindamycin. Recent studies suggest that linezolide may be more effective in patients with MRSA pneumonia.
- **Wash your hands!** Don't have a cavalier attitude about "simple" skin infections—wash your hands after seeing a patient and wear gloves if handling a potentially infected lesion. Following hospital admission, patients with suspected MRSA infection (e.g + risk factors) should be isolated until culture results are available.



CA-MRSA Oral Antibiotic Rx

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

CA-MRSA: Parenteral Antibiotic Rx

Antibiotic	Dose*
Vancomycin	1 gm IV q 12 hr
Linezolide (Zyvox)	600 mg IV q 12 hr
Dalfupristin/quinupristin	7.5 mg/kg IV q 8-12 hr
Daptomycin	4 mg/kg IV Qday
Tigecycline	100 mg IV then 50 mg Q12
* Standard dose in 70 kg pt with normal renal function	

Keep in mind these treatment caveats...

- **"Combo" therapy:** Although not proven, some experts recommend combination therapy (e.g. TMP/SMX + rifampin; minocycline + rifampin) in patients with more serious infection. Never use rifampin as a single agent since resistance may develop on therapy. Be cautious of using rifampin in patients with possible drug interactions.
- **Clindamycin resistance:** 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 the possibility of inducible clindamycin resistance.
- **? Group A streptococci:** If infection with Group A streptococci is possible (e.g. pts with simple cellulitis), add clindamycin, rifampin or a B-lactam agent (e.g. penicillin G, cefazolin) since this organism is usually resistant to TMP/SMX

Antibiotic Dosing for Houseofficers—what you need to know!

What concentration of antibiotic is necessary to kill a specific pathogen? What about the correct dose and frequency required when treating a specific infection? Important as these topics are, they are often ignored or skipped over during the standard medical school course on infectious disease. In standard ID texts (those voluminous tomes consisting of hundreds of pages), the topic is usually covered in a weighty chapter in the front of the book (this is usually the one everyone skips!).

This section aims to give you a brief, to-the-point overview of antibiotic pharmacokinetics—the stuff that every doc ought to know when treating patients. 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.

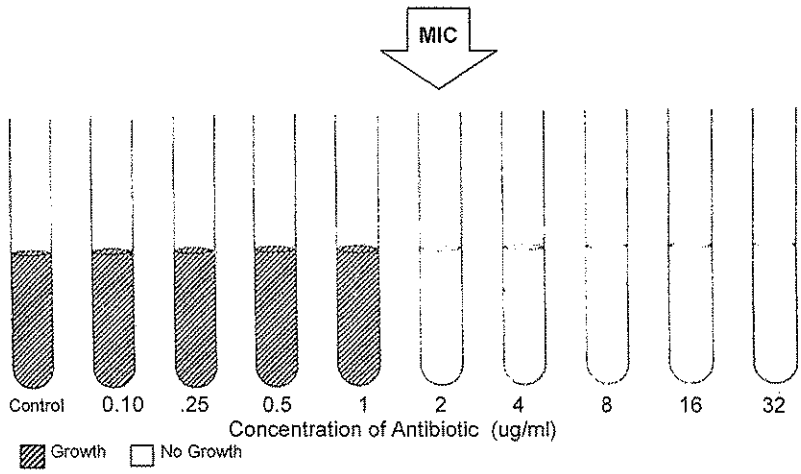


Figure 1: MIC testing
In the above example, there is a standard inoculation of bacteria in each tube along with a serial dilution of a selected antibiotic. The MIC of the organism (MIC=2 ug/ml in this case) is the *lowest* concentration of antibiotic that will inhibit growth of a specific pathogen.

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 it is rarely measured, the MBC is especially important for infections at certain hard-to-reach or "protected" sites such as the CSF (meningitis) and heart valve (endocarditis). In general, these infections are rarely cured unless the antibiotic selected penetrates the site and surpasses the MBC of the infecting organism.

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.

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).
- √ **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.

2. 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 (*Streptococcus pneumoniae*) with a susceptibility interpretation based on the **MIC** and **"breakpoint"** for the organism.

KNOW THE JARGON

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. The breakpoint *is not* usually shown on the report; however, but is nevertheless critical for resistance determination.

Case: 51-year old female with SLE presented with pneumonia and was treated with ceftriaxone + azithromycin. She responded to therapy but sputum and blood cultures showed the following...

CULTURE: *Streptococcus pneumoniae*

ANTIBIOTIC	MIC	INTERPRETATION	BREAKPOINT
PENICILLIN	2	RESISTANT	≤.05
CEFTRIAXONE (NON-MENINGITIS)	1	SENSITIVE	≤1
CEFTRIAXONE (MENINGITIS)	1	INTERMEDIATE	≤0.5
ERYTHROMYCIN	>1	RESISTANT	≤0.5
LEVOFLOXACIN	≤0.5	SUSCEPTIBLE	≤2
VANCOMYCIN	≤1	SUSCEPTIBLE	≤2

Antibiotic tested

Minimal Inhibitory Concentration

Susceptibility Interpretation

Breakpoint: Note: I've included this to help explain the MIC interpretation—it may not be included on all reports.

In this case...

- **Penicillin resistance:** With an MIC= 2 ug/ml, this isolate is considered resistant to penicillin since it is above the established "breakpoint" (≤ 0.5 ug/ml).
- **Ceftriaxone** is an appropriate choice for treatment of pneumonia but a less reliable selection for treatment of meningitis—the MIC of the organism (MIC [ceftriaxone] = 1 ug/ml) is of "intermediate" susceptibility for the higher doses required in meningitis.

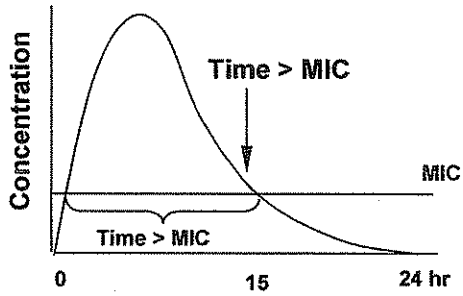
- **Other agents:** Both levofloxacin and vancomycin would be appropriate agents for treatment of pneumonia with this organism.

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 two major categories—"time-dependent" bacterial killing and "concentration-dependent" bacterial killing. It turns out that this information has major (and practical!) implications for antibiotic dosing.

Time-dependent killing

(Time > MIC makes the difference)

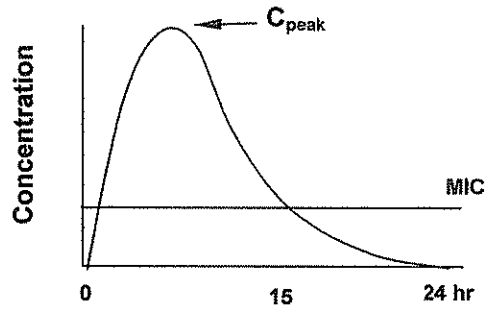


Time above MIC (Time > MIC)

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. The new thinking about concentration dependent killing led to a change in recommended dosing of aminoglycosides with a shift to "once daily" administration versus older regimens that required q 8 hour dosing.

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

	Time-dependent killing	Concentration-dependent killing
Antibiotics	B-lactam agents Carbapenems Cephalosporins Penicillins	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 (synergy) 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**.

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 and macrolides (e.g. erythromycin) tend to 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 agents kill the pathogen outright and don't necessarily rely on the immune system to complete the job.

KNOW THE JARGON

Bactericidal: Antibiotics that *kill* a specific bacterium at achievable concentrations.

Bacteriostatic: Antibiotics that *suppress* growth (but don't necessarily kill) the suspected pathogen.

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 a much higher cure rate.

  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—successful therapy requires agents with intracellular penetration such as tetracyclines, rifampin and trimethoprim-sulfamethoxazole. Because of a significant relapse rate, successful treatment usually requires at least 6-8 weeks of therapy.
- **Legionnaire's disease:** Although *Legionella pneumophila* is susceptible, in vitro, to B-lactam agents, the organism is an intracellular pathogen requiring "intracellular" antibiotics (e.g. macrolides, quinolones, doxycycline/rifampin) able to penetrate macrophages.
- **Rickettsiall infection:** *Rickettsial* organisms are energy parasites that multiply in protected intracellular compartments. Treatment requires agents such as tetracyclines with good intracellular penetration.

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 (Table 2). 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...

√ **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), 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:** This agent has relatively poor CSF penetration; however, may be one of the few agents available for treatment of penicillin-resistant pneumococcal meningitis. In this situation, clinicians usually recommend higher dosing (1.5-2 gm IV Q 12 hr) and addition of intrathecal vancomycin.

Antibiotic pharmacodynamics—*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.
- Intracellular infections such as Legionnaire's disease, salmonellosis, brucellosis, 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 both bactericidal, and able to penetrate the blood-brain barrier.

ID Clinical Syndromes

Common ID problems on the consult service

Cellulitis—tips on diagnosis and therapy

While often billed as a "simple" cellulitis, proper diagnosis and management of this condition can be quite challenging, especially in patients with "severe" cellulitis where a necrotizing soft tissue infection (e.g. the "flesh eating bacteria") could be a possibility. As you evaluate a patient with presumed cellulitis, ask yourself the following questions…

1. What is the likely bug?

The majority of cellulitis cases are due to Group A streptococci or staphylococci. Remember that these organisms are not the only culprits—question the patient carefully about risk factors that might suggest other pathogens:

Clinical history	Comments
AIDS/HIV+	*Staphylococcus aureus* is the most common cause of cellulitis among AIDS patients; the increasing incidence of MRSA reflects higher rates of this pathogen in intravenous drug users [1]. *Helicobacter cinaedi*—formerly *Campylobacter cinaedi*—can cause bacteremia and "multifocal cellulitis" in HIV+ homosexual males[2].
Animal and human bites	Animal bite wounds are typically infected with multiple organisms reflecting the oral flora of the biting animal. *Pasteurella multocida*—a penicillin-sensitive gram negative rod—is especially common following cat (and dog) bites/licks. *Capnocytophaga canimorsus* (formerly DF-2) may cause sepsis following dog bites in post-splenectomy and immunocompromised patients. *Eikenella corrodens*—a microaerophilic gram-negative bacillus—is typically seen following human bite wounds.
Facial cellulitis	In addition to group A streptococcus (erysipelas), several other respiratory pathogens can cause facial cellulitis including *Hemophilus influenzae* (infants, COPD patients [3]), meningococcus (infants) and *Streptococcus pneumoniae* (alcoholics, diabetics) [4].
Fish/seafood handling	Cutaneous exposure to fish or sea animals can lead to *Erysipelothrix rhusiopathiae* ("fish" or "seal" finger) or *Plesiomonas shigelloides* [5] infection. In patients with underlying liver disease or alcohol abuse, ingestion of raw oysters/seafood may result in *Vibrio vulnificus* infection—a syndrome characterized by bacteremia, myositis, a hemorrhagic bullous cellulitis and—in many cases—septic shock and death. Treat suspected *V. vulnificus* infection with an intravenous 3rd generation cephalosporin, doxycycline or quinolone.
Gas gangrene	If soft tissue gas is present in a severely toxic patient , consider the possibility of gas gangrene due to *Clostridia perfringens* or mixed aerobe/anaerobic infection. These patients require broad-spectrum antibiotics (including penicillin G) and aggressive surgical debridement or amputation.
Healthcare worker	HSV infection of the finger causes "herpetic whitlow", a relapsing ulcerative cellulitis often seen in health-care workers (ICU nurses, respiratory therapists, dentists) with cutaneous exposure to infected oral secretions.
Nail puncture to foot:	*Pseudomonas aeruginosa* is an important pathogen in nail puncture wounds of the foot; refer the patient for surgical exploration/debridement to prevent subsequent osteomyelitis and include a quinolone in the initial antibiotic regimen [6].
Post-surgical cellulitis	Patients with lymphedema following surgical procedures run the risk of recurrent cellulitis in the leg (site of vein graft harvest for CABG) or arm (post-axillary node dissection for carcinoma of the breast) [7] due to group A streptococcus.
Water exposure	Exposure to freshwater may lead to *Aeromonas hydrophila* cellulitis [8] ; contact with saltwater is associated with atypical *Vibrio* infection [9].

2. What is an appropriate diagnostic workup?

- ✓ **Look for an entry point:** In lower extremity cellulitis look between the toes for evidence of fungal infection—failure to treat tinea pedis leads to recurrent bouts of cellulitis.
- ✓ **Culture/gram-stain:** Unroof blisters and obtain a culture/gram-stain on any purulent discharge.
- ✓ **Blood culture:** While the yield may be low, obtain blood cultures on hospitalized patients—especially if they are septic or you suspect an unusual organism.
- ✓ **Tissue biopsy/needle aspiration:** Biopsy or aspiration of the leading edge of the cellulitis has a low yield but may be helpful in selected cases. Immunocompromised patients can have cellulitis with exotic organisms that might not be detected on routine cultures.

3. Does the patient need a surgeon?

In all patients with severe cellulitis, consider the possibility of a necrotizing soft-tissue infection (**necrotizing fasciitis, gas gangrene**)or **pyomyositis** (abscess within the muscle)—both conditions where early surgery is often necessary. When evaluating a patient with severe cellulitis, be mindful of the possibility of a necrotizing soft tissue infections (NSTI) in any patient with following signs:

- **Severe pain** out of proportion to findings on physical examination is a classic early finding of necrotizing fasciitis. If a patient still complains of significant pain despite potent pain therapy (e.g. opiates), consider the possibility of an underlying NSTI.
- **Signs of sepsis** including hypotension, confusion and high fever are common in patients with necrotizing fasciitis. Beware of the anxious, toxic-appearing patient that that states that they are "going to die"—this almost always is a sign of severe underlying disease and must not be ignored.
- **Leukocytosis (> 15K)** and other laboratory findings including sings of muscle necrosis (e.g. elevated CK) or evidence of metabolic acidosis (e.g. low bicarbonate levels; elevated serum lactate).
- **Soft tissue gas:** While a radiograph showing soft-tissue gas is diagnostic, remember that some organisms (group A streptococcus) typically *don't* produce gas!

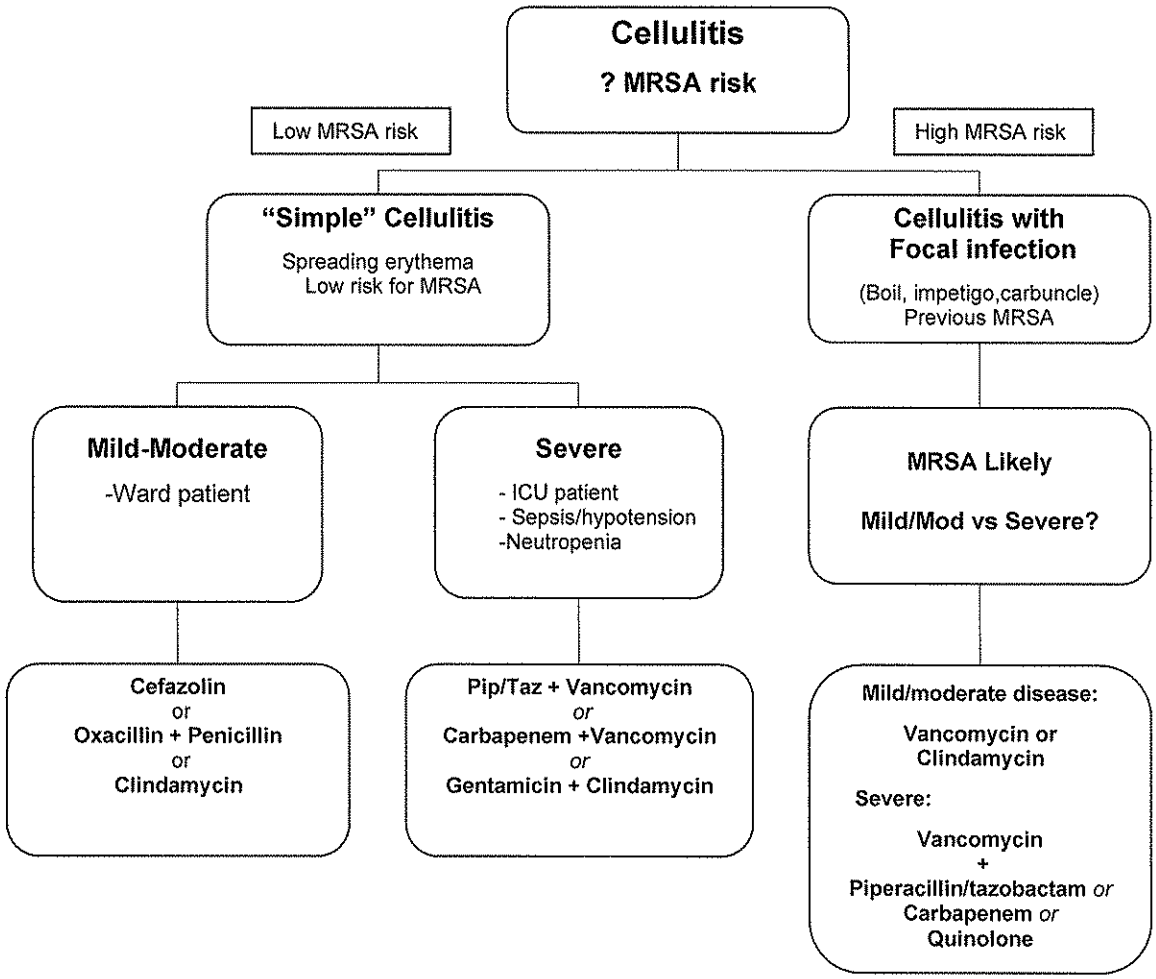
With any of these findings, get a surgeon involved earlier and consider ordering additional studies such as a CT or MRI of the infected area. order an CT (or MRI) and consider the need for immediate, early surgical intervention.

4. Could it be a cellulitis mimic?

Not all patients with a diagnosis of "cellulitis" have infection. When evaluating a suspected case, keep the following conditions (cellulitis "mimics") in mind:

- ➢ **Calciphylaxis:** Vascular gangrene in dialysis patients secondary to vascular calcification [10].
- ➢ **Charcot's foot:** Erythematous, swollen foot secondary to diabetic peripheral neuropathy with osteolysis.
- ➢ **Contact dermatitis:** Follows irritant or allergic reaction to topical antibiotics (neomycin), creams (topical herbal products) and clothing (shoe dermatitis) [11,12].
- ➢ **Deep venous thrombosis/thrombophlebitis:**
- ➢ **Gout/pseudogout:** Can completely mimic cellulitis with fever, pain and erythema [13]
- ➢ **Pretibial myxedema:** Erythematous plaques in patients with underlying thyroid disease

- **Pyoderma gangrenosum:** Painful, undermined ulcers on extremities; respond to steroids
- **Sweet's syndrome:** Erythematous, cutaneous plaques seen in leukemic patients



4. What is the recommended antibiotic therapy?

Simple cellultis (Mild to moderate): For the typical case of cellulitis, make sure that staphylococcus and group A streptococcus are covered—any one of a number of regimens can be used:

- **Cefazolin** (1 gm IV 8 hr) with stepdown to cephalexin (500 mg PO q 6hr) *or*
- **Oxacillin** (1-2 gm IV q 4-6 hr) ± **Penicillin G** (1-2 M.U. IV q 4-6 hr) *or*
- **Clindamycin** (600-900 mg IV q 8hr): Add this to regimen in pt with severe grp A strep infection

Simple cellulitis (Severe): These patients have severe cellulitis, possibly with necrotizing fasciitis. Patients with evidence of sepsis (e.g. hypotension; WBC > 20K; lactic acidosis; ICU admission) should have broad antibiotic coverage (including gram negative infection) pending culture results.

- **Piperacillin/tazobactam** (4.5 gm IV Q 8 hr) + **Vancomycin** (1 gm IV Q 12 hr)
- **Carbapenem** (Doripenem 500 mg IV Q 8 hr) **+ Vancomycin** (1 gm IV Q 12 hr)
- **Gentamicin** (3 mg/kg IV Q 24 hr) + **Clindamycin** (900 mg IV Q 8 hr)

Diabetic foot infection: Staphylococcus aureus and streptococci (grp A; grp B) are the most common organisms found in diabetic foot infection. These patients may also have "mixed" infection that includes gram negative bacilli and anaerobes (the "fetid" foot syndrome). As a consequence, initial broad empiric coverage (against all these classes of organism) is recommended.

- **Ceftriaxone** (2 gm IV Q 24 hr) + **metronidazole** (500 mg PO q 8hr) *or*
- **Cefotetan** (1-2 gm IV q 12 hr) *or*
- **Ampicillin/sulbactam:** (3.0 gm IV q 6hr) *or*
- **Piperacillin/tazobactam** (3.375 gm IV q 6 hr) *or*
- **Gentamicin or quinolone + clindamycin:** Use in septic patients or if *Pseudomonas* suspected.

Note: In patients with severe diabetic foot infection (e.g. sepsis; ICU; severe gangrene), add vancomycin and *Pseudomonas* coverage (piperacillin/tazobactam; carbapenem; quinolone) until culture results are available.

How to evaluate a patient with suspected cellulitis...

- **Look for an entry point:** Most patients with cellulitis have some "entry point". In a patient with lower extremity cellulitis, look between the toes for evidence of tinea or skin breakdown. Question the patient carefully about any skin trauma that might have led to the episode.
- **Ask about unusual exposures:** While most cellulitis is due to streptococci or staphylococci, ask the patient about any unusual exposures (e.g pets, water exposures, immunocompromised state) that might suggest specific pathogens.
- **Obtain cultures:** Whenever possible, try to culture any purulent drainage that might be present. Blood cultures generally have a low yield but should be obtained in any febrile patient admitted to the hospital, especially individuals who are immunocompromised or are particularly toxic.
- **Consider a necrotizing soft tissue infection**. Several features should immediately suggest the possibility of a necrotizing soft tissue infection. Be especially cautious in patients with severe pain (out or proportion to findings on physical examination), signs of sepsis (hypotension; high fever; toxicity) or specific laboratory findings (high leukocytosis; elevated CK; elevated lactic acid or metabolic acidosis).
- **Review the radiographs** looking for signs of soft tissue gas or underlying osteomyelitis. An MRI or CT scan may be helpful in patients with possible necrotizing soft tissue infection; however, remember that these scans may be normal in such cases and that a "negative" scan should not delay proper surgical evaluation.
- **Call for a surgical consult** in patients with suspect gangrene or necrotizing fasciitis. In a patient with severe cellulitis, involve the surgeon early. Initial findings may be uncertain and there is a definite benefit to following the time course of a condition—worsening symptoms and physical exam findings (despite appropriate threrapy) might be a clue to underlying gangrene requiring surgical intervention.
- **Start empiric antibiotics** based on the algorhythm outlined above. Assess the severity of the cellulitis—severely ill patients require potent, broad spectrum therapy until cultures are available. Be especially cautious in immunocompromised patients (e.g. HIV/AIDS; neutropenia)—they have a greater risk of necrotizing fasciitis and have a higher risk of gram negative infection.

Cellulitis—could it be necrotizing fasciitis?

The clinician confronted with a severe cellulitis must always ask the question—could this be a necrotizing soft tissue infection or necrotizing fasciitis (NF)? The answer is critical since the patient's survival may depend on prompt and aggressive surgical debidement or amputation. When considering the possibility of necrotizing fasciitis, keep in mind the following principles:

What are the clues to the possibility of necrotizing fasciitis?

On first examination, this patient might appear to have just a simple streptococcal cellulitis—patients with uncomplicated streptococcal cellulitis often have impressive soft tissue swelling accompanied by signs of moderate "toxicity" including high fever and tachycardia. Nevertheless, serious necrotizing soft tissue infections such as gas gangrene or necrotizing fasciitis may initially masquerade as a simple cellulitis—in a patient with severe cellulitis, consider the possibility of NF and look for the following clues:

- **Risk factors:** Although anyone can develop NF, special risk factors for the condition include diabetes mellitus, substance abuse (alcohol and parenteral drug use), cardiopulmonary disease, puerperium and an underlying immuncompromised state (e.g. cancer, neutropenia, HIV infection).
- **Quality of the pain:** The severity of the pain—often out of proportion to findings on physical examination—is a clue to the possibility of NF; the pain is unrelenting and often poorly responsive to opiates or NSAIDS.
- **Physical exam findings:** While there may be minimal findings on the initial examination, any signs suggesting soft tissue gas (crepitation) or cutaneous necrosis (hemorrhagic or dusky bullae) increases the possibility of necrotizing fasciitis. Despite the severe pain, localized cutaneous anesthesia is common with further spread of the infection.
- **Patient "toxicity":** Patients with NF and related conditions rapidly develop severe toxicity (e.g. hypotension, confusion, respiratory distress, severe tachycardia) suggesting underlying sepsis. Patients with type II NF (group A streptococci) will develop signs and symptoms compatible with toxic shock syndrome (TSS). A sense of extreme anxiety or fear ("I feel like I am going to die") is not uncommon in patients with life-threatening gas gangrene or NF.
- **Clinical progression:** The progression of NF can be variable—although most patients become severely ill|quite rapidly, some cases develop over several days and have a more subacute presentation.
- **Laboratory findings:** Patients with progressive NF frequently develop elevated CPK, increasing leukocyte counts (often over 10K) and laboratory findings consistent with metabolic acidiosis (↑ lactic acid levels; ↓ serum bicarbonate). In more advanced disease, hypocalcemia may be present, possibly related to underlying fat necrosis.
- **Radiographic abnormalities:** Presence of gas in the soft tissue on routine plain films or CT scan suggests the possibility of a Type 1 necrotizing fasciitis (mixed aerobic/anaerobic infection) or gas gangrene. Absence of gas does not rule out a NSTI—patients with group A streptococcal necrotizing fasciitis typically *do not* have soft tissue gas.

While no single factor "proves" that the patient has a necrotizing soft tissue infection, the presence of severity, unremitting pain, soft tissue gas on radiographs and the appearance of "patient toxicity" all point to the diagnosis. In suspect cases, involve a surgeon as early as possible since definitive diagnosis requires surgical intervention and direct observation of involved tissues.

A "Gallery of Gangrene"—classification of necrotizing soft tissue infection

The classification of necrotizing soft tissue infections remains confusing and the specific diagnosis may not always be clear in any one case. Features that help "classify" the infection include the underlying microbiology, the clinical pace of the infection (acute vs. subacute) and the level of anatomic involvement (e.g. cellulitis vs fasciitis vs myositis).

While some of these syndromes have a subacute onset and delayed progression, most are marked by a relatively rapid onset of severe disease with associated sepsis and high mortality; a high index of suspicion and early identification are keys to effective management. With this in mind, here is a list of some of the more common syndromes likely to be seen by the clinician:

- **Necrotizing fasciitis:** These soft tissue infections are marked by prominent, necrotizing involvement of the fascial plane, often with sparing or late involvement of the overlying muscle. This syndrome is further subdivided by the underlying microbiology…

  Type 1 NF: These patients have infection with mixed organisms, including at least one anaerobic species (e.g. *Bacteroides* sp.; Peptostreptococcus) in combination with a facultative anaerobe such as streptococcus or Enterobacteriaceae (e.g. *E coli, Enterobacter, Klebsiella, Proteus* species). NF type 1 is especially common in diabetics and may complicate foot cellulitis or perirectal/gastrointestinal infection (Fournier's gangren). Because of the presence of facultative anaerobes, soft tissue gas is a prominent feature of type 1 NF.

  Type 2 NF: This form of the infection is associated with group A streptococcal infection; although clinically similar to type 1 NF, the presence of signs associated with streptococcal toxic shock syndrome (generalized erythematous "sunburn-like" rash) is a clue to this particular pathogen. In contradistinction to type 1 NF, soft tissue gas *is not* seen in type 2 NF.

  MRSA-associated NF: Recent reports suggest that community-acquired MRSA infection (CA-MRSA) may present with a clinical syndrome similar to type 2 NF. For this reason, most specialists add empirical antibiotic coverage for this organism (e.g. vancomycin, clindamycin) until culture results are available, especially in those with MRSA risk factors (e.g. parenteral drug use, recent hospitalization or antibiotics, immunocompromised patients).

- **Clostridial myositis (Gas gangrene):** This is the classic "gas gangrene" seen in diabetics with soft tissue gas, intense muscle pain, and "dishwater" pus coming from affected wounds. This may occur following relatively minor trauma and is usually due to *Clostridium perfringen*; however, other clostridial species may be seen, including *Clostridium septicum* in patients with underlying gastrointestinal malignancy. Gram stain of the purulent drainage demonstrates gram-positive rods (clostridia) but few leukocytes—the organism secretes a toxin responsible for cell lysis.
- **Other syndromes:** Patients who ingest contaminated shellfish—or are exposed to brackish salt water—may develop myositis due to *Vibrio vulnificus,* a necrotizing soft tissue infection more common in patients with underlying cirrhosis of the liver.

"Deadly bugs"—antibiotic therapy for necrotizing soft tissue infection

As described above, the microbiology of these infections can be quite varied—until culture results are available, administer empiric broad-spectrum antibiotic therapy according to the following table:

Table 2: Empiric antibiotic therapy—Necrotizing Soft-tissue infection

Initial empiric therapy*	Special organisms and circumstances:
BL/BLI: Piperacillin/tazobactam or Ampicillin/sulbactam *Or* Carbapenem (Doripenem, Imipenen, or Meropenem) *Or* Aminoglycoside or Quinolone + Clindamycin	**Group A streptococcus:** Penicillin + clindamycin ***Clostridia* species:** Add penicillin (hi dose) or clindamycin **CA-MRSA:** Add vancomycin, daptomycin or linezolide ***Vibrio vulnificus:*** Add quinolone or doxycycline ***Pseudomonas aeruginosa*:** Add gentamicin or quinolone

*Many experts would add coverage for MRSA (e.g. vancomycin or clindamycin) till cultures are available
BL/BLI: B-lactamase/B-lactamase inhibitor; CA-MRSA: Community-associated methicillin resistant *Staphylococcus aureus*

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

- ✓ **? Clindamycin:** Consider adding clindamycin in patients with possible group A streptococcus NF—the antibiotic's effect on ribosomal function may serve to "turn off" toxin production by the organism.
- ✓ **? MRSA:** Nowadays, MRSA infection accounts for over 50% of community acquired staphylococcal infection. In patients with severe (life-threatening) skin/soft tissue infection, add MRSA coverage (e.g. vancomycin, clindamycin and daptomycin) until culture results are available
- ✓ **Neutropenic patients:** In neutropenic patients, add an agent with activity against *Pseudomonas* (e.g. aminoglycoside, quinolone or carbapenem) until culture results are available—although less common in "normal" hosts, *Pseudomonas aeruginosa* remains a significant pathogen in neutropenic patients and can rarely be associated with soft tissue necrosis (ecthyma gangrenosum).

Surgery, antibodies and oxygen—adjunctive therapies for NF

It's not just about antibiotics, the high mortality associated with NF emphasizes the importance of surgery and other adjunctive measures. In addition to antimicrobial therapy, keep the following treatments in mind:

- **Surgical intervention:** The strong possibility of a necrotizing soft tissue infection such as gas gangrene or necrotizing fasciitis is sufficient reason for taking the patient to the operating room for further evaluation—in questionable cases, definitive diagnosis can only be made by direct observation of the involved tissues at surgery. Surgical considerations include the following:
  - √ **Fascial space involvement:** In necrotizing fasciitis, there is often involvement of the fascial space with relative sparing of the overlying muscle—in this situation, full amputation of a limb may not be necessary if a fasciotomy can be done and the muscle remains viable.
  - √ **Gas gangrene:** Because of muscle involvement, full amputation is usually necessary in patients with clostridia-associated gas gangrene of the limb.
  - √ **A "second look":** Determining the extent of the infection is sometimes difficult at the initial surgery—patients often require repeat "second look" operations to see if any further spread has occurred.

Patients with necrotizing soft tissue infections have a high mortality—not surprisingly, additional "novel" therapies are sometimes tried in addition to the standard therapies (antibiotics + surgery) utilized in the condition. In severely ill patients with NSTI, consider the following additional treatments…

- **Intravenous immunoglobulin:** Many experts recommend administration of high dose intravenous immunoglobulin in NSTI patients—the antibodies may bind circulating toxin and reduce immune activation.
- **Hyperbaric oxygen:** Although not available at many institutions, anecdotal case reports suggest the hyperbaric oxygen treatment may be helpful in selected cases, especially in patients with necrotizing fasciitis of the perineum or abdominal wall.

While not proven in randomized controlled trials, consider these therapies in critically ill patients who are likely to have a high mortality.

What to do if necrotizing soft tissue infection is a possibility...

Although uncommon, necrotizing soft tissue infection (e.g. Necrotizing fasciitis; gas gangrene) is a life threatening infection with a high mortality in patients where therapy is delayed. When evaluating a patient with severe cellulitis, always consider the possibility of NF and keep the following in mind:

- **Suspect the diagnosis:** Remember that the diagnosis of NF or gas gangrene is frequently delayed. Although any individual could potentially acquire this infection, keep in mind the diagnosis in "at risk" patients (e.g. diabetics, HIV, alcoholics, immunocompromised patients). Be especially wary in the patient with the following findings:
  - ✓ **Severe pain,** out of proportion to other findings on physical examination
  - ✓ **Toxicity:** Patients with cellulitis and signs of severe toxicity (e.g. High fever, hypotension, signs of septic shock) could have NF.
  - ✓ **Physical exam findings:** Though these tend to be late findings, evidence of gangrene or evidence of soft tissue gas (crepitation) should immediately suggest NF or gas gangrene.
- **Order crucial laboratory tests:** No "one" laboratory test can confirm—or exclude—NF; however, the following laboratory tests may be highly suggestive of the diagnosis...
  - ✓ **WBC:** Although not always present at the initial evaluation, most patients with progressive NF eventually develop rising or increased leukocyte counts (> 20K).
  - ✓ **Muscle enzymes:** While sometimes absent, the presence of an elevated CK strongly suggests the possibility of an underlying myositis and is frequently seen in patients with gas gangrene or necrotizing fasciitis.
  - ✓ **Metabolic acidosis:** Order a serum lactate and check the patient's electrolytes for signs of metabolic acidosis—in a patient with severe cellulitis, lactic acidosis is a specific clue to the possibility of necrotizing fasciitis.
- **Review the radiographs:** Presence of soft tissue gas on a plain film is highly suggestive of gas gangrene or a mixed (aerobic/anaerobic) Type 1 necrotizing soft tissue infection. Remember, however, that group A streptococcal necrotizing fasciitis *typically lacks* evidence of soft tissue gas. While not 100% sensitive, a CT or MRI scan may provide additional clues (involvement of fascial compartment; presence of myositis) suggesting an NSTI.
- **Obtain cultures and start antibiotics** as soon as possible. In addition to broad-spectrum antibiotic therapy, consider adding clindamycin to help "turn off" toxin production in those with suspected group A streptococcal infection.
- **Request a surgical consultation** in any patient with severe cellulitis—surgical intervention is frequently necessary in necrotizing fasciitis and significant delays may increase mortality. Even if you are not sure about the presence of NF, early surgical evaluation allows key personnel to follow the patient should early surgical intervention prove necessary.
- **Consider adjunctive therapies:** Despite difficulties in proving efficacy, high dose immunoglobulin therapy (1 gm IV Q day x 3 days) is often given in patients with suspected group A streptococcal NSTI. Although controversial, hyperbaric oxygen therapy may be considered if immediately available.
- **Don't delay!** Necrotizing fasciitis is a life-threatening infection that requires immediate attention—significant delays often lead to patient mortality or extensive amputation.

Community-acquired pneumonia

Respiratory infections represent some of the most common illnesses seen in the doctor's office. They range from simple upper respiratory tract infections to the life-threatening pneumonias requiring hospitalization in the intensive care unit. When treating a case of community-acquired pneumonia (CAP), ask yourself the following questions in order to optimize diagnosis and therapy of this condition:

1. What is the likely organism?

Bacterial diagnosis is difficult since many pathogens have a similar clinical presentation and diagnostic testing remains imperfect—in most studies, over 50% of cases remain "undetermined" despite careful laboratory evaluation. A recent CAP study (see Table 1) utilized percutaneous (needle) lung aspirates (with PCR testing) to help increase the yield and reduce uncertainty. While not practical for the average case, this study emphasized several important findings:

- ✓ **Pneumococcus is #1!** Streptococcus pneumonia remains the most common organism isolated in community acquired pneumonia—it was seen in up to 30% of cases and accounted for a significant number of isolates that would have been called "negative" with standard techniques.
- ✓ **"Atypical" pathogens:** Organisms such as *Mycoplasma* and *Chlamydia pneuomophila* are important pathogens in CAP and account for over 30% of cases—antibiotics active against these pathogens (e.g. tetracycline; quinolones; macrolides) should be part of standard therapy.
- ✓ **Influenza virus** is probably the most common viral pathogen; however, this is likely to be influenced by season (winter-spring), age and vaccination status.
- ✓ **Unusual organisms** in this study were related to HIV status (MTB, PCP, cryptococcus) or local zoonotic pathogens (e.g. Q fever; psittacosis). The frequency of such pathogens will reflect local epidemiological factors (geographic regions; animal exposure) and patient demographics.

Table 1: Etiology CAP (109 cases)

Organism	#	% Cases
Streptococcus pneumoniae	27	30
Mycoplasma pneumoniae	20	22
Chlamydia pneumophila	12	13
Pneumocystis carinii	7	8
Haemophilus influenzae	6	7
Influenza A virus	5	6
Undetermined	19	17

The following pathogens (#)accounted for less than 5% of cases each: *Mycobacterium tuberculosis* (4), *Chlamydia psittaci* (4), *Coxiella burnetii* (2), *Escherichia coli* (1), *Streptococcus viridans* (1), *Enterococcus faecium* (1), *Cryptococcus neoformans* (1). Source: Ruiz-Gonzalez et al

Table 2: Pneumonia severity—CURB-65

Parameter	Definition
Confusion	Evidence of patient confusion (disorientation to person, place or time)
Uremia	BUN ≥ 20 mg/dL
Resp rate	RR ≥ 30 breaths per minute
BP	SBP < 90 mm Hg or DBP < 60 mm Hg
65	Age > 65

Score one point for each of the above parameters that are positive

2. CURB your enthusiasm—how sick is the patient?

The decision about hospitalization is not always easy; however, selected features (multilobar involvement; fever c hypotension; immuncompromised patients; older individuals) have greater risk for poor outcomes and should be admitted. Clinical scoring systems such as the British Thoracic Society CURB-65 prediction rule (see Table 2) are simple ways to help predict patients who might do poorly with outpatient management. In general, patients with a CURB-65 score ≥ 3 should be managed in an inpatient hospital setting.

Any such systems have drawbacks and may not always predict outcome. Obviously, severely ill patients (e.g. hypotension, hypoxemia, severe toxicity) require hospital admission. Strongly consider hospital admission in those with multilobar involvement and underlying immuncompromised states (e.g. diabetes; neoplasm). Patients with other "complicating" conditions (e.g. CHF; renal failure, ESLD) are also at greater risk for poor outcomes and, if possible, should be admitted for initial therapy.

3. Clinical clues of community acquired pneumonia

Although clinical diagnosis is difficult, certain clinical findings do suggest specific pathogens. During your initial evaluation, look for the following clinical clues…

Clinical feature	Pathogen
Acute onset	Bacterial pathogens—especially *S. pneumoniae*
Animal exposure	
Dogs and cats	Pasteurella sp.
Parturient cats; farm animals	Q fever (Coxiella burnettii)
Birds	Psittacosis
Corticosteroid use (CMI defects)	Nocardia, PCP, MTB, cryptococcus, aspergillosis, CMV
CXR cavity	Anaerobic abscess, MTB (upper lobe cavity); fungal disease, Nocardia
Daycare/recent antibiotic use	Risk factors for penicillin-resistant *S. pneumoniae*
Diarrhea/abdominal pain	*Legionella pneumophila*
Eosinophilia	Coccidioidomycosis, drug allergy, parasites (visceral larva migrans)
ETOH abuse	*S. pneumoniae, Klebsiella pneumoniae*, anaerobic aspiration
Foul smelling sputum	Anaerobic aspiration
Hiking/camping	Pneumonic plague, tularemia
Hilar adenopathy	MTB and fungal disease
HIV+	*S. pneumoniae, H. influenzae* in addition to PCP, MTB, cryptococcus
IVDU	*Staph. aureus* (MRSA), aspiration pneumonia
Immigrant-developing county	MTB, histoplasmosis (Central America, southern Mexico)
Localized wheeze	Bronchial obstruction due to tumor or foreign body
Miliary nodules on CXR	MTB, disseminated fungal infection
Seizure, LOC, swallowing disorder	Aspiration pneumonia (mixed aerobes and anaerobes)
Recent hospitalization, nursing home	Nosocomial pathogens: GNR (*Pseudomonas aeruginosa*), *Staph. aureus* (MRSA)
Underlying influenza	Influenza pneumonia; *Staph aureus, S. pneumoniae*

Abbreviations: CXR: chest radiograph; ETOH: Ethanol abuse; IVDU: Intravenous drug use; LOC: Loss of conciousness; MRSA: Methicillin resistant *Staph aureus*

4. CAP laboratory studies—which ones are necessary?

While the appropriate laboratory studies may vary between patients (depending upon clinical history and exposure clues…see above), most hospitalized patients merit a standard "package" of simple blood tests (CBC; chem panel) and cultures. As you evaluate your case, consider ordering the following…

- ✓ **CBC/chem panel:** The routine blood count may provide clues to underlying pathogens (e.g. eosinophilia: coccidioidomycosis; monocytosis: tuberculosis). In addition to the "routine" chem panel, obtain liver tests (atypical pneumonias such as *Legionella* and Q fever are more likely to have an associated hepatitis).
- ✓ **Cultures:** While there is some disagreement among experts, obtain sputum culture (Gram stain) and blood cultures on all hospitalized pneumonia patients.

- ✓ **? Tuberculosis:** In the county patient population, tuberculosis is always a possibility—on "at risk" patients (Homeless; HIV; upper lobe infiltrates; hilar adenopathy, foreign immigrant), obtain a PPD and sputum AFBs.
- ✓ **Serological studies:** Additional serological studies are generally reserved for "sicker" (ICU) patients or those failing to respond to standard therapy. In these cases, consider ordering studies for *Legionella pneumonia* (Urine antigen; Blood serology) and coccidioidomycosis (blood EIA). HIV tests should be obtained on a "routine" basis—especially in HIV "at risk" patients or those with atypical presentations.
- ✓ **Radiographic studies:** In many cases, a simple chest radiograph is adequate…consider additional studies (ultrasound; chest CT) in patients with "complicated" pneumonia including those with suspected effusions (empyema) or lung cavitation.
- ✓ **Additional diagnostic studies:** Patients with significant pleural fluid (>300 cc) and possible empyema should undergo diagnostic thoracentesis. Early bronchoscopy may be appropriate in selected patients—especially immunocompromised patients or those who fail to improve with initial therapy.

5. Pneumonia "mimics"—conditions that mimic CAP

Not uncommonly, patients admitted with suspected bacterial "pneumonia" respond poorly to antibiotic therapy. As part of your initial evaluation, keep in mind the possibility of CAP "mimics"—non-infectious (or infectious) conditions that resemble bacterial pneumonia but require alternative therapy. The following table lists some of these conditions, including "atypical" infections, neoplastic, rheumatologic and inflammatory syn**dromes…**

Condition	Comments
Collagen vascular	Rheumatologic conditions such as Wegener's granulomatosus, SLE, Churg Strauss Good pasture's syndrome should be considered. Underlying arthritis and/or renal involvement (? Hematuria) may be a clue.
Congestive heart failure	Acute CHF may mimic pneumonitis. In patients with a history of cardiac disease—or in those who appear volume "overloaded"—consider a trial of furosemide; pulmonary infiltrates due to CHF will clear rapidly with adequate diuresis.
COP or BOOP	"Organizing" pneumonias such as COP (Chronic organizing pneumonia) or BOOP (Bronchiolitis obliterans c organizing pneumonia) represent inflammatory lung responses, sometimes to underlying infection or drug exposure. CT may show pulmonary nodules or mass-like infiltrates—definitive diagnosis and treatment requires biopsy and corticosteroids.
Drug reactions	Specific drugs may be associated with "pneumonitis" including nitrofurantoin, amiodarone, bleomycin and cyclophosphamide
Eosinophilic pneumonia	Chronic eosinophilic pneumonia presents with "reverse" pulmonary edema pattern (peripheral infiltrates with central sparing) and associated eosinophilia. Eosinophilia on blood count may also be clue to coccidioidomycosis and parasitic diseases.
Fungal disease	Take a careful travel history looking for clues that might suggest histoplasmosis (Midwest; Central America), blastomycosis (Midwest) or coccidioidomycosis (always a potential in this area but specifically ask about travel to the Central Valley or high desert regions (Mojave; Lancaster)
HIV-related pneumonitis	Always screen for HIV risk factors and have a low threshold for HIV testing. In addition to standard pneumococcal pneumonia (the most common pneumonia in HIV), PCP, MTB and Cryptococcus are special concerns in these patients.
Neoplasms	Bronchogenic carcinoma may cause localized obstruction with lobar collapse (and post obstructive pneumonia). Bronchoalveolar carcinoma typically presents with areas of pulmonary consolidation that mimic bacterial pneumonia.

Pulmonary emboli	About a third of patients with pulmonary emboli will present with fever.
Radiation pneumonitis	One to three months following radiation to pulmonary portals. May produce a "square" pneumonia. Treat with corticosteroids.
Tuberculosis	Keep this in mind especially in immigrants from endemic regions, those with a previous + PPD and cases with characteristic radiographic findings (e.g. apical infiltrates; lung cavitation; hilar adenopathy).

6. What is the recommended antibiotic therapy for CAP?

With the difficulties inherent in etiologic diagnosis, initial therapy is broad-spectrum with activity against both *S. pneumoniae* and "atypical" pathogens:

Table 2: Therapy—Community-Acquired Pneumonia

Condition	Antibiotic therapy
Mild/outpatient	Amoxicillin (500 TID) or doxycycline (100 mg PO BID) or azithromycin (500 mg PO Qday)
Mild-moderate/inpatient	Ceftriaxone (1 gm q 24) + PO doxycycline or macrolide or Levofloxacin (500 PO/IV QD)
Moderate-severe/inpatient	Ceftriaxone (2 gm q 24) + azithromycin (500 IV Qday) or Levofloxacin (750 mg IV Qday) (Note: In severely ill patients, add vancomycin until results of cultures are available)
Anaerobic/aspiration	Cefotetan (1 gm IV q 12) or Levofloxacin (500 mg QD) + Clindamycin (900 mg IV q 8hr) Or Piperacillin/tazobactam (3.375 gm IV q 6hr)

When choosing antibiotic therapy, keep in mind the following recommendations…

- ✓ **Oral vs parenteral:** Oral therapy may well be appropriate for patients with "mild" illness; however, in hospitalized patients (especially those with severe disease), start with parenteral treatment until it is clear that the patient has responded. Never rely on oral therapy in those with significant nausea and vomiting.
- ✓ **Respiratory quinolones:** These agents (levofloxacin; moxifloxacin) have excellent oral bioavailability and may be administered via an oral route with those with lesser severity of illness (provided they do not have significant nausea/vomiting).
- ✓ **MRSA risk:** In patients with severe illness (e.g. ICU cases), cover for MRSA with vancomycin until culture results are available.

How to manage community acquired pneumonia....

- ❑ **Estimate severity:** As described above, make a decision about the need for hospital admission. While "scoring" systems (e.g. CURB-65) may be helpful, strongly consider hospital admission in immunocompromised patients (including diabetics), those with multilobar involvement, and anyone with significant toxicity as evidenced by hypotension, rapid respiratory rate, acidosis and marked leukocytosis (> 15K).
- ❑ **Laboratory studies:** Review the initial laboratory studies looking for findings suggestive of poor outcome (e.g. acidosis; marked leukocytosis; hypoxia; renal insufficiency). Order *Legionella* studies (Urine antigen) and urine pneumococcal antigen in more severely ill patients who might require ICU care. During influenza season, obtain rapid antigen testing from a nasopharyngeal swab.
- ❑ **Obtain cultures:** Order blood cultures *before* antibiotic administration. If possible, try to obtain a deep cough sputum specimen for culture and Gram stain.
- ❑ **Review radiographs:** Look for markers of severity (e.g. multilobar involvement) as well as findings (e.g. cavitation; hilar adenopathy; apical infiltrates) that might suggest specific pathogens. If the patient has evidence of pleural effusion, obtain a chest ultrasound (or CT scan) to estimate volume and need for diagnostic thoracentesis.
- ❑ **Consider the possibility of a CAP "mimic":** As outlined above, all "pneumonitis" is not necessarily due to standard bacterial pneumonia. Consider the possibility of pulmonary emboli, underlying vasculitis or neoplasm.
- ❑ **Start empiric antibiotics** based on recommendations in the above table. Use initial parenteral therapy for more severely ill individuals, although a switch to oral therapy can be quite rapid when using respiratory quinolones such as levofloxacin or moxifloxacin. In severely ill patients (ICU), add vancomycin to cover MRSA until results of cultures are available.
- ❑ **Watch for complications:** Following hospitalization, be on the alert for clinical deterioration that might suggest "complicated" pneumonia (effusion with empyema) or "metastatic" bacterial infection (e.g. meningitis, septic arthritis, endocarditis). Monitor patients carefully and consider an upgrade to more intensive care (ICU; stepdown unit) in patients who appear to be worsening.

Does your patient have Legionnaires' Disease?

1. Is your patient at risk for Legionnaires' Disease ?

The following groups are at special risk for Legionnaires' disease:

- **Immunocompromised patients**—especially those receiving high-dose corticosteroids
- **Older patients** with history of cigarette smoking, chronic lung disease or recent surgery
- **Exposure to point-source outbreak** or building with known *Legionella pneumophila.*

2. Know the "score"—the clinical likelihood of Legionnaires' Disease

Suspect Legionnaires' disease in a patient with any of the following signs/symptoms:

- **Relative bradycardia**: Hi temp…Lo pulse (NL: 102°F=110 bpm; 103°F=120 bpm; 104°F=130 bpm)
- **Extrapulmonary signs** or symptoms (confusion, lethargy, diarrhea, renal failure)
- **Fails to respond to B-lactam agent** (penicillins; cephalosporins) or aminoglycoside

The following point "scoring" system helps the clinician to predict the likelihood of Legionnaire's disease in a specific patient:

Findings*	Qualifying Conditions	Point Score	% Patients affected†
Clinical			
Headache	Acute onset	+1	44
Confusion/encephalopathy	**Acute onset**	**+2**	**30**
Lethargic	**Acute onset**	**+3**	
Ear pain	Acute onset	-3	
Productive cough or sore throat	Acute onset	-3	
Hoarseness	Acute onset	-3	
Sputum	Purulent	-3	45
Hemoptysis	Mild-moderate	-1	13
Chest pain	Pleuritic	-2	33
Loose stools/diarrhea	**Not 2nd to erythromycin or diarrhea causing drugs**	**+3**	**29**
Abdominal pain	Without diarrhea	+1	10
Abdominal pain	With diarrhea	+5	10
Relative bradycardia	**Adults, T≥ 102° F; no B-blockers, pacemaker, arrhythmia**	**+5**	**36**
Lack of response to B-lactam	**After 72 hours**	**+5**	
Acute renal failure	**Excluding toxins**	**+5**	
Laboratory			
↓ Na		+1	38
↓ PO_4	**Excluding other causes of hypoPO_4 otherwise unexplained**	**+4**	**46**
↑ **AST/ALT**		**+4**	**50**
↑ Total bilirubin		+2	
↑ Cold agglutinin titre ≥1:64		-3	
↑ Creatinine		+1	26
Microscopic hematuria	Otherwise unexplained	+2	28

* Winthrop-University Hospital Point Evaluation System for Legionnaire's Disease from Cunha B, Sem Resp Inf 1998 13:116-27. † Data from table in Akbas E, Yu EL, Legionnaires' disease and pneumonia. Postgrad Med 2001;109:135-47.

Diagnostic Point Score		
Legionella Highly probable	Legionella Probable	Legionella Unlikely
≥ 10	5-10	≤ 5

3. What laboratory tests will confirm suspected Legionnaires' disease ?

In suspected cases of Legionnaires' disease, use the following laboratory tests for confirmation:

Specialized laboratory tests for Legionnaires' Disease				
Test	Sensitivity (%)	Specificity (%)	Advantages	Disadvantages
Sputum culture	80	100	Definitive diagnosis	3-5 days required
DFA sputum stain	33-70	96-99	Rapid	+ only in severe pneumonia
Urinary antigen assay	70	100	Rapid	Only serogroup 1
Serum antibody tests	40-60	90-95	Widely available	Acute and convalescent serums necessary
Table from Akbas E, Yu VL, Legionnaires' disease and pneumonia. Postgrad Med 2001;109:135-47				

4. What is the appropriate antibiotic therapy for Legionnaires' disease ?

In a case of suspected Legionnaires' disease, include one of the following regimens in the patient's therapy:

Antibiotic	Dose	Route	Frequency
Macrolides			
Azithromycin	500 mg*	PO, IV	Q 24hr
Erythromycin	500-1,000 mg	IV	Q 6 hr
Quinolones			
Levofloxacin	500 mg	PO, IV	Q 24hr
Ciprofloxacin	400 mg	IV	Q 8hr.
Moxifloxacin	400 mg	PO, IV	Q 24hr
Other regimens			
Doxycycline + Rifampin	100 mg* 600 mg	PO,IV PO	Q 12hr Q 24hr
* Some experts recommend doubling the initial dose Table adapted from Akbas E, Yu VL. Legionnaires' disease and pneumonia. Postgrad Med 2001;109:135-147.			

Remember...

- *Legionella pneumophila* is commonly found in water supplies but rarely causes disease.
- Although non-specific, certain clinical features, especially relative bradycardia, confusion, diarrhea should suggest the possibility of Legionnaires' disease in a patient with pneumonia.
- Obtain an induced sputum culture, sputum DFA and urine antigen on all patients with nosocomial pneumonia or suspected Legionnaires' disease.
- Start empirical antibiotic therapy (azithromycin or levofloxacin) in patients with nosocomial pneumonia at OVMC.

Managing pyelonephritis in the hospitalized patient

Patients with "simple" pyelonephritis are often treated in the emergency department and sent home. When called to see sicker, hospitalized patients, consider the possibility of more complicated infection and ask yourself the following questions:

1. Is the patient clinically improving?

For a "simple" urinary tract infection or pyelonephritis the fever should decrease within 72 hours of starting therapy—patients with persistent fever (> 72 hrs) are likely to have either antimicrobial resistance, inadequate drug absorption, a pyelonephritis "mimic" or a UTI complication requiring surgical intervention (see below).

2. Does the patient have any risk factors for urinary tract infection?

Always look for an underlying source for the infection—question patients about the following UTI risk factors…

- **Diabetes:** A clear risk factor for UTI with several associated syndromes (see below)
- **Congenital urinary tract abnormalities:** More common as cause of UTI in childhood
- **Recent sexual intercourse:** Risk factor for cystitis and recurrent UTIs in women
- **Urinary tract instrumentation:** Has the patient had recent catheterization, ureteral stent placement or urinary tract surgery.
- **History of renal calculi:** May become secondarily infected—especially staghorn calculi.
- **Underlying neurological disease:** A neurogenic bladder predisposes patient to recurrent UTIs.
- **Previous history of UTI:** Recurrent UTIs may suggest underlying structural abnormality (stricture, stone)

3. Is the patient a diabetic?

UTIs are a common cause of diabetic ketoacidosis (DKA)—keep in mind the possibility of underlying emphysematous pyelonephritis in all diabetic patients—especially those with DKA or patients who fail to improve. The presence of diabetes suggests the possibility of a number of complications more common in this population…

Emphysematous pyelonephritis (EP): Almost exclusively seen in diabetics, patients with EP have gas in kidney on plain radiograph or CT secondary to glucose fermentation by urinary tract pathogens. Prompt diagnosis is important—patients with advanced infection (gas extending beyond kidney to perinephric space) usually require aggressive surgical intervention and nephrectomy for cure.

Renal papillary necrosis (RPN): Vascular compromise leads to sloughing of the renal papilla with subsequent obstruction and infection. Patients complain of "passing tissue" in the urine.

Fungal urinary tract infection: *Candida* UTIs are not uncommon problem in diabetics—especially those with a history of foley catheterization and previous antibiotic therapy. Recalcitrant *Candida* pyelonephritis may require nephrectomy. On rare occasions, diabetics develop **renal mucormycosis** or **aspergillosis**.

4. Is this a complicated UTI?

In addition to the above diabetes-associated complications, consider the possibility of the following complications of urinary tract infection—especially in the patient with persistent fever or delayed clinical response…

- **Perinephric abscess:** More common in diabetics, perinephric abscess follows bacteremia (*S.aureus*) or ascending infection (*E. coli* and other GNRs). Diagnose with CT or UTZ imaging—

patients require percutaneous catheter or open surgical drainage followed by prolonged antibiotic therapy (4-6 weeks).

- **Renal carbuncle/abscess:** Renal abscess follows bacteremia (*S. aureus*) or ascending infection (*E. coli*) in patients with complicated UTI. Although some can be cured with antibiotic-alone, larger abscesses generally require percutaneous drainage in addition to prolonged antibiotic therapy.
- **Renal calculus/obstruction:** An underlying renal calculus may lead to obstruction and recurrent infections. "Staghorn" calculi are a complication of *Proteus* sp. UTIs—bacterial urease alkalinizes the urine and fosters growth of radiolucent stones that are not visible on plain radiographs because of their low calcium content.
- **Ureteral diverticuli/stricture:** Both congenital and acquired strictures and diverticuli serve as a nidus for urinary tract infection. Complete ureteral obstruction from any cause may lead to **pyohydronephrosis**—a collection of pus in the renal pelvis. **Bladder diverticuli** and/or stones may be responsible for recurrent urinary tract infection.
- **Prostatitis/prostatic abscess:** Seen in older males, chronic prostatitis—and the occasional case of prostatic abscess—may be surprisingly occult; on prostate examination, look for prostate enlargement, tenderness and asymmetry of the prostate lobes. A "three glass urine" is helpful for diagnosis of chronic prostatis; however, avoid vigorous prostate massage in septic patients or those with acute prostatitis.
- **Urethral stricture/diverticulum:** Ureteral strictures due to previous sexually transmitted disease (*Neisseria gonorrhea*), trauma or catheterization may be a nidus of persistent infection. In males, carefully examine the course of the penile urethra looking for outpouchings (diverticuli) or firm strictures. Confirm the diagnosis with voiding cystourethrogram or urethroscopy.
- **Colo-vesicular fistula:** Seen in patients with underlying inflammatory bowel or diverticular disease, colovesicular fistulas present with recurrent UTI (due to mixed GNRs) and symptoms of air (pneumaturia) or fecal matter (fecaluria) in the urine.

5. What other conditions "mimic" pyelonephritis?

Keep in mind that other conditions mimic "routine" gram-negative pyelonephritis…

- ✓ **Renal calculi:** Even without superimposed infection, renal calculi can mimic urinary tract infection.
- ✓ **Genitourinary tuberculosis:** Don't overlook the possibility of renal TB in those with chronic, recurrent UTI—especially in immigrants from regions with high rates of tuberculosis. Common radiographic findings include strictures at the ureteropelvic and vesico-ureteral junction leading to ureteral obstruction, hydronephrosis and subsequent kidney destruction (pyonephrosis) on the affected side. Epididymo-orchitis (with sterile pyuria) is a common presentation from brucellosis in the male—question the patient about animal exposure and raw milk/cheese ingestion.
- ✓ **Fungal urinary tract infection:** In addition to *Candidia* urinary tract infection (see above), urinary tract involvement is common in blastomycosis (pyelonephritis; prostatitis) and is rarely seen in histoplasmosis and coccidioidomycosis. Immuncompromised patients run the risk of invasive aspergillosis or mucormycosis.
- ✓ **Xanthogranulomatous pyelonephritis (XPG):** A variant of chronic pyelonephritis, this condition is seen in middle age woment with recurrent UTI (usually GNRs such as E. coli or Proteus) due chronic obstruction (often 2nd to staghorn calculi or kidney stones). On CT scan patients have a tumor-like mass in one kidney with an atypical granulomatous reactions (containing lipid-laden macrophages) on pathological examination. Patients almost always require surgical excision/nephrectomy for cure. A closely related condition is renal malakoplakia—

another atypical pathological reaction to chronic urinary tract infection. Usually due to *E. coli*, tissue examination shows calcific inclusions called Michaelis-Guttman bodies.

- ✓ **Loin pain/hematuria syndrome:** This pyelonephritis mimic produces recurrent attacks of fever and unilateral flank pain accompanied by sterile hematuria.
- ✓ **Renal malignancy:** Renal tumors such as hypernephroma, lymphoma and Wilm's tumor may present with fever, flank pain and hematuria.
- ✓ **Acute glomerulonephritis:** Remember that AGN often presents with fever and hematuria—keep in mind the possibility of an underlying connective tissue disease (SLE, Wegener's granulomatosus, Goodpasture's syndrome) or infectious disorder (bacterial endocarditis, post-streptococcal glomerulonephritis). Make sure the urine is examined for red-cell casts—this finding is characteristic of AGN and is not seen in pyelonephritis.

In a patient with persistent fever and presumed urinary tract infection...

- ❑ **Check the culture results:** Review urine and blood culture results to make sure the diagnosis is correct. "Negative" baseline cultures may suggest failure to collect timely specimens (Check the nursing notes to make sure the cultures were obtained *prior* to antibiotics) or a pyelonephritis "mimic". In patients with positive cultures, obtain a followup culture after treatment is started— persistent positive cultures suggest antimicrobial resistance, inadequate drug absorption or the presence of a UTI complication requiring surgical intervention. Keep in mind the possibility of bacterial endocarditis in patients with an enterococcal or *Staphylococcus aureus* UTI.
- ❑ **Review the antibiotic therapy:** Make sure the bacteria are sensitive to the current antibiotic. Although quinolones are well absorbed via an oral route, use parenteral therapy in patients with persistent vomiting or hemodynamic instability.
- ❑ **Obtain radiographic imaging:** Consider the possibility of a complicated urinary tract infection and obtain radiographic imaging to rule out urinary tract obstruction (occult renal stone, pyohydronephrosis) or a renal/perirenal abscess. A renal ultrasound can is a rapid way to screen for obstruction and perirenal abscess. While a plain radiograph will show renal gas characteristic of emphysematous pyelonephritis, an abdominal CT scan is more sensitive examination and provides better visualization of an underlying abscess or stone.
- ❑ **Request a urology consultation:** In patients with complicated urinary tract infection—especially those with urinary tract obstruction or underlying abscess— surgical intervention is often necessary; obtain appropriate imaging and request a urology evaluation as soon as possible.
- ❑ **Consider a pyelonephritis "mimic":** Fever, flank pain and hematuria don't automatically mean that the patient has bacterial pyelopnephritis—keep in mind pyelonephritis "mimics" such nephrolithiasis, malignancy and glomerulonephritis. Consider the possibility of renal tuberculosis in immigrants from developing countries; request a PPD and obtain urine cultures for AFB in all those with "sterile" pyuria or hematuria on initial cultures.

Spontaneous Bacterial Peritonitis

Infection remains a common cause of mortality in patients with end-stage liver disease. Spontaneous bacterial peritonitis (SBP) remains one of the most common infections in these individuals. The following piece should help in evaluation and management of these patients:

1. Clinical clues suggesting SBP in patients with ascites[1]:

The presentation of SBP may be quite subtle in those with cirrhosis or ESLD—look for the following clinical clues…

- **Fever**, abdominal pain or tenderness
- **Encephalopathy:** Confusion with hyperreflexia on physical examination.
- **Unexplained leukocytosis** on blood count.
- **Bleeding:** Patients with recent esophageal variceal bleed or endoscopic procedures.
- **Unexplained clinical deterioration** in patient with cirrhosis

Signs/Symptoms	% Cases
Fever	69
Abdominal pain	59
Hepatic encephalopathy	54
Abdominal tenderness	49
Diarrhea	32
Shock	21
Hypothermia	17
No signs/symptoms	10

Source: CID 1998;27:669-76

Even a subtle change in mental status may be a clue to underlying ascitic fluid (AF) infection; perform a diagnostic paracentesis on all cirrhotic patients admitted to the hospital—especially in those with fever, abdominal pain or unexplained clinical deterioration. Remember the following…

- ✓ Ascitic fluid infection is most frequent infectious complication among cirrhosis patients
- ✓ 10% of patients with SBP *have no signs or symptoms!*
- ✓ Patients with nosocomial infection have higher incidence of gram-positive (MSSA, MRSA,VRE) and resistant GNR (ESBL) infection

2. Clinical syndromes of Ascitic Fluid (AF) infection:

In patients with suspected SBP, keep in mind the other "syndromes" of ascitic fluid infection:

Syndrome	Criteria	Comments
Spontaneous Bacterial Peritonitis	PMN count ≥ 250/mm^3 AF or blood cultures positive	Seen in 30% of cirrhotic patients per year Mortality ~ 30% per episode
Culture-negative neutrocytic ascites (CNNA)	PMN count ≥ 250/mm^3 AF cultures negative No surgically treatable intraabd infection	SBP with negative cultures Repeat paracentesis 48 hrs after starting treatment to document clinical response
Monomicrobial nonneutrocytic bacterascites (MNB)	PMN count < 250/mm^3 + AF culture ± symptoms	Symptomatic patients similar to SBP patients Repeat paracentesis in asymptomatic pts
Secondary bacterial peritonitis	PMN count ≥ 250/mm^3 AF cultures positive Surgically treatable infection	Often have polymicrobial AF Require surgical intervention
Polymicrobial bacterascites	PMN count < 250/mm^3 Gram stain or culture: multiple organisms	Usually due to inadvertent puncture of intestine during paracentesis (1/1000 cases)

In patient with suspect SBP, obtain the following tests:

- **Cell count** (SBP… PMN count ≥ 250/mm^3)
- **Ascitic fluid culture** (10 cc in each blood culture bottle) and blood culture
- **Total protein and albumin** (Increased incidence of SBP when TP ≤ 1.5 gm/dL)

- **Additional tests :** LDH, glucose, AFB smear and culture, amylase

3. Microbiology and antimicrobial therapy of SBP:

Organism	% Cases
E.coli	39
Other GNR	22
Streptococci	12
Enterococci	12
Staphylococci	9
Other organisms	6
Source: CID 1998;26:1066-70	

- ***E. coli*** remains the most common organism in SBP
- **Susceptibility:** t72% to 96% of ascitic fluid SBP isolates remain sensitive to cefotaxime
- **Resistance:** Increasing incidence of resistant bacteria (MRSA, VRE) in patients with *nosocomial* SBP—especially in those with prolonged hospitalization or previous antibiotic therapy.
- **Polymicrobial infection:** Consider intestinal perforation in patients with positive cultures for anaerobes or polymicrobial infection

Third-generation cephalosporins (cefotaxime; ceftriaxone) remain the mainstay for patients with community-acquired SBP—consider broader spectrum coverage (cefepime + vancomycin) in patients with nosocomial SBP.

Syndrome	Treatment*
Community-acquired SBP	Ceftriaxone 2 gm IV q 24 hr
Nosocomial SBP	
Hospital > 1 week Prolonged prophylactic therapy Known colonization with MRSA, VRE or resistant GNB	Cefepime (1-2 gm q 12 hr) + Vancomycin (1 gm q 12 hr)
*Add metronidazole to regimen in patients with suspected surgical infection or intraabdominal abscess	

- ✓ **Short course therapy:** A recent study suggests 5 day cefotaxime treatment as effective as 10 days of therapy
- ✓ **Oral treatment:** Other option is to switch to oral quinolone following response to parenteral therapy
- ✓ **Hepatorenal syndrome alert:** In patients with elevated creatinine, IV albumin may decrease incidence of hepatorenal syndrome

4. SBP "mimics"...When patients fail to respond to antimicrobial therapy:

In patients who fail to respond to antibiotic therapy or have persistent elevated PMN counts in AF, consider the following syndromes:

Syndrome	Features
Intestinal perforation/intraabdominal abscess	Check AF amylase; abdominal CT scan
Intestinal infarction	Elevated AF and serum amylase
Tuberculous peritonitis	PPD positive in 75% of cases Often develop lymphocytic predominance in AF AFB smear: < 10% +; AFB C/S: 33% + Dx. requires peritonoscopy with directed biopsy
Fungal peritonitis	Check serum Coxy serology; AF cryptococcal ag
Pancreatitis or pancreatic pseudocyst	Check serum and AF amylase
Peritoneal carcinomatosis	Cytology + in 50-70% of cases Colon, pancreas and ovarian CA most common

5. Prevention of SBP—Preventive measures and indications for antibacterial prophylaxis

- ✓ **Remove catheters:** In cirrhotic patients, minimize use of Foley and intravenous catheters
- ✓ **Antimicrobial prophylaxis:** Antibacterial prophylaxis reduces recurrence of SBP but does not change 1 year mortality. Consider the following patients for antibacterial prophylaxis…
  - Patients with previous or current episode of SBP
  - Individuals with advanced (Child-Pugh class 3) cirrhosis
  - Cases with low total protein (< 1 gm/dL) in ascitic fluid
  - Patients with variceal bleed or emergency endoscopy (levofloxacin 500 mg PO x 5 days)

What to do in a patient with possible spontaneous bacterial peritionitis…

- ❑ **Suspect the diagnosis:** Always consider the diagnosis in a patient with liver disease and ascites, especially if they are febrile or suffer from unexplained clinical deterioriation. Remember that the presentation may be subtle—patients may lack fever or abdominal pain.
- ❑ **Obtain a paracentesis:** This is the key test in ruling out the diagnosis—a cell count greater than 250 cells/mm3—especially if there is a high percentage of polymorphonuclear leukocytes should raise your suspicion. If possible, inoculate ascitic fluid into blood culture bottles—this will increase the yield on culture.
- ❑ **Order blood cultures:** Although the yield is likely to be low, in febrile, hospitalized patients always order or two sets of blood cultures.
- ❑ **Keep in mind the possibility of SBP "mimics":** Remember that SBP mimicked by other conditions such as TB/fungal disease, intestinal perforation and peritoneal carcinomatosis.
- ❑ **Start empiric antibiotic therapy**—these patients are fragile and delays in therapy could well increase mortality. In most cases, a third generation cephalosporin (e.g. ceftriaxone) should be appropriate.

  Note: In critically ill patients or those with possible "resistant" organisms (e.g. recent antibiotic therapy; recent hospitalization) consider "broader" coverage (e.g. carbapenem *or* piperacillin/tazobactam) until culture results are available. MRSA peritionitis is uncommon but has been described in hospitalized patients with recurrent SBP—in such cases, add vancomycin pending culture results.

The "Bedside" Diagnosis of Infective Endocarditis

Despite the availability of echocardiography, a careful physical examination still plays an important role in the diagnosis of infective endocarditis[1,2,3] When you suspect IE, make an effort to look for the following signs on examination—they may provide the additional "clues" necessary to confirm the diagnosis…

Skin: Although not always seen, these findings should immediately raise the possibility of IE:

- **Splinter hemmorhages:** While touted as the classic hallmark of IE—most "splinters" are secondary to other causes (trauma, mitral stenosis, hemodialysis) and are not diagnostic of endocarditis. The most specific lesions suggest ongoing infection and appear while the patient is in-hospital; unfortunately, they are only seen in a small number of cases (<10%). Look especially for splinter hemmorhages that are broad (>1mm), red (due to recent hemorrhage) and located in the proximal nail bed.
- **Petechiae**: The most common skin manifestation of IE, (70% of cases), look for "crops" of petechiae appearing on the chest, palate or conjunctiva.
- **Osler's nodes** : The classic clue to IE, these painful, erythematous nodules appear on the fingertips in less than 10% of patients.
- **Janeway lesions**: Another classic sign of IE, Janeway lesions are flat, hemmorhagic lesions appearing on the palms and soles.

Oral cavity: Always perform a careful oral examination in patients with suspected IE—a dental abscess or severe gingivitis may represent the source of the bacteremia. Don't hesitate to obtain a dental evaluation on your patient—dental radiographs may reveal an unsuspected (painless) abscess.

Eyes: Rarely seen nowadays, Roth spots are retinal hemorrhages with a central white spot (leukocytes)—remember that Roth spots are non-specific and can also be seen in patients with leukemia or severe anemia.

Heart: All patients with suspected IE deserve a careful cardiac exam in a quiet room. Look especially for some of the following cardiac findings…

- ✓ **New or changing murmur**: 90% of patients with IE have a murmur—approximately 30% have a new or changing murmur (provided that someone has listened to the patient previously!)
- ✓ **Diastolic murmur:** A new diastolic murmur is an especially important clue to the possibility of IE. The short, soft murmur of aortic regurgitation is often missed by examiners. To increase the likelihood of hearing an "AR" murmur, sit the patient up, have them lean forward and listen for a short, high-pitched murmur (immediately after the second heart sound) along the left (and right) sternal.
- ✓ **Tricuspid regurgitation**: Best heard at the left lower sternal border (LLSB) with patient lying down (increases venous return). Only 30% of patients with tricuspid endocarditis will have murmur on first exam—listen carefully on daily basis since the finding may appear during hospitalization. The murmur tends to *increase* with inspiration or leg elevation.
- ✓ **Continuous murmur**: Suspect rupture of aneurysm of Sinus of Valsalva (aortic valve) with fistula to left atrium, right atrium and right ventricle.
- ✓ **Prosthetic valves**: Look for a regurgitant murmur or change in valve clicks (diminished intensity)

Abdomen: Look for splenomegaly—an important clue to the presence of IE. Examine the patient when they are in a right lateral decubitus position—this significantly increases the chances of feeling the spleen.

Bone/joint: Check the joints (especially the knee joint) for signs of septic arthritis (swelling; warmth) and palpate the length of the spine for evidence of tenderness that might suggest vertebral osteomyelitis or diskiitis.

CNS: Question the patient about symptoms of transient ischemic attacks and perform a careful neurological examination to rule out stroke.

What to do if you suspect infective endocarditis...

- ❑ **Start with the hands:** In suspected IE, look at the hands for Janeway lesions, Osler nodes and splinter hemorrhages (fingernails). Remember that benign "splinters" are frequently associated with hand trauma—the important ones are those that appear while the patient is under observation. Remember to examine the patient on a daily basis.
- ❑ **Examine the eyes and oral cavity:** Look at the conjunctiva and oral cavity (palate) for petechiae. Try to perform a fundiscopic exam looking for the rare (but highly diagnostic) "Roth spot".
- ❑ **Listen to the heart:** Pay special attention to the presence of any new murmurs or rubs. Diastolic murmurs are especially significant—have the patient lean forward and listen carefully for the short, high-pitched murmur of aortic regurgitation.
- ❑ **Look for splenomegaly:** Roll the patient into a right lateral decubitus position and examine the patient for splenomegaly.
- ❑ **Don't forget the remainder of the skin examination:** In addition to the hand findings noted above, examine the skin for new crops of petechiae, the most common dermatologic finding in infective endocarditis.

Remember to repeat your examination on a daily basis—the sudden appearance a new sign or symptom may be an important clue to the possibility of infective endocarditis. Although the new technology offers many benefits, daily cardiac ascultation by a knowledgeable examiner is still cheaper than repeated echocardiography!

The "Duke criteria"—does this patient have endocarditis?

Physicians have long recognized that there is no "pathognomonic" test for endocarditis—the diagnosis of the condition depends on a constellation of clinical and laboratory findings. The presence of the "classic" findings such as a new heart murmur, splenomegaly and skin findings (Osler's nodes; Janeway lesions) are certainly helpful, but not all patients have these manifestations.

Several clinical "scoring" systems have been developed to standardize research and assist the clinician in making the diagnosis. The most recent iteration—the Duke Criteria—employs some of the latest technology—including echocardiography—and provides a helpful framework for making the diagnosis in a suspected case…

First, evaluate your patient for the presence of *Major* and *minor criteria*…

Major criteria:

1. Blood culture
   a. 2 separate blood cultures positive for…
      i. Viridans streptococci, *Streptococcus bovis*, HACEK (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*) organisms
      ii. Community-acquired *Staphylococcus aureus* or enterococcus in the absence of a primary focus
   b. Positive cultures > 12 hours apart
   c. Positive blood cultures: 3 of 3, majority of ≥4 with 1st and last ≥ 1 hr apart
2. Endocardial involvement
   a. Echocardiography: Oscillating intracardiac mass on a valve or supporting structure, in the path of a regurgitant jet stream, or on implanted material in the absence of an alternative explanation, valve ring abscess, or new dehiscence of a prosthetic valve.
   b. New regurgitant murmur

Minor criteria

1. Predisposing heart condition or IVDU
2. Fever (≥38° C)
3. Systemic or pulmonary emboli, mycotic aneurysm, intracranial hemmorhage, conjunctival hemmorhages, Janeway lesions
4. Immunologic phenomenon: glomerulonephritis, Roth's spot, Olser's node, rheumatoid factor
5. Echocardiography consistent with but not definitive of endocarditis
6. Microbiologic/serologic findings consistent with but not definitive of endocarditis

Next, determine the likelihood of endocarditis using the following criteria….

1. Definitive diagnosis

a. Pathology/microbiology of vegetations or embolized vegetations obtained at surgery or autopsy.
b. 2 *Major criteria*
c. 1 *Major* / 3 *minor*
d. 5 *minor criteria*

2. Possible diagnosis: Findings consistent with infective endocarditis that fall short of a definitive diagnosis of endocarditis, but not rejected.

3. No endocarditis: No pathology at surgery or autopsy, clinical resolution with ≤ 4 days of antimicrobial therapy, or firm alternative diagnosis.

Remember…The good clinician uses these as guidelines—every patient is different and the ultimate decision on therapy depends on a combination of clinical judgement and laboratory findings.

Bedside evaluation and management of infective endocarditis

You've just been called to evaluate a patient with fever, a heart murmur and suspected infective endocarditis (IE). Despite the availability of modern technology, a careful physical examination still plays an important role in the diagnosis and management of this uncommon, but serious, infection[1,2,3]. When evaluating a suspected case, use the following checklist to guide diagnosis and management:

- **Examine the hands and head:** Although uncommon (most are seen in less than 10% of cases), presence of these "classic" lesions suggests underlying IE:
  - **Splinter hemorrhages:** Although often related to previous trauma, the presence of "new onset" 1 mm longitudinal bands in the proximal nail bed are a clue to the diagnosis of IE in suspected cases. Examine the nail beds daily looking for "splinters" as well as the characteristic clubbing that is sometimes seen in patients with subacute bacterial endocarditis.
  - **Osler's nodes:** Painful, erythematous nodules on the fingertips.
  - **Janeway lesions:** Flat, non-painful hemorrhagic lesions on palms and soles—seen in acute IE.
  - **Roth spots:** On fundiscopic examination, hemorrhagic retinal lesions with a central white spot due to leukocytes; also seen in patients with leukemia and severe anemia.
  - **Conjunctival and palatal petechiae:** Hemorrhagic petechiae on conjunctiva or oral mucosa (soft palate). In addition, look for crops of petechiae appearing in other skin locations such as the anterior chest.
  - **Gingivitis/dental abscess:** While not a specific sign of endocarditis, the presence of dental disease is a clue to a possible source in a patient with suspected IE. Obtain a dental evaluation—especially in those with bacteremia (eg. viridans streptococci) suggesting an oral source.
- **Carefully examine the heart:** A careful cardiac examination in a quiet room is especially important—90% of patients with IE have a murmur sometime during their course. Examine the patient daily and pay particular attention to a changing murmur or the development of a new, regurgitant murmur. Here are some bedside tips to help elicit these often subtle findings …
  - **Tricuspid regurgitation (TR):** Tricuspid endocarditis is seen in the intravenous drug user or patient with an infected, indwelling central catheter. The murmur can be quite soft and may not be heard on hospital admission. When examining a patient for TR, lay the patient flat and listen carefully along the right sternal border for the high-pitched, systolic "SHHH" characteristic of the murmur. As a right-sided murmur, TR typically shows accentuation with respiratory inspiration and bedside maneuvers that increase venous return to the right side of the heart. Examine the venous pulse in the neck to see if the patient has the CV wave characteristic of tricuspid regurgitation.
  - **Aortic regurgitation (AR):** The AR mumur is difficult to hear and often missed without a careful physical examination. If possible, sit the patient on the side of the bed and have them bend forward while you listen —this brings the heart closer to the chest wall and makes it easier to hear the murmur. Ask the patient to exhale and hold their breath; listen with the stethoscope diaphragm at the left lower sternal border for the characteristic blowing, decrescendo murmur occurring immediately following S2.
  - **Mitral regurgitation (MR):** If you hear a systolic murmur at the apex, don't forget to listen in the axilla for the transmitted murmur of mitral regurgitation. In patients with rupture of the posterior mitral leaflet, the murmur may radiate to the back.
  - **Continuous murmur:** In a patient with suspected IE, the presence of a new, continuous murmur suggests the possibility of a ruptured sinus of Valsalva—a fistula from the aortic valve to the right ventricle, left or right atrium. This complication usually requires emergency surgery.

- **Prosthetic valves:** In patients with a prosthetic aortic valve, listen for a new regurgitant AR murmur (this suggests perivalvular infection with a regurgitant leak) or a change in the metallic "click" sounds heard with a mechanical prosthetic valve (the presence of a vegetation may dampen the heart sounds).

  Examine the patient daily looking for signs of congestive heart failure (S3 gallop; lower lobe pulmonary rales)—the presence of a new regurgitant murmur suggests progressive infection and may be a harbinger of life-threatening cardiac failure.

- **Check the electrocardiogram:** In a patient with suspected IE, examine the electrocardiogram—the presence of 1° block (prolonged PR interval) suggests the possibility of an aortic root abscess and impairment of cardiac conduction along the bundle of His. Progression of this lesion may lead to a 2° AV block or a life-threatening, 3° complete heart block.

- **Rule out embolic infection:** Patients with IE and endocarditis run the risk of "metastatic" infection at other sites due to bacteremia or infected emboli. In a patient with IE, be on the lookout for the following complications:

  - **Stroke:** Embolic stroke is the most common CNS complication of IE and may be the initial presenting complaint—perform a careful neurological exam and keep in mind the possibility of IE in all patients with a "febrile stroke".
  - **Mycotic aneurysm:** Suspect the presence of a leaking cerebral mycotic aneurysm in all IE patients with a severe or persistent headache—this complication can occur despite several weeks of apparently successful antibiotic therapy and may be the harbinger of a life-threatening subarachnoid hemorrhage.
  - **Septic pulmonary emboli** are especially common in patients with right-sided endocarditis—patients present with pleuritic chest pain, hemoptysis and wedge-shaped peripheral infiltrates on chest radiograph.
  - **Splenic abscess:** Splenomegaly is common in IE and should be sought in all suspected cases—patients with persistent bacteremia and fever may have an underlying splenic abscess. On physical examination, look for LUQ abdominal tenderness and listen carefully with the stethescope over the spleen for a telltale splenic friction rub
  - **Perinephric/renal abscess:** Look for flank pain or tenderness that may be accompanied by flank swelling.
  - **Glomerulonephritis:** Always check the urinanalysis for hematuria and pyuria—the presence of red-cell casts suggests an underlying immune-mediated nephritis. Gross hematuria may be seen in patients with a renal mycotic aneurysm.
  - **Vertebral osteomyelitis:** Although back pain is common in IE, persistent spinal pain suggests the possibility of diskiitis, vertebral osteomyelitis, or an associated **epidural abscess**. Carefully examine the spine searching for focal tenderness and obtain a spinal MRI on those with suspected spinal involvement.
  - **Septic arthritis:** Examine all joints for swelling or tenderness—musculoskeletal complaints are common in IE and occasional patients may have metastatic infection to a joint.

- **Call the laboratory:** In a patient with suspected IE, draw at least 3 sets of blood cultures, preferably over the course of one hour. Ask the laboratory to hold the cultures for a full four weeks—some fastidious organisms (e.g "HACEK" organisms) require prolonged cultivation or special techniques to promote growth in blood culture media.

  If blood cultures are positive, check antibiotic susceptibilities— the minimal inhibitory concentration (**MIC**) is an index of the organism's antibiotic susceptibility and helps guide antibiotic choice. When the diagnosis of IE is uncertain, the presence of an elevated erythrocyte sedimentation rate or a +

rheumatoid factor—although non-specific— help support the diagnosis.

- **Order an echocardiogram:** Echocardiography is critical in the modern diagnosis and management of endocarditis. The transthoracic echocardiography (TTE) is about 60% sensitive for diagnosing IE and is useful as an initial screen. Obtain transesophageal echocardiography (TEE) in suspect cases—this test is close to 95% sensitive and is the procedure of choice to identify aortic root abscess or prosthetic valve endocarditis. Look for the presence of vegetations, valvular incompetence, pericardial effusion and aortic root or myocardial abscess.

- **Choose the correct antibiotic therapy:** Choose definitive therapy based upon the blood culture results or the suspected pathogen in those with negative blood cultures. Remember that antibiotic therapy in IE must be prolonged and potent—use agents that are "bactericidal" in order to maximize the likelihood of cure. Combination antibiotic therapy is required in selected conditions such as enterococcal endocarditis and prosthetic valve endocarditis. The American Heart Association website (www.americanheart.org) contains current recommendations for antibiotic therapy.

- **Know the indications for surgery:** Antibiotic therapy alone may be insufficient in some cases. Consider surgical excision of the valve in the following situations:

  - Persistent (> 1 week) bacteremia despite effective therapy
  - Poorly controlled congestive heart failure due to valve destruction or persistent bacteremia
  - Prosthetic valve endocarditis
  - Aortic root or myocardial abscess
  - Difficult-to-treat organisms (e.g. fungi, mycobacteria, *Chlamydia psittaci*, *Coxiella burnetti*, brucellosis)
  - Recurrent embolization with vegetation present on echocardiography.

Remember to repeat the physical examination on a daily basis—the sudden appearance of a new sign or symptom may be an important clue to the possibility of infective endocarditis. Although the new technology offers many benefits, daily cardiac ascultation and a careful physical examination remain important tools in the diagnosis and management of this condition.

The CNE (Culture-negative endocarditis) Conundrum

The patient has a fever and murmur—a recommended echocardiogram shows a 9 mm mobile "vegetation" on the mitral valve but 5 days later the blood cultures are reported as "negative. Does the patient have really have endocarditis and what is the best way to identify the putative pathogen? This scenario—a patient with clinical signs of endocarditis and "negative" blood cultures—is known as "culture-negative endocarditis" (CNE) and raises the possibility of valve infection with a number of unusual, difficult-to-grow or exotic pathogens. When confronted by such a case, keep in mind that most cases ultimately fall into one of five categories…

1. **Previous antibiotics:** The most common cause of CNE is recent antibiotic therapy prior to drawing cultures. Ask your patient about any recent antibiotic therapy—even a single dose of oral antibiotic may be enough to sterilize blood cultures for some time.

2. **Fastidious organisms:** Unless notified in advance, most laboratories throw out "negative" blood cultures after 5 days—while economical, such a practice overlooks organisms requiring longer incubation periods (up to 4 weeks) or special, enriched media for optimal growth. Important pathogens in this category include the fastidious "HACEK" bacteria that may require several weeks of incubation before blood cultures turn positive…

   Hemophilus aphrophilus
   Actinobacillus actinomycetemcomitans
   Cardiobacterium hominis
   Eikenella corrodens
   Kingella kingae

These organisms are penicillin-sensitive, *gram-negative* bacteria found in the oral cavity; cases of endocarditis with these pathogens typically have a subacute/chronic course of illness and present with bulky vegetations on echocardiogram. Other difficult-to-grow bacteria in this category include B6-dependent streptococcci (*Abiotrophy* sp.) and *Neisseria gonorrhea*—an organism more commonly associated with an acute, rapidly progressive endocarditis.

3. **The "Zoonotic" pathogens:** This term refers to bacteria acquired from animals or animal-related products. They are difficult to grow on blood culture and usually require serology for diagnosis. While therapy with combination antibiotics may be effective in some of these cases, many patients require valve excision for definitive cure. Always ask patients about animal or pet exposure and keep in mind the following pathogens:

   - **Bartonella species:** *Bartonella* species are the cause of cat-scratch disease (*B. henselae*) and "Trench fever" (*B. quintana*); both pathogens are associated with rare cases of culture-negative endocarditis and are difficult to grow on routine blood cultures. Trench fever is most commonly seen in homeless adults who acquire the infection following exposure to feral cat populations (the pathogen is transmitted by cat mites and intimate cat exposure is not required). If you suspect *Bartonella*, obtain blood serology in order to confirm the case.

   - **Q fever** (*Coxiella burnettii*): This pathogen is more common in rural areas where patients have exposure to infected domestic animals such as sheep or goats. Recent outbreaks suggest that parturient cats are sometimes infected with this organism and produce aerolization of the pathogen during the birth of kittens. Diagnose this infection with *Coxiella* serology for phase I and phase II antigens; patients with chronic Q fever endocarditis have increased antibody titers to phase I antigens.

   - **Psittacosis** (*Chlamydia psittaci*): A history of bird exposure in a patient with CNE should raise the possibility of psittacosis endocarditis; diagnose this infection by serology.

- **Brucellosis:** Exposure to infected domestic animals (cows, goats, pigs) or related-products (contaminated raw meat or cheese) may lead to chronic brucellosis endocarditis; most patients have a history of preexisting valvular disease. While the organism can be grown in the laboratory, obtain *Brucella* serology on suspected cases since many cases are "culture-negative".

4. **Miscellaneous "No growth" pathogens:** These are organisms that will not grow on standard laboratory cultures and require special culture media or serological techniques. While uncommon, they are a particular problem in individuals with prosthetic valve endocarditis…

   - **Legionella**: Although extremely rare as a cause of endocarditis, an outbreak of prosthetic valve endocarditis was associated with the use of contaminated water to clean wounds following cardiac surgery. In suspected cases, obtain blood serology since the organism requires special laboratory techniques to grow from the blood.

   - **Mycobacteria**: Atypical mycobacteria (*M. fortuitum, M. chelonae*) may cause both native valve and prosthetic valve endocarditis. Using lysis-centrifugation techniques, the organisms can occasionally be isolated on blood culture although most cases are confirmed by culture of valve material obtained at the time of surgery.

   - **Fungi**: Most cases of fungal endocarditis (*Candida* species; aspergillosis) are associated with prosthetic valve infection, or—in those with native valve involvement—a history of underlying immunodeficiency or intravenous drug use. Various "geographic" fungi may rarely cause endocarditis—*Histoplasma capsulatum* sometimes causes endocarditis as part of acute or chronic disseminated histoplasmosis.

5. **"Non-infectious" vegetations:** Remember that not all cardiac vegetations are related to infective endocarditis—other conditions such as SLE (Libmann-Sacks endocarditis), related rheumatological diseases (Adult Still's disease; rheumatic fever) and neoplasms (atrial myxoma, pheochromocytoma, primary cardiac tumors, secondary metastasis to the myocardium) may present with cardiac lesions mimicking infective endocarditis. *Marantic* endocarditis is seen in patients with an underlying "hypercoagulable" state due to underlying disseminated cancer (usually adenocarcinoma) or extreme inanition following chronic infection or illness.

What to do in a suspected case of "culture-negative" endocarditis…

- ☐ **Notify the laboratory** of the possibility of endocarditis—discuss the case with the laboratory microbiologist and make sure the standard blood cultures are held for a full 4 weeks. Obtain blood cultures for fungi and mycobacteria to help exclude more exotic pathogens.
- ☐ **Be wary** of writing off organisms as blood culture "contaminants"— such organisms may prove to be true pathogens if repeatedly isolated.
- ☐ **Question the patient** carefully about animal or pet exposures—such exposures may provide clues to the etiology of a puzzling case of endocarditis.
- ☐ **Order serologies** for more exotic pathogens (*Brucella*, Q fever, *Chlamydia* sp., *Bartonella*) if initial cultures remain negative.
- ☐ **Keep in mind** the possibility of endocarditis "mimics" such as SLE, atrial myxoma and marantic endocarditis
- ☐ **Surgery:** In patients requiring an embolectomy or valve excision, send the tissue to the laboratory for microscopy (special stains; electron microscopy) and cultures; use of tissue PCR technology may help answer a diagnostic puzzle when routine studies are negative.

Uncovering the clues to bacterial meningitis

You are called to the emergency room to see a patient who has fever, headache and neck stiffness—what is the likelihood that this patient has bacterial meningitis? Is it safe to perform a lumbar puncture? If present, what is the source of the meningitis? To help answer these questions, keep in mind the following principles when evaluating a suspect case…

1. "Does the patient have meningitis?"—a compendium of bedside clues.

Physicians have traditionally relied on a number of bedside clinical signs to assist in the clinical diagnosis of meningitis—unfortunately these signs are often not seen and can occasionally be misleading. Although still valuable[1], these signs must be applied with a realization of their limitations…

Sign	Description
Nuchal rigidity	With the patient in a supine position, gently flex the neck forward—the presence of neck stiffness or pain on forward flexion is a positive sign of nuchal rigidity.
Kernig' s sign	With the patient lying down, flex the hip to 90° and try to extend the knee—a positive Kernig's sign is the presence of a "contracture" or extensor spasm at the knee when trying to extend the knee beyond 135°.[2]
Brudzinski's sign	Passive flexion of the patient's head produces hip and knee flexion
Jolt sign	Ask patient to turn his head horizontally at a frequency of 2 to 3 rotations per second—worsening of a baseline headache represents a positive sign.[3]

When present, these signs are helpful in Nuchal rigidity can be especially misleading because of the large number of patients—especially older individuals—with degenerative arthritis of the neck and other localized pathologies. Remember that neck stiffness on *forward* flexion is characteristic of meningitis—patients with localized neck pathology often show resistance of neck rotation or lateral flexion—signs not characteristic of acute meningitis. A recent study (Table 1) of 297 patients with "suspected meningitis" seen in an emergency room setting (Of the 80 patients with meningitis, only 3 had documented bacterial meningitis) reviewed the diagnostic accuracy of symptoms and signs associated with the condition. Traditional signs associated with meningitis—nuchal rigidity, Kernig's sign and Brudzinski's sign—although specific, were not very sensitive. An earlier study reviewed 279 episodes of proven or presumed community-acquired bacterial meningitis (Table 2); in this study, two thirds of patients had the classic "triad" of fever, nuchal rigidity and change in mental status[4].

Table 1: Diagnostic accuracy of meningitis signs

Test	Sen (%)	Spec (%)
Nuchal rigidity	30	68
Kernig's sign	5	95
Brudinski's sign	5	95

Data extracted from CID 2002;35:46-52. Table 3

Table 2: Clinical findings in bacterial meningitis

Clinical finding*	% cases
Temperature ≥ 37.7°C [100°F]	95
Nuchal rigidity	88
Abnormal mental status	
Confused or lethargic	51
Responsive only to pain	22
Comatose	6
Seizures	15
Focal CNS findings	24

* Data from 279 episodes of meningitis reported in NEJM 1993;328:21-8

Several conclusions about bacterial meningitis can be drawn from these case reviews…

- Fever and headache are seen in almost all patients with acute bacterial meningitis.
- The presence of signs of meningismus (nuchal rigidity, Kernig's sign, Brudzinski's sign) are a "red flag" for meningitis; however, *absence* of these signs does not rule out the condition.

- Focal CNS findings (seizures, hemiparesis, aphasia, visual field abnormalities, gaze preference) are seen in less than 25 % of patients at clinical presentation (If present, consider the possibility of encephalitis or brain abscess)

Fever, nausea/vomiting and photophobia are helpful in suggesting acute meningitis but are by no means seen in all cases. The clinician needs a high index of suspicion for this not-uncommon infection and must be willing to perform a lumbar puncture in any suspected case—bedside examination alone is often unreliable in ruling out the condition.

2. Is it safe to do a lumbar puncture?

Once bacterial meningitis is considered, the next decision revolves around the safety of an immediate diagnostic lumbar puncture. Although there is a risk of cerebral herniation in bacterial meningitis (even with a negative CT scan) the risk is much higher in patients with focal CNS lesions such as a brain abscess or cerebral tumor. In general, avoid an immediate tap in a patient with significant focal neurologic findings or in those with a subacute/chronic clinical history (days to weeks of illness)—the risk of an underlying focal lesion is just too high to justify the procedure. In patients with a clinical history characteristic of acute bacterial meningitis (sudden onset of fever and severe headache), evaluate the following parameters when determining the safety of performing a lumbar puncture:

- **Level of consciousness:** At the bedside, determine the patient's level of consciousness and make note of it in the medical record—the presence of severe confusion, stupor or coma suggest increased intracranial pressure and increase the possibility of a CNS mass lesion.

- **Presence of papilledema:** Perform a bedside fundiscopic examination looking for signs of papilledema—although uncommon in bacterial meningitis, the presence of papilledema suggests increased intracranial pressure and may be a sign of an underlying mass lesion. Unfortunately the *absence* of papilledema does not necessarily indicate a normal intracranial pressure—papilledema may be absent in patients with a rapid development of symptoms.

- **Focal neurological findings:** While meningitis may have a stroke-like presentation, the presence of signficant focal neurological findings (e.g. hemiparesis, ataxia, cranial nerve abnormalities) raise questions of a CNS mass lesion and are a relative contraindication to an immediate lumbar puncture prior to a CT of the brain.

Do not perform an immediate lumbar puncture if any of these three signs are present—obtain a blood culture, start antibiotics and then tap the patient *if* a brain CT scan shows no evidence of mass lesion or intracranial shift.

3. What is the source of the meningitis?

Once you suspect bacterial meningitis, look or an underlying source—most cases of bacterial meningitis represent seeding of the meninges from a bacteremia or direct invasion from a contiguous site of infection. During your evaluation, make sure to question the patient about significant risk factors and look for following clues on physical examination:

- **Dental abscess/gingivitis:** Although more commonly associated with brain abscess or cerebritis, underlying dental infection (abscess, gingivitis) is sometimes the source for bacterial meningitis.
- **Acute and chronic otitis media:** *Always* perform an otoscopic exam in a patient with suspected meningitis. Acute otitis media due to pneumococcus or *Hemophilus influenza* is an important predisposing factor in both children and adults. The patient with chronic otitis/mastoiditis is at risk for temporal lobe brain abscess, cerebritis or subdural empyema—be wary of performing a lumbar puncture in these cases unless the CT results show that a tap is safe.

- **Sinusitis:** An acute sinusitis is sometimes the source of bacterial meningitis. Look for the presence of nasal discharge and palpate the sinuses (frontal and maxillary) for local sinus tenderness—a CT scan of the head permits better visualization of the sphenoid and ethmoid sinuses.
- **Spinal defects:** Examine the patient's spine carefully from "crown to coccyx" looking for a cyst, dimple or tuft of hair suggesting an underlying spinal malformation or dermal cyst. Although more common as a cause of meningitis in children, these lesions are sometimes seen in adults and can be the cause of recurrent meningitis.
- **CSF leaks:** Ask the patient about any previous head trauma resulting in loss of consciousness or skull fracture—such events may lead to a CSF leak years later and are commonly associated with pneumococcal meningitis. Question patients carefully about a history of clear, "watery" drainage from the nose or ear—although commonly ascribed to "allergy" or "ear infection" such a finding might suggest a chronic CSF leak.
- **Endocarditis:** Although uncommon in the antibiotic era, Osler's triad (pneumonia, endocarditis, meningitis) was a well-described complication of pneumococcal bacteremia during the pre-antibiotic era. Perform a careful cardiac examination listening for an underlying murmur—aseptic meningitis is a frequent finding in patients with cerebral emboli or mycotic aneruysm prior to rupture. Examine the chest radiograph looking for an underlying pneumonia.
- **Genital examination**: In sexually active patients, consider the possibility of disseminated gonococcal infection with meningitis and obtain screening tests (urethral culture, urine GC test) for asymptomatic *N. gonorrhea* colonization.
- **Skin:** Roll the patient over and perform a careful skin examination—petechiae are one of the earliest findings in meningococcal infection and are first seen in dependent areas such as the back or buttocks; only later do patients develop the widespread petecchiae and purpura seen in full-blown meningococcemia. Examine the patient carefully for localized skin infections such as impetigo, furuncles or carbuncles—although staphylococcal meningitis is uncommon, such lesions may serve as a source for occult bacteremia leading to endocarditis and central nervous system infection.
- **Other risk factors:** Remember that several risk factors—alcoholism, diabetes mellitus, HIV infection —clearly increase the risk of bacterial meningitis—question the patient carefully about these conditions and look for signs of underlying occult HIV infection (unexplained lymphadenopathy, oral thrush, oral hairy leukoplakia, shingles and extensive tinea pedis). Other immunocompromised states also place a patient at greater risk for meningitis; corticosteroid use is a particular risk factor for *Listeria* meningitis

The Encephalitis Enigma—CNS viral infection

Encephalitis remains a diagnostic and therapeutic challenge—the cause is often a mystery and patients (fi they survive) are frequently left with significant neurological deficits. This piece will describe the main causes of this condition and outline an approach to managing this uncommon, but important disease. When confronted with an unexplained encephalitis case, take a careful history looking for epidemiological clues that might suggest and etiology.

1. Viral encephalitis—a microbiological "mystery"

The microbiological cause of "viral" encephalitis often remains a mystery—even in the best studies, over 50% of cases remain "undiagnosed". Although the incidence of various pathogens varies with geographic location, a study from **Los Angeles county** public health (Table 1) outlines the most common pathogens found in the immediate region. Important findings from this study include the following:

- ✓ **"Unknown" country:** As with several other series, over 50% (63%) of encephalitis cases showed no obvious pathogen after routine studies.
- ✓ **West Nile virus** was an especially common in 2007—.most of these patients were older (mean age 65) and acquired infection during the summer or fall.
- ✓ **Herpes simplex** remains the most common form of "treatable" viral encephalitis—it is a sporadic illness (no seasonal preference) and tends to affect an older age group (mean age=46 in CEP study).
- ✓ **Enterovirus** is equally common, but most prevalent in children (mean age=11 yrs) during the summer and early fall.

Table 1: LA County Encephalitis (2007)

Etiology	% Cases*
No pathogen isolated	63
West Nile virus	18
Herpes simplex	6
Enterovirus	6
Varicella zoster virus	2
Epstein Barr virus (EBV)	2
Adenovirus	2

Source: LA county public health
* 65 cases in 2007

Table 2: California Encephalitis Project

Etiology	% Cases*
No pathogen isolated	63
Infection: Confirmed or probable	16
Infection: Possible	13
Non-infectious	8

Source: Glaser et al. CID 2006;43:1565-77.
* 1570 patients: 1998-2005

California Encephalitis Project (CEP) is a multiyear ongoing attempt to determine the cause of "unexplained" encephalitis in California. Although most cases remain "unknown" (Table 2), enterovirus and HSV are the most common cause of viral encephalitis in "confirmed" cases. Uncommon bacterial causes of encephalitis include *Mycobacterium tuberculosis* and cat scratch disease (*Bartonella* sp.). "Possible" cases (negative CSF studies but + serology) include a number of pathogens but highlight the importance of *Mycoplasma pneumonia*— especially in pediatric populations—and "common" respiratory pathogens such as influenza and adenovirus.

Table 3: CEP—"Confirmed" cases

Etiology	# Cases*
Viral	
Enterovirus	43
Herpes simplex-1	40
Varicella Zoster (VZV)	23
West Nile virus (WNV)	19
Epstein Barr (EBV)	17
Bacterial	
M. tuberculosis	19
Pyogenic bacteria	14
Bartonella (Cat scratch)	13

Source: Glaser et al. CID 2006;43:1565-77.
* 248 patients (16%): 1998-2005

Table 4: CEP—"Possible" infectious cases

Etiology	# Cases*
Mycoplasma	96
Enterovirus	28
Influenza A/B	22
Adenovirus	14
Herpes simplex-1	13
Chlamydia	10
Human metapneumonia	4
Mixed respiratory infection	5
Varicella zoster virus	4

*< 4 cases (≤ 1%): HHV-6; RSV; Brucella; Rotavirus; Parainfluenza; Bartonella; EBV; CJ prion
Source: Glaser et al. CID 2006;43:1565-77.

2. Clinical clues to the diagnosis of encephalitis…

- **How old is the patient?** In adults, a large percentage of *diagnosed* cases are due to *Herpes simplex* type 1—arboviral infection is almost as common depending upon the time of year and local "epidemic" conditions. In children, enteroviruses, *Mycoplasma pneumoniae* and childhood exanthems—measles and chickenpox—play a much more important role. HSV 2 is the most common cause of viral encephalitis in neonates—*Listeria monocytogenes* encephalitis may also mimic viral disease in this population.

- **What diseases are active in the community?** When evaluating any encephalitis case, be aware of infectious conditions endemic in the local community. In temperate climates, influenza is usually active between late Fall and early Spring. Illness due to *Mycoplasma pneumoniae* sometimes occurs in outbreaks—look for a history of pulmonary disease and involvement of other family members. Surveillance by public health authorities may detect arboviruses in mosquito populations prior to human cases.

- **What season is it?** The time of the year provides important epidemiological clues since some pathogens have a definite seasonal predilection. The following table outlines the most common associations…

Pathogen	Season
Arbovirus	Summer—early Fall in the United States
Chickenpox	Winter--spring
Enteroviruses	Summer-early Fall
LCM	Winter (When mice come into homes)
Measles	Winter
Mumps	Winter-spring (Associated with parotitis…check a serum amylase)

- **Where does the patient live—where have they traveled?** Mosquito—and tick-borne—encephalitis are common around the world with various viruses linked to specific geographic regions. Take a careful residence/travel history and evaluate any encephalitis case in light of the following epidemiological features…

Pathogen	Geographic history
Eastern equine encephalitis	East, Gulf Coast, South
Japanese encephalitis	Southeast Asia
La crosse	Central, East
St. Louis	Central, West, South
Tick borne encephalitis	Eastern Europe; Russia
Venezuelan	East coast US; South and central America
West Nile virus	Now throughout the United States with increased spread to Western states
Western Equine	Midwest, West
Dengue	Central America; Caribbean; Southeast Asia

- **Was the patient recently vaccinated?** Carefully question the patient about recent vaccinations. Vaccines for mumps, measles and chickenpox are occasionally associated with encephalitis due to a post-immunization demyelination disorder. If smallpox vaccination becomes widespread, additional cases of *Vaccinia*-associated encephalitis are likely to be seen, especially in children.

- **Has the patient had any recent animal bites or contact?** On rare occasions encephalitis follows exposure to pets or wild animals. Encephalitis is a well-known complication of cat-scratch disease due to ***Bartonella henselae***—ask patients about cat/kitten exposure and look for the localized adenopathy often seen with the condition. **Lymphocytic choriomeningitis**

(LCM) virus is associated with exposure to small mammals (mice, hamsters, gerbils) in the laboratory. ***Herpes simae* (Type B)** infection following primate/monkey bites leads to wound infection with subsequent encephalitis; mortality rate is extremely high.

Rabies is an important cause of viral encephalitis in developing countries—ask about animal bites as well as travel to potentially endemic areas. Patients may forget a previous wound as the incubation period may be over one year following exposure! In the United States, cases may be due to dog/cat exposure, although is more likely associated with bat.

- **Is there a history of sexual contact or HIV risk factors?** Primary HIV infection may present with unexplained encephalitis—as patients about recent sexual contacts and—in addition to HIV serology—obtain an HIV PCR to rule out primary HIV infection. Other sexually transmitted diseases—syphilis, lymphogranuloma venereum (LGV) and *Herpes simplex* (type II)—may rarely present with primary encephalitis.

3. Are there any clues on the cerebral radiographs? Although radiographic findings are often non-specific, selected patterns suggest specific pathogens. Examine the radiograph (MRI), keeping in mind the following findings:

MRI Findings	Possible pathogens
Temporal lobe involvement	HSV; HHV-6
Midbrain (Thalamus; Globus pallidus)	Arboviruses (JE; West Nile virus; St Louis)
Brainstem	HSV; Listeria; Tuberculosis
White matter involvement	ADEM; PML; HIV encephalitis
Hydrocephalus	TB; fungal

Abbreviations: ADEM: Acute disseminated encephalomyelitis; JE: Japanese encephalitis; PML: Progressive multifocal leukoencephalopathy

4. Could this be a viral encephalitis "mimic"? Although CNS complications are seen in many diseases, certain conditions—both infectious and non-infectious—have a high frequency of CNS involvement and may mimic viral encephalitis. As part of your evaluation, keep in mind the following conditions…

Condition	Clinical features
Bacterial	
Bacterial cerebritis	Early cerebritis may mimic viral encephalitis; subsequent MRI shows development of abscess. Look for dental infection or pyogenic source.
Listeria encephalitis	Most common in patients receiving corticosteroids. May present with brainstem (rhomboencephalitis) and/or focal cerebellar involvement.
Cat-scratch disease	More common in children; + cat exposure; √ serology for *Bartonella*
Whipple's disease	Pts present c oculomasticatory dysrhythmia
Lyme disease	Look for history of tick exposure and characteristic rash; Dx with serology
Syphilis	Take careful history of sexual contacts; Dx with serology
Mycobacterium tuberculosis	CSF generally shows low glucose; + PPD; +PCR in CSF
Mycoplasma encephalitis	Recent hx of respiratory infection; more common in children, adolescents
Parasitic disease	
Toxoplasmosis	Usually in immunocompromised patients—especially steroid treated or HIV
Cysticercosis	Rare cysticercosis encephalitis in young women
Non-infectious	
Cerebral granulomatous vasculitis	
Systemic lupus erythematosus	Look for other signs of lupus and check ANA in patient
Hashimoto's encephalitis	Associated with occult thyroid disease—check anti-thyroglobulin antibodies
Paraneoplastic encephalitis	Older patients with underlying malignancy—antibody tests may be helpful.
MELAS syndrome	Genetic metabolic syndrome with mitochondrial dysfunction, endocrine disorder (diabetes), lactic acidosis and seizures (MELAS)
Lymphoma	Primary CNS lymphoma–Many associated with EBV infection

Once you suspect the possibility of encephalitis, use the following checklist to guide diagnosis and management...

- ❑ **Take a careful history**, keeping in mind diagnostic clues described above. Remember that encephalitis patients are often poor historians because of their underlying confusion. Take the time to speak with patient's family members and friends—they may be able to provide historical detail that will help make a diagnosis.

- ❑ **Perform a physical exam**, with special attention to the following...
  - ✓ **Level of consciousness:** By definition, patients with encephalitis have altered consciousness or focal findings on neurological exam.
  - ✓ **? Meningismus:** Although meningismus can be seen with encephalitis, presence of a "stiff neck" suggests a meningitis component and the possibility of bacterial or viral meningitis.
  - ✓ **Fundiscopic examination:** Look for the presence of cotton wool spots (HIV; WNV) and document presence (or absence) of papilledema.
  - ✓ **? Presence of lymphadenopathy:** Look for generalized lymphadenopathy (HIV; WNV) or localized adenopathy (Cat scratch disease).
  - ✓ **Neurological exam:** Look carefully for focal findings (common in encephalitis) or signs of upper motor neuron disease (e.g. Babinski sign).

- ❑ **Examine the patient radiographs**, keeping in mind specific patterns which are more common with selected pathogens (e.g. Temporal lobe → HSV). Take the time to review the films with a neuroradiologist.

- ❑ **Review the cerebrospinal fluid (CSF) results:** For the most part, CSF findings in encephalitis are somewhat non-specific (usually a lymphocytic pleocytosis with an elevated protein and normal glucose). Findings that may be helpful include low CSF glucose (mumps; TB; fungal disease), CSF eosinophilia (parasitic disease; Hodgkin's, coccidioidomycosis) and neutrophilia (common in bacterial infection but also seen in TB [occasionally] and West Nile viral infection.

- ❑ **Order the following tests,** in addition to routine laboratory testing...
  - ✓ **Serology:** HIV; HIV PCR (blood); *Mycoplasma* serology; EBV; ELISA West Nile (IgG/IgM)
  - ✓ **Cerebrospinal fluid:** HSV PCR; IgM (West Nile); Enterovirus PCR (if summer/fall); MTB PCR; Coxy serology

  Additional tests may be appropriate depending upon the clinical presentation and history.

- ❑ **Consider the possibility of a non-viral "mimic"**...Approximately 10% of cases will turn out to be secondary do "non-viral" infections. In addition to standard testing, obtain an ANA, thyroid functions (including antithyroid antibodies) and CSF cytology. Additional testing may be appropriate depending upon the patient's response to therapy and extra CNS findings.

- ❑ **Start the patient on empiric antibiotic therapy**...Considering the possible "treatable" pathogens, I favor the following "cocktail" while awaiting preliminary studies...

  Acyclovir 10 mg/Kg IV Q 8 hr
  Doxycycline 200 mg IV Q 12 hr x 3 days...then 100 mg IV/PO Q 12 hrs
  Ampicillin 2 gm IV Q 4 hr x 10 days

- ❑ **Reassess the patient** periodically, as new data and information comes in.

Chronic meningitis—clues to a perplexing puzzle

Chronic meningitis is defined as a "constellation of signs and symptoms of meningeal irritation that lasts longer than 4 weeks accompanied by CSF pleocytosis" (this is a fancy term for increased cells and protein). In addition to headache and meningismus, patients may develop cranial nerve abnormalities or signs of increased intracranial pressure (obtundation; papilledema). Patients with long-standing or poorly controlled meningitis may develop hydrocephalus requiring surgical shunting.

1. Clues to etiology of chronic meningitis on CSF examination:

A definitive diagnosis is frequently delayed since it may be difficult to isolate a pathogen from the CSF. Although the CSF findings are often non-specific, the predominant cell type in the pleocytosis may serve to narrow the differential diagnosis. When evaluating CSF pleocytosis in these patients, keep in mind the following associations…

Table 1: Etiology and CSF pleocytosis in Chronic Meningitis

Lymphocytic/mononuclear cell predominance	Neutrophil predominance	Eosinophil predominance
Tuberculosis Cryptococcosis Coccidioidomycosis Other fungi: Blastomycosis: Histoplasmosis: Sporotrichosis Candida: Brucellosis Tularemia Syphilis	Bacterial Actinomycosis Nocardiosis Fungal Mucormycosis: Aspergillosis: Early tuberculosis Acanthamoeba: Drug-induced meningitis:	Chemical meningitis Lymphoma Coccidioidomycosis Parasitic Cysticercosis Angiostrongyloides cantonenis Gnathostomiasis

Table modified from Hirsch DJ et al. Chronic meningitis in Gorbach et al, Infectious Diseases, W.B. Saunders Co. 1992.

Additional clues on CSF examination…

Pleocytosis < 50 cells/um	Low CSF glucose (Hypoglycoracchia)
Behçet's disease Benign lymphocytic meningitis Carcinoma Cryptococcus in HIV-infected patients Sarcoidosis Vasculitis	Bacteria (Actinomycosis; Nocardiosis) Carcinoma Cysticercosis Fungi (all) *Mycobacterium tuberculosis* Postsubarachnoid hemorrhage Sarcoidosis Syphilis Toxoplasmosis Enteroviral meningitis in hypogammaglobulinemia CMV meningoencephalitis in AIDS patients

Table modified from Mandell et al, Principles and Practice of Infectious Disease, 5th edition , Churchill-Livingston 2000.

2. Evaluation of the chronic meningitis patient—clues on history and exam

A careful history and physical examination are essential to narrowing the list of possibilities. Specifically question the patient about:

- **History:** The following history might prove clues to etiology of chronic meningitis…
  - ✓ **TB exposure:** Family history of TB or travel/residence in endemic areas
  - ✓ **Travel:** Travel to regions endemic for geographic fungi or parasitic disease

- ✓ **Food:** Ingestion of raw milk/cheese (brucellosis)
- ✓ **Animal exposure:** Tularemia (hunting), brucellosis (domestic farm animals)
- ✓ **Gardening/soil exposure:** Sporotrichosis, geographic fungi

- **Physical examination:** While the physical examination often demonstrates non-specific findings (meningismus, cranial nerve abnormalities), examine the patient carefully for the following clues to the underlying process:
  - ✓ **Eyes:** Perform a careful fundiscopic examination looking for choroid tubercles (tuberculosis), retinal nodules (sarcoidosis) or chorioretinitis/uveitis (Vogt-Koyanagi Harada syndrome; Behcet's disease).
  - ✓ **Skin:** Examine the entire skin surface for nodules or lesions that can be biopsied
  - ✓ **Liver:** Presence of hepatomegaly suggests underlying granulomatous disease or carcinoma—consider liver biopsy in patients with elevated alkaline phosphatase, hepatomegaly or liver nodules on CT/ultrasound
  - ✓ **Spine:** Examine the spine from head to sacrum looking for dimples (underlying dermoid cyst) or tenderness (local inflammatory process or tumor)

3. Laboratory/radiographic studies in chronic meningitis:

Proper examination of cerebrospinal fluid often leads to a definitive diagnosis in patients with chronic meningitis. Selected serologies (in both CSF and Blood) should be ordered based on clues from the history and physical examination.

- **CSF:** Collect large volumes (at least 5-10 cc) of cerebrospinal fluid for the following tests:

  Culture for fungi and mycobacteria (Hold cultures 6-8 weeks for slow-growing pathogens)
  CSF India Ink test and cryptococcal antigen
  CSF VDRL (Syphilis)
  PCR for *Mycobacterium tuberculosis* (+ in 25-65% of cases of tuberculous meningitis)
  Fungal serology (coccidioidomycosis, histoplasmosis, blastomycosis, sporotrichosis) if indicated
  CSF cytology (carcinoma)
  Clonal studies of CSF lymphocytes (R/O lymphoma)

- **Serum:**

  Serum HIV test
  Serum RPR and treponeme-specific test (MHA-TP; TPPA, FTA-ABS)
  Fungal serologies if indicated by exposure history
  Rheumatologic studies: ANA (SLE);
  Serum ACE levels (Sarcoidosis)

- **Additional studies:**

  PPD with anergy panel
  CT Brain: 1 mm basilar cuts with bone windows (epidermoid cyst-recurrent meningitis)
  MRI Brain: ? Basilar enhancement consistent with basilar meningitis
  Brain/meningeal biopsy: Relatively low yield but may be helpful in selected cases

4. Meningitis "mimics"—disorders that mimic chronic meningitis "syndrome".

In addition to the chronic infectious syndromes described above, there are additional (most idiopathic or non-infectious) syndromes that need to be considered in patients with the chronic meningitis syndrome. When evaluating these patients, keep in mind the following conditions:

Condition	Comment
Sarcoidosis	Check chest radiograph and serum/CSF ACE levels
CNS/systemic vasculitis	Look for peripheral findings and check appropriate serologies (ANCA; ANA) Limited CNS vasculitis may require diagnosis via cerebral angiogram
Behcet's disease	History of recurrent oral/genital ulcers, arthritis, uveitis, recurrent thrombophlebitis
Vogt-Koyanagi-Harada syndrome	Bilateral uveitis; hearing loss; poliosis (white "shock" of hair)
Whipple's disease	"Infectious" condition with non-cultureable pathogen (*Trophyma whippleii*) that requires PCR for definitive diagnosis. Look for other symptoms including chronic diarrhea, adenopathy, and characteristic neurological findings (altered mental status with psychiatric manifestations; hypothalmamic abnormalities and ocular/facial myoclonus)
Carcinomatous meningitis	Includes metastatic adenocarcinoma as well as Hodgkin's and non-Hodgkin's lymphoma. Diagnosis may require multiple (> 3) CSF cytologies as well as flow cytometry (for lymphoma evaluation)
Malignant angioendotheliomatosis	A form of intravascular lymphoma that presents with CNS complaints (headache,CVA, neuropathy, dementia) and skin papules/nodules (30% pts); lymphadenopathy typically absent. Dx: skin or meningeal biopsy Rx: chemotherapy
Cerebral mass lesion	Brain abscess or malignancy

What to do in the patient with suspected chronic meningitis...

- ❑ **Take a careful history:** As described in the earlier lists, there are numerous pathogens that can present with this syndrome. A thorough history that includes travel, food ingestion, animal and work exposure is critical in generating a likely cause.
- ❑ **Physical examination:** Most of the findings will be non-specific; however, it is important to clearly document the level of consciousness and any associated neurological abnormalities. Additional findings include skin abnormalities (nodules; papules), lymphadenopathy, hepatosplenomegaly and findings consistent with rheumatological disease (e.g. arthritis, iritis, rash). Obtain a fully dilated eye examination in order to rule out retinal nodules (MTB; sarcoid), uveitis (Behcet's; VKH) and retinal vasculitis.
- ❑ **Laboratory studies:** In addition to the standard blood studies, obtain HIV serology, fungal serologies (depending upon the geographic exposure), a PPD (or Quantiferon gold interferon gamma releasing assay), fungal and rheumatologic studies.
- ❑ **Review the CSF findings:** As noted in the earlier tables, the nature of the CSF pleocytosis clearly is helpful in sorting out the possibilities. Specifically look for the presence of hypoglycorrhachia (low CSF glucose), CSF pleocytosis (lymphocytosis vs neutrophils) and CSF protein level. In carcinomatous meningitis is a possibility, order CSF serology and CSF flow cytometry studies.
- ❑ **Obtain cultures:** Large volume (5-10 cc) cultures are critical to maximize the isolation of fungal or mycobacterial pathogens. Request additional studies such as CSF MTB PCR and fungal

serologies (coxy, blasto and histo EIA; cryptococcal antigen) depending upon the geographic exposure history.

- ❑ **Radiographic studies:** Findings on the MRI such as meningeal thickening are non-specific but will help to confirm presence of chronic meningitis. Carefully review the chest radiograph—presence of calcified nodules suggest the possibility of underlying granulomatous disease.
- ❑ **Consider a meningeal biopsy:** If all other studies are negative, a meningeal biopsy may be diagnostic, especially in patients with granulomatous disease, carcinomatous meningitis and selected types of CSF vasculitis (small vessel CNS granulomatous vasculitis).
- ❑ **? Empiric antibiotic trial:** Although it is always best to "make a diagnosis" prior to beginning therapy, empiric TB or anti-fungal therapy may be appropriate in selected cases, especially in PPD+ patients or those with specific geographic exposures. A trial of corticosteroids may be appropriate, but only after extensive attempts to exclude infectious pathogens and other conditions—a "steroid-responsive" chronic meningitis has been recognized in a certain percentage of long-term "undiagnosed" cases.

Uncovering the etiology of chronic meningitis may be frustrating—signs and symptoms are often non-specific and cultures/CSF studies are frequently negative. A careful history and physical combined with judicious laboratory testing will go a long way to narrowing the possibilities. Examine and question the patient frequently to search for clues that may have been overlooked on previous examinations. Empiric therapy for tuberculosis or fungal disease may be indicated while CSF studies are pending.

What to do when you suspect TB meningitis

When you are suspicious of the possibility of TB meningitis, the following checklist should help increase the chances of confirming the diagnosis and starting the patient on proper therapy:

1. **Is the clinical presentation compatible with TB meningitis?** Patients usually present with a subacute onset of fever and headache. On lumbar puncture look for a lymphocytic pleocytosis with a low CSF glucose (< 50% serum glucose level). AFB smears are *usually* negative and cannot be relied on to rule out the condition. Remember that the clinical spectrum of TBM is wide—patients may present with an acute onset (similar to bacterial meningitis) or demonstrate focal lesions (tuberculomas) suggestive of a cerebral tumor.

2. **Review patient history for TB clues and past exposures:** Take a careful epidemiologic history with special attention to previous TB exposure (Specifically ask about TB in close family members or friends) and the results of any past PPD testing.

3. **Check the patient's PPD and HIV status:** If possible, repeat the patient's PPD—about 75% of patients with TBM will have a + PPD at some time during their illness. Although the patient may initially be anergic, the PPD may turn positive during therapy as a reflection of improving immunological status. Even AIDS patients with advanced disease can sometimes mount a limited PPD response—repeat the test to make sure it was applied properly and examine the test site yourself.

4. **Examine the chest radiograph for signs of pulmonary TB:** About 50% of patients with TBM will have evidence of active or inactive tuberculosis (pleural thickening, cavities, infiltrates, hilar adenopathy, miliary pattern) on chest radiograph. Obtain sputum smears and cultures on all patients with such findings, even if they are not symptomatic. Examine the radiograph carefully for the calcified granulomas suggestive of previous primary tuberculous infection (Ghon complex).

5. **Look for signs and symptoms of disseminated TB:** Sometimes the diagnosis of TB meningitis is confirmed when MTB is isolated from an extrapulmonary site—check the patient's urinalysis (genitourinary TB), liver tests (elevated alkaline phosphatase in miliary TB), eyes (dilated fundus exam for choroid tubercules) and spine (Pott's disease) for other manifestations of disseminated tuberculosis.

6. **Request an MRI:** Almost all patients with TBM will have some abnormality on brain MRI—remember to request a contrast-enhanced scan since this increases the likelihood of detecting the basilar meningitis so characteristic of the condition. Review the scan with a neuroradiologist.

7. **Repeat the lumbar puncture—obtain a large volume (10 cc) of CSF:** The evolution of the CSF response is as important as the results from the initial tap—patients with TBM tend to have persistently elevated—or rising—CSF counts with a lymphocyte predominance; the CSF glucose may initially be normal but will often drop with progressive disease. The CSF pleocytosis of untreated viral meningitis frequently improves on subsequent taps and patients rarely develop significant hypoglychorrachia (low CSF glucose). The more CSF you can send the to the laboratory the better—the chances of a positive smear, culture or PCR test improve when the laboratory has access to larger samples.

8. **Obtain a CSF MTB-PCR:** Although helpful if positive (40-60% of cases), don't *exclude* TBM based on a negative test—there are frequent "false negative" tests in patients that subsequently grow out MTB.

9. **Consider a trial of anti-TB therapy:** The decision to start TB therapy is frequently a clinical one since the initial tests (AFB smears, MTB-PCR) are often negative. Significant delays in therapy clearly lead to worse patient outcomes—if you seriously suspect TBM, start empiric 4-drug therapy as

soon as possible. As of this writing, the current recommended *12 month* combination regimen is …

Isoniazid, rifampin, pyrazinamide, ethambutol x 2 months , followed by
Isoniazid, rifampin x 10 months (Add pyridoxine 25-50 mg PO daily with isoniazid)

10. **Be patient—response to therapy takes time!** Remember that treatment often leads to a paradoxical reaction—patients sometimes clinically *worsen* (increased fever; increased CSF pleocytosis) during the first several weeks following initiation of treatment; such a reaction suggest that the decision to start therapy may well have been correct. Patients with severe illness often require many weeks of therapy before demonstrating a convincing clinical improvement.

11. **Watch for the complications of TB meningitis:** Observe the patient for any of the following syndromes…

Complication	Comment
Cranial nerve palsy	Most common in CN III, IV, VI, VII—consider use of corticosteroids.
Vascular stroke	Commonly seen in basal ganglia/internal capsule, pons due to inflammatory vasculitis of penetrating vessels; obtain MRI and consider cortico steroids.
Hydrocephalus	Patients develop increasing headache and obtundation—order an emergency CT scan and obtain a neurosurgery consult as soon as possible.
Seizures	Obtain a CT scan (look for a tuberculoma) and start anti-seizure medications (remember that rifampin accelerates the metabolism of many medications including some anti-seizure agents).

12. **Know the indications for corticosteroids in TB meningitis:** Although still somewhat controversial, studies suggest a benefit of using corticosteroids in patients with serious TBM. The following situations are considered indications for corticosteroid use:

More severe (MRC stage II, III) disease (altered mental status, neurological abnormalities)
Increased intracranial pressure (>25 cm H_2O) or impending herniation syndrome
Spinal block
Patients who deteriorate on institution of antituberculosis therapy
Associated tuberculoma

Use the following protocol:

Adults: Prednisone, 1 mg/kg per day, or dexamethasone, 8-16 mg/d
Children: Prednisone, 1-4 mg/kg per day, or dexamethasone, 8 mg/d ().3-).6 mg/kg per day)
Note: Dosage maintained for 3-6 wk, the tapered over 2-4 wk.

Despite modern advances in the diagnosis and therapy of central nervous system infection, the management of the patient with suspected TB meningitis remains a considerable challenge. Do not delay therapy waiting for "cultures to come back"—start treatment as soon as possible in clinically suspect patients and aggressively search for clues to confirm the diagnosis.

References:

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A CNS "Pocket of Pus"—Pyogenic brain abscess

A pyogenic brain abscess—a focal collection of pus within the brain—is an uncommon infection that has devastating consequences if missed by the clinician. What follows are answers to some of the most common questions regarding this rare but serious condition:

1. What is the typical clinical presentation of brain abscess?

In many patients, the relatively non-specific clinical presentation delays the diagnosis. Clinical studies of symptoms in brain abscess (see Table 1) suggest the following important observations:

- A dull, persistent headache—seen in over 80% of patients—is the most common symptom.
- Focal signs of an intracranial mass lesion (e.g. hemiparesis, focal seizure, aphasia) may be present but their absence does not rule out brain abscess.
- Only about 50% of patients present with fever—many patients lack the signs (fever, chills, leukocytosis) commonly seen in infection.
- Headache accompanied by nausea and vomiting suggests increased intracranial pressure—examine the patients fundi for signs of papilledema.

2. What are the most common sources of brain abscess?

Seeding of the brain from local cranial infection (e.g. otitis, sinusitis, dental infection) accounts for over 50% of cases in most studies (Table 2). Bacteremia from more distant, extracranial infection (endocarditis, lung abscess, intraabdominal infection) is a less common—but important—source of brain abscess. Brain abscess associated with cyanotic congenital heart disease is more common in children but may be problem in the future with increasing numbers of patients reaching adulthood. Most studies show that up to a third of patients may have a "cryptic" brain abscess presenting without an obvious entry point for the infection.

Table 1: Signs/symptoms of brain abscess

Signs and symptoms	% pts with brain abscess*
Headache	84
Fever	55
Nausea/vomiting	50
Cranial nerve palsy	50
Lethargy	40
Hemiparesis	32
Hyperreflexia	33
Aphasia	30
Seizure	30
Nuchal rigidity	24
Papilledema	17

*% of 203 patients—adapted from Consultant Jan,

Table 2: Source of brain abscess

Source	% of pts with brain abscess*
Otitis	26
Sinusitis	16
Dental	10
Extracranial infection†	9
Trauma or neurosurgical	9
CCHD+	7
Pulmonary	6
Miscellaneous	5
Cryptogenic	14

* Total of 121 cases from 2 recent studies
+ Cyanotic congenital heart disease

3. What laboratory and radiographic tests are valuable in diagnosing brain abscess?

Unfortunately, most laboratory tests are non-specific and rarely helpful in diagnosing brain abscess; the leukocyte count and sedimentation rate are often elevated but may be normal in patients with documented brain abscess. Although rarely positive (<5% of cases), obtain blood cultures to help rule out underlying endocarditis.

In those with suggestive symptoms, a cerebral CT scan (with contrast) or a brain MRI are the most sensitive tests for diagnosing brain abscess. **Do not perform a lumbar puncture** in a patient with a suspected brain abscess—patients with brain abscess may have an elevated intracranial pressure and run a significant risk of cerebral herniation following the procedure. In general, cerebrospinal fluid examination is rarely helpful in brain abscess and usually shows a non-specific pleocytosis which is of little diagnostic value.

4. What are the most common pathogens seen in brain abscess? What is the most appropriate initial empiric antibiotic therapy?

Table 3 outlines the most common bacterial pathogens depending upon location and source of the abscess—choice of empiric intravenous antibiotics depends on likely pathogens. Recent studies suggest that cefotaxime and metronidazole—combined with neurosurgical aspiration of the lesion—provides an excellent outcome in the majority of cases with standard bacterial pathogens.

Table 3: Brain abscess in adults: microbiology and empiric antimicrobial therapy

Source of abscess	Site of abscess	Microbial flora	Antimicrobial therapy*
Paranasal sinus Dental infection	Frontal lobe	Aerobic and anaerobic streptococci; anaerobic gram-negative bacteria (e.g. *Fusobacterium, Porphyromonas* species)	Cefotaxime and metronidazole
Otogenic infection	Temporal lobe, cerebellum	Streptococci, Enterobacteriaceae *Bacteroides* species (includes *B. fragilis*) *Pseudomonas aeruginosa*	Penicillin, metronidazole and ceftazidime
Metastatic spread	Multiple cerebral lesions common, especially in middle cerebral artery distribution, but any lobe can be involved	Depends on source: Endocarditis *Staphylococcus aureus*, viridans streptococci Urinary tract Enterobacteriaceae, Pseudomonaceae† Intra-abdominal Streptococci, Enterobacteriacea,,anaerobes Lung Abscess Streptococci, anaerobes	Nafcillin, metronidazole and cefotaxime
Penetrating trauma	Depends on site of wound	*Staphylococcus aureus* *Clostridium* species Enterobacteriaceae	Nafcillin and cefotaxime
Postoperative	Depends on site of neurosurgical procedure	*Staphylococcus epidermidis* *Staphylococcus aureus* Enterobacteriaceae Pseudomonaceae	Vancomycin and ceftazidime or cefepime

* Base initial empiric antimicrobial therapy on probable source of abscess; base subsequent therapy on culture and Gram stain results.
† Use cefipime or ceftazidime instead of cefotaxime if *Pseudomonas aeruginosa* is suspected.

In suspected pyogenic brain abscess, keep in mind the following...

- **Take a careful history:** Question the patient about potentially "entry" points including recent dental work (or toothaches), sinusitis, skin infections and recent hospitalization (e.g. line infections). Specifically ask the patient about HIV risk factors and a history of TB exposure.

- **Perform a careful physical exam:** In addition to a neurological examination (? Focal findings), make sure you perform a careful dental exam (? Any tooth abscess or severe gingivitis), ear examination (? Chronic otitis) and cardiac auscultation (? Heart murmur suggesting endocarditis).

- **Important laboratory studies:** In addition to routine blood counts and serum chemistries, obtain the following:
  - ✓ **Blood cultures:** Checks 3 sets and review chart for previous bacteremia episodes
  - ✓ **HIV testing:** Toxoplasmosis, Cryptococcus and lymphoma can mimic pyogenic brain abscess
  - ✓ **RPR/TPPA:** Syphilitic gumma can present with focal mass lesions
  - ✓ **PPD:** In immunocompromised patients, TB may present as a tuberculoma

- **Radiographic studies:** In addition to standard cerebral scans (CT scan; MRI), consider the following tests in selected cases:
  - ✓ **Dental X-rays:** ? Occult dental abscess
  - ✓ **Sinus films:** ? Sinusitis—this is often apparent on CT scan
  - ✓ **Echocardiogram:** R/O underlying endocarditis or intracardiac shunt (open Foramen of Ovale)
  - ✓ **Cerebral PET scan** may aid in differentiating infection from cerebral neoplasm

- **Consider brain abscess "mimics",** especially brain tumors (primary or metastasis), demyelinating disease ("tumefactive" MS can mimic brain abscess) and HIV-related conditions (e.g. toxoplasmosis, cryptococcosis, lymphoma)

- **? Empiric antibiotics:** In non-toxic, stable patients, delay therapy till diagnostic needle aspiration. Consider empiric antibiotic therapy in febrile, septic patients especially those with severe or progressive neurological deficits. Choose empiric antibiotic therapy based on the likely source (see Table 3).

- **Neurosurgery:** Most patients with pyogenic brain abscess will require neurosurgical intervention for diagnostic needle aspiration or therapeutic drainage of the lesion. Obtain a neurosurgery consult as soon as possible.

Housestaff primer—Management of sepsis and septic shock

1. What is the definition of sepsis and septic shock?

The term "sepsis" has been used rather loosely in the past. Investigators in the early 1990s needed a common set of criteria as a means of defining the condition for clinical trials. They recognized that following an insult, there is a continuum of patient response that ranges from mild (SIRS) to severe (severe sepsis or septic shock)…

Infection/Trauma → SIRS → Sepsis → Severe Sepsis

SIRS: Systemic Inflammatory Response Syndrome-A clinical response arising from a nonspecific insult. Including ≥ 2 of the following:
- Temperature ≥38 C or ≤36 C
- HR ≥90 beats/min
- Respirations ≥ 20/min
- WBC count ≥12,000/mm3 or ≤4,000/mm3 or >10% immature

Sepsis: SIRS with a presumed or confirmed infectious process

Severe sepsis: Sepsis with ≥ 1 sign of organ failure
-Cardiovascular: Shock (refractory hypotension BP<90 mm Hg)
-Renal
-Respiratory
-Hepatic
-Hematologic
-CNS
-Unexplained metabolic acidosis

2. Early recognition of septic shock:

Early intervention and therapy of sepsis clearly leads to improved outcomes—several hours may make the difference between death and survival. When called about febrile patients, keep in mind the following clinical signs that might be early clues to developing septic shock:

- Unexplained patient confusion
- Mild or severe hypotension
- Increased respiratory rate and respiratory alkalosis
- Unexplained metabolic acidosis
- Leukocytosis or leukopenia

3. Appropriate treatment and interventions:

- **Antibiotics:** Early, prompt antibiotic therapy is *critical* for patient survival. After the initial evaluation, obtain appropriate cultures and choose the most appropriate therapy based on the likely source. Order parenteral antibiotics and make sure they are administered as soon as possible (within 1 hour)—do not assume that the drugs have been given without receiving confirmation!

- **Intravenous fluids:** Following antibiotics, aggressive volume resuscitation with maintenance of an adequate mean arterial blood pressure (MABP=65-75 mm Hg) and urine output (goal, > 20-30 mL/hr) is critical. In hypotensive patients, administer a bolus of 500-1000 cc of IV fluids (isotonic sodium chloride or lactated Ringer's solution) over 5-10 minutes; repeat doses in those with continued hypotension or poor tissue perfusion up to 4-8 liters per 24 hr period). Be cautious in elderly individuals and those with underlying congestive heart failure or low albumin—consider using a pulmonary Swan-Ganz catheter to help gauge fluid administration in those with tenuous cardiac status (maintain PCW between 10-14 mm Hg). The "best" fluid for volume resuscitation remains controversial—each product has both advantages and disadvantages:

  ✓ **Crystalloids:** 0.9% Normal saline or Lactated Ringer's Solution are most readily available but more likely to lead to peripheral and pulmonary edema as they leave the intravascular space.

- ✓ **Colloids:** 5% Human serum albumin or hydroxyethyl starch are more costly but less likely to precipitate pulmonary edema since fluid is more contained within the intravascular space.
- ✓ **Blood products:** Consider whole blood in those with severe anemia (HgB < 10 g/dL) and evidence of decreased oxygen delivery or underlying coronary artery disease.

- **Vasoactive agents:** If blood pressure remains low following a fluid challenge, start a vasoactive agent to maintain mean arterial blood pressure between 65 to 75 mm Hg. A randomized control study of 32 patients with septic shock unresponsive to fluids demonstrated improved hemodynamics, increased urine output and faster resolution of lactic acidosis in those receiving norepinephrine in comparison to dopamine.

Drug	Dose	Comments
Norepinephrine	0.05-5 ug/kg/min	Drug of choice for patients with septic shock Superior to dopamine in controlled studies
Dobutamine	5-20 ug/kg/min	Useful in patients with persistently low cardiac index or LV dysfunction
Dopamine	5-20 ug/kg/min	Weak vascoconstrictor—not generally recommended in septic shock
Epinephrine	0.05-2 ug/kg/min	Similar to norepinephrine
Phenylephrine	2-10 ug/kg/min	Similar to norepinephrine but little effect on cardiac output
Source: Fitch SJ, Gossage JR. Postgrad Med 2002;111:53-66.		

- **Oxygen balance:** Lactic acidosis reflects poor tissue perfusion secondary to hypotension and local tissue abnormalities. Although unproven in randomized control trials, supplemental oxygen is likely to be helpful in septic patients. Intubate and mechanically ventilate patients with low pO_2—especially in those with underlying lung disease, severe pneumonia or risk factors for aspiration.

- **Additional adjunctive measures:** The following adjunctive measures have been utilized in patients with septic shock:

  - ✓ **Corticosteroids:** Use of corticosteroids is controversial. Studies from earlier periods (1980s and 1990s) *failed* to demonstrate significant benefits from steroid administration in sepsis. Nevertheless, a recent placebo controlled trial in septic shock demonstrated a trend towards improved survival in those receiving corticosteroids (hydrocortisone 100 mg IV q 8hr). Consider the use of corticosteroids in those with suspected adrenal insufficiency—especially patients with a previous history of corticosteroid therapy or individuals with possible meningococcemia.

  - ✓ **Temperature control:** At least one study suggests that fever control may improve oxygen consumption septic patients. Use acetominophen (per NG tube or suppository) in patients with high fever (> 40°C)—especially in patients with limited cardiac reserves. *Avoid* use of an external cooling blanket except in those with extreme hyperthermia (temp > 41.5 °C) or heat shock—in septic shock, a cooling blanket may *increase* oxygen consumption and has no benefit over simple antipyretic agents.

  - ✓ **Recombinant human activated protein C (rhAPC):** Consumption of protein C and uncontrolled intravascular clotting play a role in the severe end-organ damage seen in patients with severe sepsis. A large randomized placebo-control trial (1,600 patients) of rhAPC (drotecogin alpha; Xigris®) in severe sepsis demonstrated a 6.1% reduction in mortality at 28 days. *Exclusion criteria* include bleeding risk (platelet ct.<30K; recent heparin, coumadin or aspirin, thrombolytic therapy); GI bleed within 6 weeks, risk of CNS bleed (recent head trauma, cerebral aneurysm, recent stroke, need for intracranial surgery);chronic renal failure requiring dialysis; liver disease with cirrhosis, jaundice or chronic ascites; known hypercoaguable state; history of transplantation (bone marrow,lung,liver, pancreas or small bowel) or acute pancreatitis.

Staphylococcal bacteremia...Five questions to guide therapy

Staphylococcus aureus remains common and potentially dangerous pathogen, causing anything from potentially "minor" skin infections (e.g. boils, carbuncles) to life-threatening bacteremia. When confronted by a case of staphylococcal bacteremia,ask yourself the following questions:

1. Who is at risk for staphylococcal bacteremia?

Anyone colonized with *Staphylococcus aureus* can develop staphylococcal bacteremia; however, the risk varies depending upon factors such as presence of indwelling catheters, underlying immunodeficiency (HIV; chemotherapy) and various chronic medical conditions (diabetes, alcohol abuse, rheumatological disease). The following table gives an idea of the relative risk (compared to the "normal" host) of staphylococcal bacteremia:

Table 1: Risk of Invasive *Staph aureus* infection*

Underlying condition	Relative risk
Hemodialysis	257
Peritoneal dialysis	150
HIV	24
Solid organ transplantation	21
Heart disease	21
Cancer	13
Intravenous drug use	10
Alcohol abuse	8
Diabetes mellitus	7
Stroke	6
COPD	4
SLE/Rheumatoid arthritis	2

Adapted from Laupland KB eta al. JID 2003;187:1452-9

- ✓ **Hemodialysis patients** clearly have the highest rate of staphylococcal bacteremia—in the febrile dialysis patient, always consider anti-staphylococcal coverage in the septic patient.
- ✓ **Inherited leukocyte defects** including Hyper-IgE syndrome (Job's syndrome), Chediak-Higashi syndrome and Down's syndrome also place patients at greater risk for staphylococcal bacteremia.

2. What is the source of the bacteremia?

In many cases, a careful history or physical examination will ferret out the source of staphylococcal bacteremia. *Staphylococcus aureus* is commonly found on the skin—not surprisingly, skin infection such as cellulitis, boils and impetigo are common sources for this condition. In patients with nosocomial (or healthcare-associated) bacteremia, the presence of an infected, indwelling catheter is an especially common source. When trying to determine the source of staphylococcal bacteremia, look for the following sources:

- ➢ **Skin infection:** In community-acquired cases, there is almost always a history of some skin infection or skin breakdown. Question the patient carefully about recent boils, impetigo or paronychia—even seemingly minor infections might be the source for a potentially life-threatening bacteremia. Patients with underlying skin conditions (e.g. psoriasis; atopic dermatitis) are also at risk for staphylococcal bacteremia—these patients are more likely to be colonized with *Staph aureus* and the skin breaks provide a ready entry point.
- ➢ **Intravenous devices:** Indwelling catheters are an especially common source in hospitalized patients—even if the catheter appears uninfected, if present for > 48 hours it is very likely to be a potential source.

- **Intravenous drug use:** Of course, the individual who is constantly injecting themselves remains at high risk for staphylococcal bacteremia—these individuals are likely to be *Staph* carriers and introduce the bugs if the skin is not properly decontaminated (the drugs themselves are rarely contaminated with *Staph* aureus).

3. Does the patient have endocarditis?

After you've established that the patient has the real thing—and not just a blood culture "contaminant"—the next step is to determine if they've got underlying endocarditis. Although there is variability between populations, studies suggest that approximately 15-40 % of individuals with staphylococcal bacteremia will have underlying endocarditis. In patients with presumed staphylococcal bacteremia, carefully examine the patient for the following signs of endocarditis:

- **Murmur:** Is there a new or changing cardiac murmur? New diastolic (aortic regurgitation) or regurgitant murmurs (mitral regurgitation; tricuspid regurgitation) are of particular significance. Listen for an AR murmur by having the patient lean forward and exhale.
- **Peripheral signs:** Peripheral signs of endocarditis are not especially common but look for the presence of petechial eruption (conjunctiva; anterior chest; oral cavity), Osler's nodes (10%), Janeway lesions (10%) and splinter hemorrhages (10%), all of which point to the possibility of underlying endocarditis. Make sure you check for presence of underlying splenomegaly and urinalysis abnormalities (especially presence of staphylococcus in the urine), both of which are further supportive of a diagnosis of infective endocarditis.
- **Myocardial abscess:** Does the patient have an aortic root abscess? Check the exam for an aortic regurgitation murmur and the EKG for signs of first, second or third degree heart block.
- **Echocardiogram:** Obtain an echocardiogram; a TTE has a sensitivity of 60%--a TEE is over 90% sensitive in detecting underlying endocarditis.

4. Has the bacteremia seeded other organs?

Important because of the therapeutic implications (and a common cause of persistent fever), staphylococcal bacteremia commonly causes "metastatic" infection to other organs. In any patient with staphylococcal bacteremia, look for evidence of embolic infection in the following organs:

Know the numbers—"Staph" bacteremia and associated complications

Outcomes	#	%*
Uncomplicated	412	
Complicated	228	
Infective endocarditis	89	39
Septic arthritis	54	24
Deep tissue abscess	41	18
Vertebral osteomyelitis	22	10
Epidural abscess	17	8
Septic thrombophlebitis	17	8
Psoas abscess	13	6
Meningitis	12	5
Other complications	16	7
Mycotic aneurysm	5	
Empyema/Pneumonia	5	
Pericarditis	3	

* % of complications

A six year study of over 700 patients with staphylococcal bacteremia outlines the relative incidence of complications. Over a third of cases (228 pts) had "complicated" infection evidenced by infective endocarditis (39%), septic arthritis (24%) and/or distant metastatic spread. Mortality was approximately 20% in patients with complicated SAB compared to 10% in patients with uncomplicated SAB.

When you evaluate a patient with staphylococcal bacteremia, look specifically for the following complications:

- **Brain abscess:** Large brain abscesses are uncommon following staphylococcal bacteremia—CNS involvement is more likely to be due to cerebral microabscesses that cause headache and global confusion.
- **Mycotic aneurysm/CNS bleed:** A mycotic aneurysm may become symptomatic at any time during therapy—be especially wary if patients complain of new onset moderate-severe headache. If in doubt, perform a lumbar puncture (? CSF hemorrhage) and MRI angiogram.
- **Purulent pericarditis:** In patients with chest pain, listen carefully for a pericardial friction rub and check the EKG for signs of diffuse ST-T wave elevation
- **Septic pulmonary emboli:** Most common with tricuspid endocarditis, patients with septic pulmonary emboli present with chest pain/cough, pleural friction rub and wedge-shaped infiltrates on chest radiograph.
- **Splenic abscess:** Patients will complain of RUQ pain—on physical examination look for splenomegaly, RUQ tenderness and the presence of a RUQ friction rub.
- **Perinephric abscess:** Patients complain of flank pain and have costovertebral angle tenderness on physical examination.
- **Epidural abscess:** Patients will complain of back pain and usually have localized spinal tenderness. Neurological abnormalities (sensory level, decreased rectal tone, loss of reflexes) are seen as a *late* manifestation of illness. Check a spinal MRI.
- **Septic arthritis:** Check all joints for warmth, erythema and effusion.

5. What is the recommended therapy for staphylococcal bacteremia?

Therapy for staphylococcal bacteremia depends upon the likely source, presence of endocarditis and susceptibility of the infecting organism. The following guidelines are only suggestions for therapy—individual cases may require longer duration treatment depending upon possible complications.

Condition	Comments	Therapy
Bacteremia from IV line (no endocarditis)	Remove line and √ for endocarditis (TTE)	2 weeks IV oxacillin *†
Tricuspid endocarditis		
Uncomplicated	No evidence of septic foci (aside from lung infiltrates) with prompt response to antimicrobials	2 weeks IV gentamicin + oxacillin
Complicated	Septic foci; persistent fever	4-6 weeks IV oxacillin (± gentamicin x 5 days)
Left-sided endocarditis		
Uncomplicated		4-6 weeks IV oxacillin
Complicated-root abscess	Antibiotics + hemodynamic stabilization + surgery	IV oxacillin + surgery
Penicillin allergy		
Non-anaphylaxis	Maculo-papular rash only; no hives/wheezing	IV cefazolin‡
Anaphylaxis	Hives, wheezing, hypotension—avoid B-lactam	IV vancomycin§

* Nafcillin or oxacillin: 2 gm IV every 4 hr
† Optional addition of gentamicin: 1 mg/kg IM or IV every 8 hrs for 3-5 days; Benefit of additional aminoglycosides has not been established.
‡ Cefazolin: 2 gm IV every 8 hr; other first-generation cephalosporins may be used in equivalent doses; AVOID use in patients with immediate-type hypersensitivity to penicillin.
§ Vancomycin: 30 mg/kg per 24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored.
(Note: For all patients, rifampin (300 mg PO q 8 hr) should be considered in patients with persistent bacteremia or fever)

Common questions and controversies:

What about therapy in the penicillin-allergic patient?

Use first-generation cephalosporins (e.g. cefazolin) in patients with less serious reactions to penicillin (e.g. maculopapular rash). Patients with a history of serious, life-threatening reactions (e.g anaphylaxis) should receive an alternative agent such as vancomycin.

What are the chances of treating bacteremia without removal of an infected catheter?

Not very good if the patient has *Staphylococcus aureus* sepsis. This is a difficult bug to treat and antibiotic therapy-alone is usually unsuccessful—if possible, remove the catheter as early as possible. This is not necessarily the case with *Staphylococcus epidermidis* bacteremia; although catheter removal is usually the best policy, patients can sometimes be treated with a prolonged course (2-4 weeks) of intravenous antibiotic.

What are the indications for valve surgery in infective endocarditis?

The following are indications for surgical excision of an infected cardiac valve…

- **Persistent bacteremia** (>1 week) despite appropriate therapy and no other obvious source.
- **Large vegetation** (> 1 cm) with persistent bacteremia (> 1 wk) or previous embolism
- **Refractory heart failure** secondary to valve destruction or poorly controlled infection.
- **Aortic root or mitral valve ring abscess**
- **"Resistant" organisms** unresponsive to antibiotic-therapy alone including fungi, Q fever, *Brucella* species, mycobacteria.
- **Prosthetic valve endocarditis**

What to do if your patient has staphylococcal bacteremia…

- ❑ **Identify an entry point:** Look for a focal skin infection, history of a line or IVDU.
- ❑ **Exclude endocarditis:** Examine the patient carefully for a murmur or the peripheral signs (skin changes, splenomegaly) of endocarditis. Most patients should have an echocardiogram—a TEE has a higher sensitivity (95%) than a TTE (65%), but the TTE is a convenient screening test.
- ❑ **Rule out metastatic foci** such as vertebral osteomyelitis, perinephric abscess, septic arthritis and splenic abscess. A thorough physical exam (with "targeted" radiographs) usually does the trick.
- ❑ **Check antibiotic susceptibilities:** Does your patient have MSSA or MRSA—call the laboratory to find out the MICs of the organism.
- ❑ **Start antibiotics** depending upon the likely susceptibilities of the organism. It may be safest to use vancomycin until the susceptibilities are available. Length of therapy depends on the likelihood of endocarditis and the presence of metastatic foci.
- ❑ **Consider the need for surgery:** Patients with valve involvement or metastatic foci (e.g. perinephric abscess, septic arthritis, epidural abscess) may require surgery.

Disseminated Gonococcal Infection

Disseminated gonococcal infection (DGI) is the most common cause of septic arthritis in adults below the age of 30. It is important to differentiate it from a number of similar rheumatologic conditions (see below) since DGI often responds dramatically to antibiotic therapy. In a patient with fever, rash and arthritis, always consider the possibility of DGI and keep in mind the following points:

1. What is the typical clinical presentation of DGI?

Patients with DGI classically present with signs of fever and skin lesions (arthritis-dermatitis) representing the initial bacteremic spread of the organism. Patients with purulent septic arthritis are thought to represent a later stage of disease after the organism localizes to a specific joint. In reality, there is considerable clinical overlap among these syndromes and signs of focal infection (arthritis, endocarditis, meningitis) may be the patient's presenting complaint. Paradoxically, patients with DGI usually *do not* complain of urethritis or cervicitis—the *Neisseria* strains responsible for DGI often fail to illicit signs or symptoms at the initial site of infection. Clinicians categorize DGI into one of several clinical syndromes…

Syndrome	Clinical features	% Pts
Arthritis-dermatitis	Triad of fever, arthritis (migratory polyarthralgia, tenosynovitis) and dermatitis. The tenosynovitis is usually asymmetric, and located on flexor/extensor tendons of the wrist and hand. Dermatitis: Erythematous macules that evolve to hemorrhagic/necrotic pustules. More common in upper extremities; rare on face, neck and lower extremities	60
Monoarticular arthritis	Knee most common but also seen in hip, wrist, finger joints WBC in joint usually > 30K with poly predominance. Requires more prolonged parenteral antibiotic therapy	40
Rare syndromes		< 5
Endocarditis	Acute endocarditis with rapid destruction of aortic valve Rare cases of purulent pericarditis	
Meningitis	Clinical presentation similar to other causes of bacterial meningitis	
Perihepatitis	Fitzhugh-Curtis syndrome(GC perihepatitis) presents with RUQ pain and ↑ LFTs Friction rub over liver may sound like person "running through deep snow".	

2. What tests will confirm the diagnosis of DGI?

The diagnosis of DGI depends primary on the presence of characteristic clinical findings and response to a therapeutic trial of antibiotics. Nevertheless, in order to confirm your clinical suspicion—and rule out the possibility of other conditions—obtain blood, joint fluid and mucous membrane cultures where indicated. Culture and Gram stain any **skin lesions**—the yield is low but could provide clues to the correct diagnosis. Aspirate any **joint** with suspected fluid and send off a leukocyte count and glucose in addition to cultures for *Neisseria gonorrhea*. Attempts to aspirate a tenosyovitis are generally not indicated because of the extremely low yield.

Patients with DGI are often asymptomatic carriers of *N. gonorrhea* on **mucous membranes** –in those with suspect DGI, *always* obtain urethral (male), cervical (female), rectal and pharyngeal cultures despite absence of symptoms. *Neisseria gonorrhea* is a fastidious organism that quickly dies in transport—use special transport swabs or request appropriate agar media from the laboratory (Thayer-Martin media) and plate the screening cultures at the bedside

The following table shows the effectiveness of various laboratory screening measures in DGI:

	Percent of patients with positive test	
Site	**Culture**	**Gram stain**
Skin lesions	10	10
Joint fluid	20-30	10-30
Blood	10-30	—
Mucosal (pharyngeal, urethral, cervix, rectum)	80-90	—

3. What is the appropriate therapy for DGI?

Patients with DGI usually respond dramatically to appropriate antibiotic therapy— always question the diagnosis if such a response fails to occur. The tenosynovitis begins improving within 24 hours and is frequently completely gone within 3 to 4 days; the septic arthritis also improves rapidly although usually slower than tenosynovitis. Frequent needle aspiration or open drainage of a septic joint is rarely necessary in DGI—reserve these procedures for patients who fail to respond to therapy or when the causative organism is in doubt. Although *Neisseria gonorrhea* strains causing gonorrhea are often resistant to penicillin (over 30% of cases), isolates responsible for DGI are usually exquisitely sensitive to the drug. The following table gives the most recent CDC recommendations for therapy of uncomplicated DGI:

Treatment†	**Alternative regimens**
Ceftriaxone 1 g IM or IV every 24 hours.	Cefotaxime 1 g IV every 8 hours,OR Ceftizoxime 1 g IV every 8 hours,OR Ciprofloxacin 400 mg IV every 12 hours, OR Ofloxacin 400 mg IV every 12 hours, OR Levofloxacin 250 mg IV daily, OR Spectinomycin 2 g IM every 12 hours
All of the preceding regimens should be continued for 24--48 hours after improvement begins, at which time therapy may be switched to one of the following regimens to complete at least 1 week of antimicrobial therapy:	
Cefixime 400 mg orally twice daily,OR Ciprofloxacin 500 mg orally twice daily, OR Ofloxacin 400 mg orally twice daily, OR Levofloxacin 500 mg orally once daily.	

Not proven in trials for DGI but likely to be effective based on antimicrobial susceptibilities
† Prolonged, higher dose parenteral therapy required for patients with endocarditis and meningitis
Source: 2002 CDC Recommendations for Rx of Sexually Transmitted Diseases

Hospitalization is recommended for initial therapy, especially for patients who may not comply with treatment, for those in whom diagnosis is uncertain, and for those who have purulent synovial effusions or other complications. Patients treated for DGI should be treated presumptively for concurrent *C. trachomatis* infection, unless appropriate testing excludes this infection.

4. What other conditions can mimic DGI?

In patients who present with a fever and arthritis—or in those who fail to respond to antibiotic therapy—keep in mind other conditions that will mimic DGI:

Table: Mimics of Disseminated Gonnococcal Infection	
Meningococcemia	Caused by related organism (*Neisseria meningiditis*) and can completely mimic DGI Rash tends to be more petecchial, purpuric rather than pustular or bullous Tenosynovitis rare in meningococcemia; joint involvement less common than DGI
Endocarditis/bacteremia	Bacteremia from other organisms (staphylococci, strep, GNR) can mimic DGI Endocarditis rarely causes tenosynovitis or frank septic arthritis
Rheumatic fever (RF)	May have preceeding history of pharyngitis in RF RF:migratory arthralgias/arthritis with pain out of proportion to findings on PEX Rash in RF (erythema migrans) different from DGI Evidence of Group A streptococcal infection (+ throat culture; + strep serology)
Reiter's syndrome (RS)	Often causes symmetric oligoarthritis (e.g. involvement of both knees) rare in DGI Psoriaform rash on palms and soles (keratoderma blennorrhagicum) distinctive in RS Circinate balantis (erythema on glans penis), oral ulcers, red eyes also seen in RS Fails to respond to antibiotics; Rx with NSAIDS
Other connective tissue syndromes	Systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis mimic DGI Usually can be differentiated by lack of response to antibiotic and other clinical features

Disseminated gonococcal infection—Points to remember...

- ✓ **Clinical presentation**: Always consider the possibility of DGI in a patient with fever, rash and arthritis.
- ✓ **Appropriate cultures:** Patients with DGI rarely complain of symptomatic urethritis or pharyngitis—make sure to obtain blood cultures as well as screening cultures of the urethra, cervix, pharynx and rectum in suspected cases.
- ✓ **Response to therapy:** DGI patients usually improve dramatically on appropriate antibiotics—question the diagnosis in those failing to respond to therapy.

Sources:
1. Cucurull E, Espinoza LR. Gonococcal Arthritis in *Rheum Dis Clin NA.* 1998 24:305-22.
2. Mills J. Brooks GF. Disseminated Gonococcal Infection in *Sexually Transmitted Diseases* ed. Holmes. 1984.

Syphilis serology—Managing a + RPR

Despite a confusing "alphabet soup" of laboratory tests, an understanding of syphilis serology is vital for both diagnosis and management of the condition. Fortunately, a simple classification will help clear up the confusion to ensure that you don't miss this important diagnosis…

1. **Syphilis serology:** Keep in mind that all syphilis serology can be divided into one of two types of tests—**non-treponemal tests** (used for screening and following therapy) and **treponemal tests** (used for confirmation of infection):

   Non-treponemal tests: The non-treponemal tests relying on host antibody response to cardiolipin—a host tissue lipopolysaccharide antigen exposed following treponemal infection. Although non-specific—there are a number of causes of false positive tests (see Table 1)—**non-treponemal** tests remain the basis for syphilis screening and therapeutic monitoring. The following tests are commonly available…

   - **RPR (Reactive Positive Reagin)**
   - **VDRL (Venereal Disease Research Laboratory)**

   The laboratory reports these tests with a titer—in those with primary or secondary syphilis, a four-fold decrease in titer should occur with successful therapy.

   Table 1: Causes of False positive non-treponemal tests

Acute condition (< 6 months)		Chronic condition (> 6 months)
Pneumonia Viral Pneumococcal Mycoplasma Hepatitis Tuberculosis Infectious mononucleosis Chancroid	Chickenpox HIV Measles Malaria Immunizations Pregnancy Laboratory error	Liver disease Malignancy Intravenous drug use Aging Connective tissue disorders Multiple blood transfusions
Table from Birnbaum NR et al. Amer Fam Phys 1999:		

   Treponemal tests: Based on detection of antibody against treponeme-specific antigens, treponemal tests are more specific than non-treponemal tests and generally remain positive for life. The test is either positive or negative—they are not reported as a titer and will *not* become negative following therapy. In all patients with a + RPR, check one of the following tests to confirm the diagnosis of syphilis:

   - **FTA-ABS (Florescent treponemal antibody absorbed)**
   - **MHA-TP (Microhemmaglutinin antibody-treponema pallidum)**
   - **TPPA (Treponema pallidum particle agglutination)**

   TPI (Treponema pallidum immobilization): The "gold standard" of syphilis serology, this test has an extremely low false-positive rate but requires maintenance of supply of live *Treponema pallidum* organisms—something only available in a few research laboratories. When patient serum is added to a preparation of live treponemes under microscopic examination, immobilization of the organisms indicates presence of specific anti-treponemal antibody. This test is helpful in the rare situation (connective tissue disease) when a positive treponemal test is thought to be false-positive.

As compared to non-treponemal tests (e.g. RPR, VDRL), treponemal tests are much less likely to be false positive. Nevertheless, false positive tests are occasionally seen with selected acute conditions (see Table 2)

and chronic, long term diseases such as SLE. If you suspect a "false positive" treponemal test, consider obtaining a TPI test (see above description).

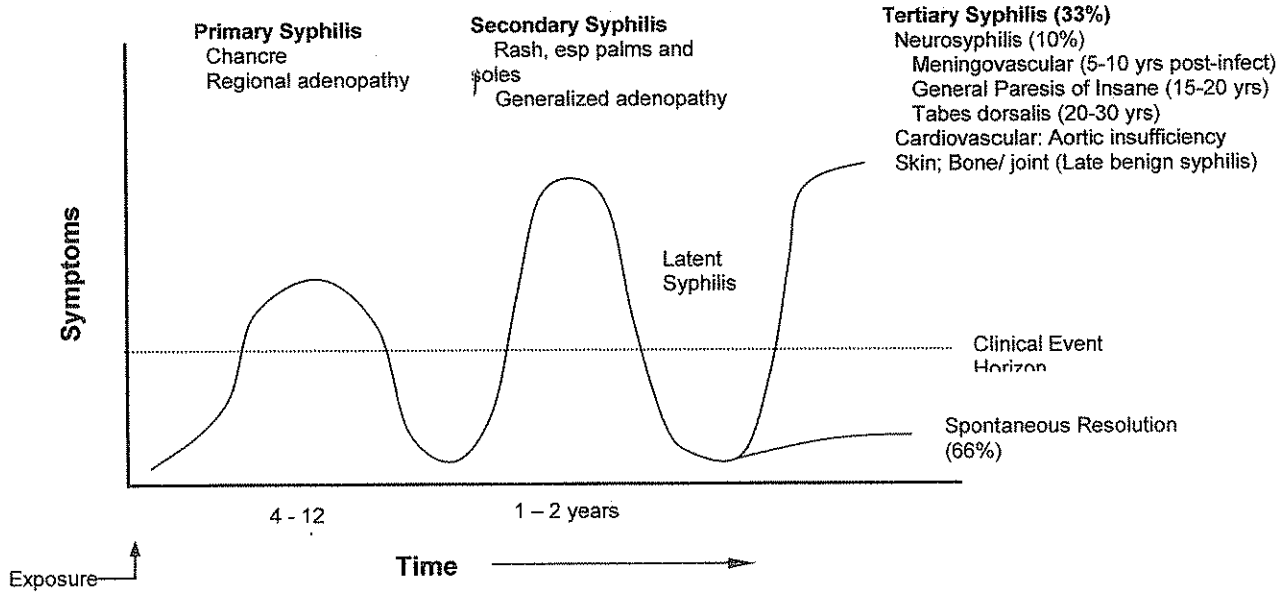
Table 2: Causes of false-positive treponemal serologic tests for syphilis

Acute condition (<6 months)	Chronic condition (> 6 months)
Infectious mononucleosis Lyme disease Leprosy Malaria	Systemic lupus erythematosus
Table from Birnbaum NR et al. Amer Fam Phys 1999:	

2. Clinical staging of syphilis

Decisions about syphilis treatment require "staging" the disease, based on the clinical presentation and serological results. Several features of this approach should be kept in mind…

- ✓ **Primary syphilis:** In a patient with suspected primary syphilis (chancre; local adenopathy), duration of the lesion will influence the likelihood of positive, confirmatory serology—a positive test may be negative in early stages of ulcer formation (first 1-2 weeks) but should be positive by week #4.
- ✓ **Secondary syphilis:** Almost all patients with clinical secondary syphilis have positive serology by standard testing.
- ✓ **Tertiary syphilis:** In about a third of patients with late stage syphilis, the standard non-treponemal screening test (RPR) *may be negative*—obtain a "treponemal" test (e.g. MHA-TP; TPPA; FTA-ABS) if you suspect late disease.



RPR	90 %	100 %	60 %
TPPA	90 %	100 %	95-100 %

How to manage the patient with a positive syphilis serology...

❑ Ask the patient about a previous history of syphilis or positive serology...

- ✓ Has the patient ever received an "injection" for treatment of an STD?
- ✓ Were any sexual partners diagnosed with syphilis or STDs?
- ✓ Ask if patient's parents had a + test for syphilis or "bad blood" ?
  (The patient's positive serology could be secondary to congenital syphilis)
- ✓ ? History of residence in rural Africa, Latin America or Middle East
  (exposure to Yaws, Pinta or Bejel will give + RPR and TPPA)

❑ Examine the patient carefully for clinical signs of syphilis

- ✓ Examine the genitalia, rectum and oral cavity for presence of chancre or local adenopathy
- ✓ Look for signs of secondary syphilis (rash, generalized adenopathy, oral/rectal lesions)
- ✓ Examine the patient for the clinical findings of congenital syphilis:
  Frontal bossing, Hutchinson's incisors, saddle-nose deformity, interstitial keratitis
- ✓ Look for signs of tertiary syphilis...
  Cardiovascular: ? Aortic regurgitation murmur; Aortic aneurysm c "eggshell" calcification
  Neurosyphilis: ? Argyle-Robinson pupil: accommodates to late but doesn't react
  ? Presence of Babinski sign
  ? Focal neurological findings
  ? Dementia or personality change

❑ Determine whether a lumbar puncture is necessary:

- ✓ Patient has neurological or ophthalmic signs/symptoms on examination
- ✓ History of extraneurologic tertiary syphilis (cardiovascular; bone/joint; skin; gummas)
- ✓ Treatment failure (serum titer fails to decrease fourfold after therapy)
- ✓ Asymptomatic patients with late latent syphilis (> 2 yrs) or syphilis of unknown duration
  (Some experts recommend LP in asymptomatic HIV/AIDS pts only if titer ≥ 1:16)

❑ Treat the patient according to CDC guidelines*...

Syphilis stage	Treatment
Primary, secondary or early latent (duration < 1 year)	Benzathine penicillin (2.4 million units) IM q wk x 1 wks
Late latent or tertiary syphilis (Cardiovasc; skin; bone)	Benzathine penicillin (2.4 million units) IM q wk x 3 wks
Neurosyphilis	Penicillin G 4 million units IV q 4 hr x 2 wks *or* Procaine penicilln 2.4 mu (IM) q day x 2 wks + daily probenacid
* see	

Note: Always ask patient about history of penicillin-allergy prior to treatment!

A Neurosyphilis Primer

In the preantibiotic era, neurosyphilis was a widespread problem that accounted for up 20% of admissions to long-term psychiatric facilities. In the "modern" penicillin era, central nervous system syphilis is far less common; however, diagnosis is often delayed because of atypical clinical presentations or failure of the physician to consider the diagnosis. The clinical presentation often depends upon the time since primary infection—acute syphilitic meningitis is an early manifestation (within 1-2 years of primary infection) whereas conditions such as general paresis or tabes dorsalis may take up to 30 years to develop. While the following "classic" syndromes are well described in the textbook, keep in mind that some patients may present with signs or symptoms suggesting an overlap of these syndromes:

1. Acute syphilitic meningitis (1-2 yrs post infection):

- Patients present with an acute "aseptic meningitis" picture characterized by fever, headache, photophobia and meningismus; less than 10% of patients have the typical rash commonly seen in secondary syphilis.
- Typically occurs within 1-2 years following primary infection
- Associated findings include cranial nerve abnormalities (40%) with III, VI, VII and VIII (deafness) being most prominent. Rare patients develop hydrocephalus or signs of cerebral involvement such as seizure, aphasia, delirium or hemiplegia.
- Cerebrospinal fluid examination (CSF) shows a mononuclear cell pleocytosis (10-500 cells/mm^3), low CSF glucose (40% of cases) and elevated CSF protein. Using modern tests, the CSF and serum serology is almost always positive.
- Patients respond promptly to high dose intravenous penicillin G.

2. Meningovascular syphilis (5-10 yrs post infection):

- Usually presents 5-10 years after primary infection with median age of 30-50 years old.
- Patients suffer from infarction of small-medium size cerebral vessels secondary to an obliterative endarteritis.
- In addition to fever and headache, clinical findings include hemiparesis (85%), aphasia (31%), and seizures (14%) depending upon the location of the vessel affected.
- CSF examination shows a CSF pleocytosis (10-100 cells/mm^3); CSF VDRL is almost always positive
- A spinal form of meningovascular syphilis is seen in less than 5% of cases. Patients with **spinal vascular syphilis** (1-2 years following primary infection) present with a sudden onset of flaccid paralysis due to an acute spinal transverse myelitis. **Syphilitic myelomeningitis** is usually gradual or delayed in onset (20-25 years following primary infection) and presents with lower extremity weakness similar to multiple sclerosis or subacute combined degeneration of the cord (B12 deficiency).
- Prognosis is good if penicillin is instituted early although patients may suffer some permanent neurologic damage due to vascular strokes.

3. General paresis (15-20 yrs post infection):

This is the cerebral parenchymal form of syphilis responsible for the classic psychiatric manifestations described with the disease. It typically occurs 15-20 years following primary infection although its' onset may be much earlier in selected cases.

- **Clinical presentation:** At the onset, the clinical manifestations may be quite subtle with personality changes, increased forgetfullness and depression. In later stages of the disease (2-5 years following onset) patients develop full-blown dementia and severe psychiatric disorders. PARESIS is a helpful mnemonic for remembering the primary manifestations of the disease:

Personality changes: Emotional lability, carelessness in appearance, inappropriate behavior

Affect: Depression is most common; some will develop paranoia, mania and grandiose delusions

Reflex: Focal neurological findings may be found—especially in advanced stages of disease

Eye: Pupillary abnormalities (unequal, poorly reactive to light) are common (57%) including the classic Argyle Robertson pupil (small, fixed pupils—accommodate but do not react to light) in later stages (25% of cases).

Speech: Slurred speech is common (28% of cases) in early stages with late onset of aphasia

Intellect: Gradual memory loss; impaired ability to learn and concentrate.

Seizures: Focal and generalized seizures are common as the disease progresses

- **Diagnosis:** Up to 50% of cases will have a *negative* serum non-treponemal serology. The CSF is almost always abnormal with pleocytosis, elevated protein or a positive VDRL.
- **Response to penicillin** therapy is variable—patients with early diagnosis often improve with treatment although individuals with advanced disease typically have a poor prognosis.

4. Tabes dorsalis (20-25 yrs post infection):

- Uncommon in developed countries, tabes dorsalis is due to chronic granulomatous inflammation of the spinal cord and posterior roots. The disease has a relatively late onset (20-25 years after primary infection) and is typically seen in the fifth and sixth decade of life.
- Clinical features of the syndrome include:

Symptom/sign	Comment
Pupillary abnormalities (94%)	There is sluggish pupillary reaction to light in early tabes with the classic Argyle Robertson pupil (48%) in later stages of the disease.
Reflex abnormalities (80-95%)	Posterior root involvement leads to diminished ankle and knee jerk reflexes; Babinski sign usually absent although may be seen if meningovascular syphilis is present.
Lightning pains (75%)	Sudden, severe paroxysms of pain that most commonly occur in the lower extremities; may be intermittent or last for days.
Ataxia (48%)	Ataxia is more common with advanced stages of disease. Patients typically develop a broad-based, stamping gait due to vision loss and changes in position sense.
Bladder disturbances (33%)	Involvement of sacral roots leads to a flaccid, hypotonic bladder with urinary incontinence.
Paresthesias (24%)	Often accompanied by loss of position and vibratory sense in lower extremities; loss of deep pain perception on forceful pinching of the Achille's tendon.
Visceral crises (18%)	Severe paroxysms of pain in the abdomen, chest, larynx and rectum that mimic surgical conditions such as acute appendicitis or myocardial infarct.

- The serum non-treponemal test (RPR, VDRL) may be *negative* in between 10-40% of cases; the serum treponemal test (TPPA) is positive in almost 100% of cases. CSF findings are variable with a CSF pleocytosis (50%), elevated CSF protein (50%) and a + CSF VDRL (75%).
- Patients should receive high-dose penicillin G although symptoms (e.g. lightning pains) often persist despite treatment.

Source: Swartz M. Chap. 31: Neurosyphilis. In Holmes KH et al. Sexually Transmitted Diseases. McGraw-Hill.. 1984.

Neutropenic fever—pyrexia in a patient without "polys"

The febrile neutropenic (FN) patient—usually a result of chemotherapy—represents a special infectious risk—bacterial infections in these patients progresses rapidly and is often fatal if therapy is delayed. The following checklist presents an approach to these patients will help initiate prompt and appropriate therapy.

1. What are the indications for empirical antibiotic therapy of fever in the neutropenic host?

Studies from the 1970's support aggressive treatment of the febrile neutropenic patient as soon as fever is identified—in these patients, significant delays in therapy are often fatal. In the neutropenic patient, criteria for treatment include both of the following:

Definitions—Neutropenic Fever

Fever: A single temperature ≥ 38.3°C (101°F) or a temp ≥38.0°C (100.4°F) for ≥ 1 hour.

Neutropenia: A neutrophil count of <500 cells/mm3, or a count of <1000 cells/mm3 with a predicted decrease to <500 cells/mm3

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 positive 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

In searching for a potential source, keep in mind that the low granulocyte count impairs the host inflammatory response—don't overlook minimal findings on physical examination that could point to a significant underlying infection. Examine the patient on a daily basis—new findings may appear and help identify the source. When you perform a physical examination, pay special attention to the following sites:

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)

3. What are the most common causes of bacteremia in the neutropenic patient?

Although not always documented (only 20% of neutropenic patients have documented positive blood cultures), bacteremia remains an important cause of fever in the neutropenic patients. In early studies of neutropenic fever (1960s), gram-negative pathogens (*E. coli*; *Pseudomonas* sp.) predominated. These organisms most likely represented organisms present in the intestinal microflora.

More recent studies (1990s) suggest a higher incidence of bacteremia due to gram-positive organisms, especially *Staphylococcal* species such as coagulase negative staphylococci. Factors responsible for this trend include the common use of implantable central venous catheters (a risk factor for staphylococci), more widespread use of antibiotic prophylaxis regimens (often with activity against gram-negative pathogens) and increasing use of intensive chemotherapeutic regimens (leading to a higher risk of mucosal ulceration).

Table 1: Causes of bacteremia in patients with febrile neutropenia

Organism	% cases	Organism	% cases
Staphylococcus aureus	5	*Escherichia coli*	15
Coagulase-negative staphylococci	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.

- e spectrum of pathogens and antibiotic susceptibilities varies from institution to institution— familiarize yourself with local susceptibility patterns to help predict 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—significant delays in therapy could prove life-threatening. Any one of several possible antibiotic regimens (IDSA guidelines) could be used for initial empiric therapy—most hospitals have a standard regimen based on local antibiotic susceptibility patterns:

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**

In addition to the above considerations, 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)	Add Acyclovir
Nephrotoxicity	Avoid aminoglycosides—consider use of B-lactams and quinolones (with dose adjustement)
Sepsis/ARDS	Add Aminoglycoside or carbapenem Dose c Vancomycin till C/S available

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

Patients with neutropenic fever, on average require 3-5 days to respond to antibiotic therapy. When the patient remains febrile following 5 days of antibacterial therapy, other conditions/pathogens become important. Although the possibility of invasive fungal infection becomes greater in this situation, keep in mind the following conditions as a potential cause of persistent fever:

- **Resistant bacteria:** Repeat physical examination and review the patient's cultures. Consider adding additional agents if resistant organisms are identified. Empirical treatment with vancomycin is sometimes helpful—particularly if the patient has an indwelling central venous catheter. In the patient with no obvious source of infection, changes in antibiotic therapy rarely lead to defervescence if the patient is already on a broad-spectrum regimen.
- **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 (looking for the "wedge shaped" infiltrates or nodules of invasive aspergillosis). Consider adding empirical antifungal therapy to the patient's antibiotic regimen.
- **Drug fever:** Drug allergy is most common with B-lactam agents—consider substituting an antibiotic from a different class in those with suspected drug fever.
- **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 metronidazole.
- **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 may be the cause of the fever.

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). 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:

- **Voriconazole:** 6 mg/kg IV q 12 hr x 2 doses...then switch to 4 mg/kg IV q 12 hr
  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

What to do in the neutropenic patient with fever...

- **Evaluate the patient ASAP:** Patients with neutropenic fever can deteriorate quite rapidly and there is a high associated mortality—when called about a case, see them as quickly as possible and don't delay. On your exam, pay special attention to the "high yield" areas on physical exam—the oral cavity, lungs, abdomen (? RLQ tenderness suggestive of neutropenic colitis) and perirectal area (? Abscess or fissure).
- **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.
- **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.

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!

Pneumonia in the Immunocompromised Host

Evaluating pulmonary infiltrates in the immunocompromised host is one of the most challenging tasks for the infectious disease clinician. When approaching these cases, try to use the following "six step" program to narrow the possibilities…

1. What is the patient's underlying disease?

The patient's underlying disease—and presumed immune defect—often can help narrow the possibilities and predict the likely pathogens. For example, neutropenic patients are at risk for standard bacterial pathogens. Patients with defects in cell mediated immunity (CMI) are at increased risk for parasitic, viral, fungal and mycobacterial infection. Generate a list of possibilities by considering the patient's underlying disease…

- **Neutropenia** (Leukemia; s/p chemotherapy; aplastic anemia): Standard bacterial pathogens (GNR, staphylococci, streptococci); Fungi (aspergillosis, candida) in patients receiving antibiotics
- **Cell mediated immunity defects** (AIDS, corticosteroids, lymphoma): Consider PCP, mycobacteria, cryptococcus, nocardia, listeriosis, *Legionella*, and viral pathogens (CMV, HSV,VZV)
- **Hypogammaglobulinemia** (CVID; multiple myeloma; s/p splenectomy): These patients have difficulty with encapsulated bacterial pathogens such as pneumococcus, *Hemophilus influenza* and meningococcus.
- **Barrier breakdown** (GI ulceration; Foley catheterization; IV catheters): The bacterial flora at site of breakdown or obstruction is the most common culprit. In ventilator patients, noscomomial pneumonia due to gram negative bacteria and staphylococci is especially common.

2. Clinical onset and progression of the syndrome?

Like criminals, many pathogens have a *modus operandi* or characteristic onset and progression. Question the patient carefully about the mode of onset and length of the illness. In general, standard bacterial pathogens (GNR, pneumococcus, staphylococci) have a fairly **acute onset** with chills/rigors; patients frequently present to the physician within 24-48 hours of onset (If there is a significant delay, they are not likely to survive!). Mycobacteria, fungal and viral pathogens tend to have a **subacute/chronic** onset with a delayed presentation—patients may be sick for several days prior to arrival in the physician's office.

3. What is the chest radiographic pattern?

While it is difficult to make a specific pathogen diagnosis based on radiographic pattern alone, many pathogens do have characteristic radiographic findings that permit narrowing of the diagnosis. On chest radiograph, look for the following patterns:

- **Focal pneumonia:** This includes both lobar as well as patchy bronchopneumonia. In this situation consider standard bacterial pathogens (GNR, *S.* pneumoniae, staphylococci) as well as *Legionella pneumohila,* reactivation tuberculosis (especially if there is upper lobe involvement) and early fungal infection (Aspergillosis and Candida).
- **Focal pneumonia with cavitation:** The presence of cavitation is a clear indication of certain pathogens. Look for nocardiosis, tuberculosis (especially upper lobe cavities), aspergillosis (usually a later finding after neutropenia has resolved), anaerobes and occasional bacterial pathogens (*Staph aureus* or GNR).
- **Focal pneumonia with peripheral "wedge":** Right-sided endocarditis with emboli; invasive aspergillosis or mucormycosis

- **Lobar pneumonia with collapse:** Bronchial obstruction due to tumor or enlarged mediastinal lymph node
- **Focal or diffuse pneumonia with hilar adenopathy:** TB, fungi, tumor (lymphoma)
- **Diffuse pulmonary infiltrates (alveolar or fine reticular-nodular pattern):** PCP, Viral (CMV), Occasional cryptococcus or bacterial pathogens, lymphangitic spread
- **Diffuse pulmonary infiltrates (miliary or nodular pattern):** Mycobacteria, fungi, metastatic tumor

4. What is the patient's response to antibiotics?

If the patient has already been taking antibiotics—and failed to respond—this may allow you to rule out certain pathogens. Keep in mind the following caveats:

- **What antibiotic prophylaxis has the patient been receiving?** Patients taking TMP/SMX are less likely to have PCP; quinolones prophylaxis makes gram negative infection less likely (or the GNRs might be resistant to the antibiotic)
- **Did the fever respond to the initial therapy?** In a neutropenic patient, failure to respond to initial therapy suggests a resistant bacteria or fungal/mycobacterial agent.

5. Are there any important epidemiological clues?

As with any infection, take a careful exposure history including…

Country of origin:
Developing countries: ? TB exposure or + PPD
Residence in tropical regions: *Strongyloides stercoralis* (?abdominal pain/diarrhea)
Central America/Midwest: Reactivation histoplasmosis
Southeast Asia: *Penicillium marnefei*
Central valley/High-desert exposure: Coccidioiodomycosis
Midwest or Mississippi river valley: Histoplasmosis, blastomycosis

Animal exposure:
Dogs: *Pasteurella multocida*, *Capnocytophaga canimorsus* (DF2)
Cats: *Pasteurella multocida*
Reptiles: *Salmonella* sp.
Birds: psittacosis

Recent transfusion:
CMV, HIV, toxoplasmosis, *Yersinia enterocolitica*,
Malaria, trypanosomiasis (Chaga's disease)

Recent hospitalization:
Nosocomial pathogens—MRSA, Vancomycin resistant enterococcis (VRE)
ESBL GNR, Multi-drug resistant GNR (*Pseudomonas aeruginosa, Acinetobacter* species)

6. Consider the possibility of non-infectious "mimics"…

Although we automatically assume the patient with fever and pulmonary infiltrates has an infection, don't forget to consider the following non-infectious causes of fever and pulmonary infiltrate…

- **Neoplasm:** Lymphangitic spread of carcinoma; leukemic infiltrates
- **Rheumatologic:** Lupus pneumonitis; Wegener's granulomatosus (+ cavities and sinus involvement)

- **Drug-induced pneumonitis:** May see eosinophila

  Bleomycin: Toxicity with O2 exposure, Radiation therapy (RT); can see BOOP
  Cyclophosphamide: "white lung" following RT
  Methotrexate: + eosinophilia; radiosensitizer
  Mitomycin C: Hemolytic-uremic syndrome with pulmonary hemorrhage
  Radiation recall: Remote hx of RT—pneumonitis induced by chemo (e.g. doxorubicin)

- **Radiation pneumonitis:** Acute—1-3 months following RT; Follows contours of RT field and does not respect normal anatomic boundaries; Responds to corticosteroids; Delayed fibrosis up to 2 yrs post RT
- **BOOP (Bronchiolitis obliterans c organizing pneumonia):** Rxn to infection, drugs; Dx by biopsy; Rx with steroids
- **Pulmonary emboli:** Low grade fever; unexplained tachycardia/tachypnea; ? hemoptysis; √ DVT
- **Transfusion reactions:** Serious transfusion reactions sometimes present with pulmonary edema

What to do in the immunocompromised patient with a "pneumonitis"...

Pneumonia in the immuncompromised patient remains an infectious disease challenge. Although the specific pathogen may be difficult to predict, looking for the above clues and patterns may help to narrow the differential diagnosis. When confronted by one of the cases, keep in mind the following:

- ❑ **Take a detailed history** with attention to the patient's underlying disease and any epidemiological clues.
- ❑ **Identify the time of onset** and clinical course of the condition—pay special attention to the progression of the condition (acute vs. subacute vs. chronic) as this will help separate out the possible pathogens.
- ❑ **Review the chest radiographs**—categorization (focal vs diffuse; ? cavitation; ? hilar adenopathy) will help separate out the potential agents. In uncertain cases, a chest CT scan may provide additional information that helps limit the differential diagnosis.
- ❑ **Contact the laboratory** and review the microbiology studies—additional studies for selected pathogens may well be appropriate.
- ❑ **Consider the possibility of non-infectious "mimics"**—there are a number of conditions (outlined above) that can "mimic" infection.
- ❑ **Obtain a pulmonary consult**—consider bronchoscopy or open lung biopsy in selected cases.
- ❑ **Consider empiric antibiotic therapy:** Depending upon the likely possibilities, consider empiric antibiotic therapy in patients who are severely ill or clinically deteriorating. Antibiotics may be delayed in "non-toxic", clinically stable patients pending further evaluation.

Pneumonia in the immuncompromised host remains a challenging condition where the nature of the pathogen is not always obvious. In some situations (e.g. the neutropenic host) we have to make a "best guess" of likely pathogens based on the patient's underlying disease (e.g. immune defects) and clinical presentation. When in doubt, don't be afraid to obtain specialist expertise (e.g. pulmonary; infectious disease) in support of your evaluation.

Managing the PPD+ patient

New criteria for management of LTBI (Latent tuberculous infection) emphasize reserving PPD testing and chemotherapy for patients at "high risk" for development of tuberculosis. When your patient has a "+ PPD" test, utilize the following 5-step program to decide who should receive INH chemotherapy:

1. Determine if the PPD is "positive":

Experts have done away with a single "cutoff" for a positive test—current criteria (Table 1) depend on the patient's underlying condition and likelihood of MTB exposure. Before deciding to treat for latent tuberculosis, make sure the skin test is really positive and consider repeating the test if there is any doubt. If there is a history of BCG vaccination, obtain an interferon gamma releasing assay (e.g. blood Quantiferon gold test) to rule out a "false positive" PPD.

Table 1: Criteria for a positive PPD

Reaction ≥ 5 mm induration	Human immunodeficiency virus (HIV)-infected persons Recent contacts of tuberculosis case patients Fibrotic changes on chest radiograph consistent with prior TB Patients with organ transplants or other immunosuppressive conditions Individuals receiving the equivalent ≥ 15 mg/day of prednisone for > 1 mo
Reaction ≥ 10 mm of induration	Recent immigrants (< 5 yrs) from high prevalence countries Injection drug users Residents/employees of high-risk settings Hospitals/healthcare facilities, nursing homes, jails, homeless shelters TB laboratory personnel Clinical conditions associated with progression to active TB Diabetes, silicosis, renal failure, neoplasms, s/p gastrectomy
Reaction ≥ 15 of induration	Persons with no risk factors for TB

Warning: The amount of induration—not the amount of redness—is the key criteria for a "positive" test. Redness may appear at the inoculation site within the first 24 hours but this does not necessarily signify a positive test unless it is accompanied by induration.

2. Be cautious—make sure the patient does not have active TB:

It is important to rule out active tuberculosis in any patient prior to starting chemotherapy for LTBI—treatment of active disease with a single agent may lead to drug resistance. Order a baseline chest radiograph on all treatment candidates and question patients carefully about symptoms suggesting underlying active tuberculosis (chronic cough, fever, night sweats, weight loss). Perform sputum examination for AFB (induced sputum x 3) on those with pulmonary symptoms or significant chest radiograph abnormalities (pulmonary fibrotic changes; alveolar infiltrates, lung cavitation).

3. Determine if your patient should receive isoniazid (INH)

Once you have determined that the skin test is truly positive, decide on whether your patient really is a candidate for INH prophylaxis. Current guidelines recommend stratifying patients into "high-risk" and "low-risk" categories for TB reactivation—patients in the "high risk" category have a greater risk of TB reactivation and are likely to receive the greatest benefit from INH chemotherapy.

For the most part, "high-risk" patients include individuals with recent (<2 yrs) exposure to active pulmonary TB as well as those with underlying medical conditions with a greater risk for TB reactivation. In patients with a +PPD, consider offering INH chemotherapy to the following groups of "high-risk" patients (next page):

Table 2: Indications for preventive therapy in patients with a positive PPD or presumed recent exposure to active tuberculosis

Categories of patients	Specific groups
Persons/groups with presumed recent MTB infection	Pts with recent (<2 yrs) exposure to active pulmonary tuberculosis Hx of recent (within past 2 yrs) PPD conversion from negative to positive
Recent (< 5 yrs) immigrants from regions with high prevalence of MTB	
Persons/groups with high rates of TB transmission and infection	Homeless persons HIV patients, Patients with history of injection drug use Residents/employees of institutional settings including hospitals, homeless shelters, correctional facilities, nursing homes and residential homes for patients with AIDS
Persons/groups with high rates of TB transmission and infection	Diabetes mellitus, silicosis, chronic renal failure/hemodialysis Gastrectomy or s/p jejunoileal bypass Fibrotic changes on CXR suggestive of prior TB infection Immunosuppressive states Solid organ transplantation, HIV infection Underlying neoplasms : (especially CA of head/neck, lung CA, leukemia/lymphoma) Prolonged corticosteroid use (≥ 15 mg/day prednisone for > 1 month) Underweight patients (Underweight by ≥ 10% ideal body weight)

4. Is the patient at risk for INH hepatotoxicity?

While a patient may fit current guidelines for treatment with INH, remember that the drug does have side effects and rare fatalities occur due to severe hepatitis. The incidence of INH-induced hepatitis increases with age (Table 3) and is likely to be higher in those with underlying liver disease. While not absolute contraindications, be cautious about the use of INH chemoprophylaxis in the following patient populations:

Table 3: Risk of hepatitis during INH treatment

Age group	Risk*
< 20 yrs	0
20-34	2.4
35-49	9.2
50-64	19.2
> 64	7.3

* One yr Rx: number/100,000
Source: ARRD 1975;111:573.

- **Underlying liver disease:** Patients with underlying liver disease and chronic viral hepatitis are likely to have a higher rate of INH-hepatotoxicity. These individuals will require more careful followup if started on INH. Avoid the drug in symptomatic patients or those with acute hepatitis.
- **Age:** The incidence of INH-hepatotoxicity increases with age—more careful monitoring of those with age > 50 is appropriate.
- **Pregnancy:** Women have a higher incidence of INH-hepatotoxicity and the risk appears particularly high during pregnancy or the immediate post-partum period. Most experts recommend avoiding INH prophylaxis in pregnant women unless the risk of infection is particularly high (e.g. recent exposure to active pulmonary TB).
- **Hepatotoxic drugs:** Although the actual risk remains unclear, concurrent alcohol abuse or administration of other hepatoxic drugs likely represent a risk for INH hepatotoxicity—while not a contraindication to treatment, monitor such patients more carefully if you make the decision to start INH.

5. Treat high-risk patients with anti-TB chemotherapy:

Although TB chemoprophylaxis remains quite safe, INH-induced liver test abnormalities occur in up to 20% of patients and may be life-threatening in rare cases. The option to treat is always a risk/benefit decision and may not always be best in selected cases—make sure the patient understands the risks of therapy and document your discussion in the medical record. After you have made a decision to treat the patient, chose therapy from one of the regimens outlined in the following table (Table 2: next page)

Table 2: Recommended drug regimens for treatment of latent tuberculosis infection (LTBI) in adults

Drug regimen	Interval/duration *	Comments
Isoniazid	Daily x 6-9 months	Shorter course (6 mo) not recommended for HIV-infected patients or those with fibrotic lesions on CXR
Rifampin + pyrazinamide	Daily x 2 months	Recent studies suggest severe hepatotoxicity in some pts—careful monitoring required Avoid rifampin in HIV-infected pts—may use rifabutin
Rifampin	Daily x 4 months	Use in pts who cannot take INH or tolerate pyrazinamide
* Most regimens can be given on twice-weekly basis under directly observed treatment (DOT)		

6. Provide proper followup in patients receiving INH and related drugs:

Whatever regimen you choose, proper followup is essential in avoiding the risks of drug toxicity. Prior to drug treatment, examine the patient and obtain baseline studies (LFTs, CBC) in all patients planning to receive treatment. Subsequent followup depends on patient reliability and underlying risk factors for drug toxicity. All patients require monthly clinical followup (office examination or phone contact)—monitor liver tests in patients with abnormal baseline LFTs or liver disease. The frequency of such testing is unclear; however, most experts would check monthly LFTs until it is clear that the patient is stable on medication. When monitoring patients, remember the following caveats:

- ✓ **Warn patients:** Make sure the patient is aware of the side effects of drug treatment—especially the symptoms associated with hepatotoxicity (abdominal pain, fever, jaundice, loss of appetite). Instruct them to call their physician or visit a clinic/ER if they develop symptoms lasting longer than a few hours. Warn them about the dangers of continuing medication in the face of symptoms—most patients dying from INH-hepatotoxicity have continued to take the drug despite development of clear-cut clinical symptoms.
- ✓ **Clinical monitoring:** Monitor patients (Office visit or phone contact) on a monthly or bi-monthly basis. While many practitioners repeat the liver tests one month after starting therapy, repeated laboratory testing is not required for most patients provided they are asymptomatic or have no other risks for hepatotoxicity. Patients with a greater risk for hepatotoxicity (e.g. underlying liver disease, elderly pts, pregnant women) should probably have periodic laboratory testing although this can be determined on a case-by-case basis.
- ✓ **Discontinue treatment** in symptomatic patients or those with liver tests (AST/ALT) > 5 times normal. Patients receiving INH often develop asymptomatic abnormalities in liver tests—patients with milder abnormalities (3-5 x normal) may continue therapy but should be watched closely and reeducated about symptoms associated with hepatotoxicity.

What to do if the patient requires INH prophylaxis...

- **Is the patient at risk for tuberculosis?** Patients should meet the ATS guidelines for preventive therapy of latent tuberculosis. This includes a documented positive PPD or an asymptomatic patient with recent exposure to an active case of tuberculosis. PPD+ individuals with a particularly high risk for TB reactivation include patients receiving immunosuppressive agents (e.g. corticosteroids, anti-TNF agents) and those with underlying diabetes or neoplasm.
- **Rule out active tuberculosis:** Always evaluate the patient for the possibility of active tuberculosis. This includes a careful history (? Pulmonary symptoms), physical examination and targeted laboratory tests to rule out disseminated tuberculosis in patients with extrapulmonary findings. Obtain a chest radiograph on all patients with a +PPD and order an induced sputum on symptomatic patients or those with chest radiographs suggestive of active disease pulmonary disease (pulmonary cavity or infiltrates, hilar adenopathy).
- **Are there any risk factors for INH heptotoxicity?** While there are no absolute contraindications to INH therapy, be cautious when using the drug in patients with underlying liver disease or risk factors for INH toxicity. Underlying chronic hepatitis or liver disease is not an absolute contraindication to therapy but does suggest caution Most experts avoid use of INH preventive therapy during pregnancy or in the immediate post-partum period since there is a higher rate of hepatotoxicity in these patients. Be careful when using INH in older individuals—the rate of INH hepatotoxicity is 8X higher in patients over the age of 50.
- **Check baseline liver tests** prior to starting INH including AST, ALT and total bilirubin. Evaluate patients with abnormal baseline liver tests and rule out alcohol use, chronic viral hepatitis, biliary tract disease and liver toxicity due to other medications. While underlying viral hepatitis or alcohol abuse does not rule out giving INH, follow these patients generally require more frequent clinical evaluations and laboratory tests.
- **Warn the patient about INH hepatotoxicity:** Most fatal cases of INH hepatotoxicity have occurred when patients continue to take the medications despite developing signs of hepatitis. Always carefully explain the signs of hepatoxicity (nausea, vomiting, abdominal pain, jaundice) and warn patients about continued therapy in the case of these symptoms. Document your discussion and make sure patients know what to do should they develop symptoms.
- **Careful clinical and laboratory followup:** See the patient in two to four weeks to make sure that they are asymptomatic and tolerating the drug. As a precaution, I usually obtain repeat liver tests to make sure the patient is not developing sub-clinical hepatitis. Mild to modest elevations in enzymes (≤ 3 x normal) are not especially concerning provided the patient is asymptomatic and has a normal physical examination. Subsequent followup (q 1-2 months) can be by telephone if the patient is at low risk for hepatitis.

Does your patient have pulmonary tuberculosis?

One third of the world's population (over 2 billion people) have been exposed to tuberculosis and are at risk for reactivation with active disease. Considering the nature of the patient population in Los Angeles, it wouldn't be surprising if some of them ended up at your doorstep. The following checklist provides practical information on when to think about tuberculosis, and how best to make the diagnosis when it is part of the differential.

Clinical and epidemiological clues to MTB

While some of the findings can be quite non-specific, certain clinical and epidemiologic features (Table 1) should suggest the possibility of pulmonary tuberculosis. Persistent cough—accompanied by fever, weight loss and hemoptysis—should always raise a "red flag" for TB. Although anyone can potentially develop tuberculosis, certain "at-risk" populations clearly have a higher incidence—recent immigrants (from endemic regions), "institutional" patients (e.g. shelters, nursing homes, jail) and the homeless are at special risk. Healthcare workers (that means us!) also have an increased risk due the nature of our jobs.

Table 1: When to suspect MTB—clinical and epidemiological clues

History of a +PPD or previous exposure to active tuberculosis
Immigrant from an MTB-endemic region
Substance abuse including IVDU and EtOH
CAP* that fails to respond to one week of treatment
Persistent cough (> 3 weeks) accompanied by fever, hemoptysis, weight loss or night sweats
HIV patient with unexplained cough or fever
Residents or employees of high risk settings (Hospitals, nursing homes, prison, jail, homeless shelter)
Chest radiographic findings suggesting MTB (see below)

* CAP: Community-acquired pneumonia

Table 2: Rates of active TB in US residents depending upon country of origin

Region of origin	*Crude rate (per 100,000 person-years)*	*Region of origin*	*Crude rate (per 100,000 person-years)*
United States	*7.8*	*Latin America*	
Asia		*Mexico*	*36.2*
Phillipines	*89.2*	*Haiti*	*133.0*
Vietnam	*120.0*	*Sub-saharan Africa*	*58.5*
Korea	*57.0*	*Middle East*	*20.4*
Mainland China	*56.4*	*Eastern Europe*	*11.9*
		Western Europe	*5.4*

Adapted from JAMA 1997;278:304-7.

Keep in mind the following points...

- **? Previous exposure:** Always ask patients about previous skin tests and TB exposure. To increase your "yield" ask the patient specifically about active tuberculosis in family members or friends—some patients will unknowingly deny TB "exposure" even though one of their family members died from the condition!
- **"At risk" illnesses:** In the United States, specific underlying medical illnesses put patients at special risk for TB reactivation—always keep TB in mind when dealing with HIV patients (NYC: 7 out of 100 pts) and chronic renal failure (SF: 6 per 100 dialysis pts).
- **Country of origin:** The incidence of TB varies throughout the world and is mirrored in immigrants to the United States (see Table 2)—keep these "stats" in mind when estimating TB risk.

Radiographic clues to the possibility of pulmonary tuberculosis

When evaluating a chest radiograph for the possibility of MTB, keep in mind the following caveats...

- **Reactivation:** With reactivation TB, patients typically have "upper lobe" involvement (RUL: apical/post segment; RLL: superior segment), often with/without pulmonary cavitation.
- **Primary pulmonaryTB:** Patients with "primary" pulmonary TB (new infection in previously unexposed patient) more often present with lower/middle lobe consolidation with/without hilar

adenopathy; development of a pulmonary cavity is uncommon except in some cases with progressive primary disease.

- **Atypical presentations:** Immunocompromised patients (e.g. diabetes, HIV, immunosuppression agents) don't necessarily follow these rules—non-specific lower lobe infiltrates or diffuse, patchy bronchopneumonia may be seen, sometimes with associated diffuse infiltrates that mimic *Pneumocystis* pneumonia.

Table 3: CXR features suggestive of pulmonary TB

Upper lobe infiltrate (Apical and/or posterior segments)
Infiltrate: Sup. segment of lower lobe
Pulmonary cavitation
Disseminated pulmonary nodules
Hilar/mediastinal adenopathy
Evidence of previous pulmonary TB
Apical scarring
Ghon complex (LL and hilar Ca^{+2})
Pleural effusion

Table 4: Diagnostic tests for pulmonary tuberculosis

Diagnostic test	Sensitivity
+ Sputum AFB smear	50
+ Sputum NAAT* probe	75
+ Sputum AFB culture	80-90

*NAAT: Nucleic Acid Amplification Tests (RNA: Gen-Probe MTB Direct: DNA: Roche Amplicor MTB)

Bagging a red snapper—laboratory testing in pulmonary tuberculosis

Once you suspect tuberculosis, make aggressive attempts to confirm the diagnosis—a positive AFB smear (along with a positive culture) will help confirm your suspicion and guide subsequent therapy. The following tests are routinely used for documentation of infection (see Table 4):

Sputum AFB smear: Discovered in the late 1800s, AFB smears remain the mainstay of rapid diagnosis of pulmonary tuberculosis. Although most protocols recommend 3 separate sputum samples, the first two specimens are likely to pick up close to 90% of cases.

Nucleic acid amplification tests (NAAT): Molecular diagnostic techniques include RNA-based (MTB Direct) and DNA-based (Amplicor) analysis of sputum samples. Whenever possible, obtain at least one sputum for NAAT testing—the technique is more sensitive than standard AFB smears and permits rapid confirmation of MTB in patients with a positive Ziehl-Neilsen stain.

Sputum culture: Definitive diagnosis of pulmonary tuberculosis requires culture of MTB. Although there is a 2-8 week delay in obtaining results, isolation of MTB confirms the diagnosis and permits susceptibility testing, an important piece of information in an era of increasing concerns about drug resistance.

When utilizing sputum-based testing for MTB, keep the following in mind...

- ✓ **Sputum induction:** Accurate testing depends upon obtaining a proper sputum sample—when there is uncertainty about the adequacy of sputum specimens, ask respiratory therapy for a formal sputum induction using 3-5% hypertonic saline. While experts recommend 3 separate sputums (each collected at least 8 hours apart with at least one AM specimen), the yield is likely to be highest (80%) on the initial sputum collected.
- ✓ **Bronchoscopy:** In pulmonary tuberculosis diagnosis, sputum induction is likely to be as sensitive as bronchoscopy—reserve bronchoscopy (with BAL and/or transbronchial biopsy) for patients unable to produce sputum or those who require biopsy for definitive diagnosis (e.g. only one third of patients with miliary TB have a positive AFB smear—up to two thirds have granuloma on TBBX).
- ✓ **Gastric aspirate:** When patients are unable to produce sputum, consider obtaining an early AM gastric aspirate—this procedure is almost as sensitive as a sputum induction and is helpful in young children or confused patients where sputum collection is a problem. Be careful with interpretation of AFB smears from gastric contents— definitive diagnosis of MTB requires isolation of the organism on culture and smears may sometimes be "false positive" due to atypical mycobacteria in the stomach.

Management of pulmonary tuberculosis

Current anti-tuberculosis regimens rely on combination therapy with potent drugs in an effort to prevent the emergence of resistance (see below) and shorten the length of treatment. These 6- month "short course" regimens enhance compliance and appear to be as effective as longer treatment courses with less potent agents. Attempts to further reduce length of therapy to 4 months or less have an unacceptably high relapse rate and are not currently recommended.

What is the current recommended antibiotic therapy for patients with suspected tuberculosis?

The current recommended short course regimen for patients with drug-sensitive pulmonary tuberculosis is outlined in Table 1. If the initial cultures demonstrate drug-resistant MTB, subsequent therapy is based on susceptibility testing and is likely to be much more prolonged (sometimes up to 2 years!). Patient compliance is a key factor in short-course regimens— the most successful regimens utilize directly observed therapy (DOT) since poor compliance leads to an increased relapse rate as well as the possibility of drug resistance.

Table 1: Short course combination therapy in pulmonary tuberculosis

First two months* (RIPE)	Remaining 4 months†
Isoniazid (300 mg PO daily) Rifampin (600 mg PO daily) Pyrazinamide (25 mg/kg PO daily) Ethambutol (15-25 mg/kg PO daily)	Isoniazid 300 mg PO daily Rifampin 600 mg PO daily
* Start with 4 drugs in areas with high incidence of resistant tuberculosis † If initial isolate is susceptible to all agents	

This "short course" regimen is based on several assumptions…

- The initial 4-drug regimen provides extra coverage in case the patient has multi-drug resistance (MDR) to one of the major agents in the "backbone" (either isoniazid or rifampin).
- Pyrazinamide has excellent activity against slowly multiplying, intracellular organisms—in patients with "susceptible" organisms, there is no benefit in extending therapy beyond two months.
- Consider the use of IM streptomycin in patients with sick patients with cavitary tuberculosis—this agent works particularly well against the large number of organisms found in the high pH environment of the pulmonary cavity.

What are the major side effects of the recommended antibiotics?

Drug	Major side effect	Recommended monitoring
Isoniazid	Hepatitis	√ baseline and followup LFTs
	Peripheral neuropathy	Add vitamin B6 to regimen
Rifampin	Hepatitis	√ baseline and F/U LFTs
	Rash	Especially common in AIDS patients
	Interstitial nephritis	√ BUN/Cr
	Drug interactions (CYP450)	Review medication list
Pyrazinamide	Hepatitis	√ baseline and F/U LFTs
	GI disturbance	
	Hyperuricemia (gout)	√ baseline uric acid
Ethambutol	Optic neuritis	Baseline and F/U eye exam
Streptomycin	Ototoxicity	Baseline/ F/U hearing tests
	Nephrotoxicity	Baseline and F/U BUN/Cr

Practical tips for managing tuberculosis and avoiding drug resistance

When managing a case of suspected pulmonary tuberculosis, keep in mind the following recommendations:

- **Always consider the possibility of MTB:** Have a high index of suspicion for tuberculosis in patients admitted with pulmonary illness, especially in patients with clinical features suggestive of pulmonary TB (subacute illness, upper lobe infiltrates, hilar adenopathy, granuloma on chest radiograph). Remember that pulmonary TB may present with atypical features—immunocompromised patients (cancer, diabetes or HIV) are more likely to present with lower lobe infiltrates or non-specific CXR manifestations.
- **Place patient on respiratory isolation:** Place hospitalized patients with suspect or active TB on respiratory isolation in order to prevent secondary spread to patients and staff. Patients may come out of hospital respiratory isolation if they have an alternate diagnosis *or* three negative AFB smears confirmed by the laboratory.
- **Order appropriate tests to rule out tuberculosis:** In addition to the standard tests (sputum AFB x 3), request an **"MTB Direct"** on the first sputum—this nucleic acid (RNA) based test has a higher sensitivity than standard sputum smears and will confirm MTB in a patient with a positive AFB smear.
- **Check baseline laboratory tests to monitor drug toxicity:** The main concern is the possibility of drug-induced hepatitis—order baseline liver tests and obtain serology for viral hepatitis in patients with abnormalities. While not a contraindication to INH therapy, alcoholics and those with underlying liver disease have a higher incidence of INH-induced hepatitis.
- **Monitor clinical response:** Patients receiving appropriate therapy for pulmonary tuberculosis should demonstrate a clinical response with decreased fever, decreased cough and increased well being. Fever may continue (although usually the peaks are lower) for some time following initiation of effective therapy. Repeat sputum AFB smears 1-2 weeks later; a decreased organism load is a sign that the patient is responding to therapy.
- **Never add one drug to a failing regimen:** In patient with a diagnosis of TB, avoid adding a single drug to a "failing" regimen—the individual may have resistant MTB and single-drug therapy will only lead to the ultimate failure of the new drug. If clinical failure suggests an inadequate treatment regimen, consult with a TB expert and consider adding at least two or three new agents to the regimen.
- **When is the patient ready for discharge?** If a patient has been started on anti-tuberculous therapy, they may be discharged home regardless of followup smear results once they are clinically improving (↓ fever, cough) and have the approval of TB control. Suspected MDR-TB cases represent a special case—in the hospital setting, they must remain on respiratory isolation until sputum cultures are negative; discharge to home requires evidence of sputum clearing (+4 → +1 AFB smear) and clear signs of clinical improvement.
- **Warn the patient about potential side effects:** Several drugs may cause life-threatening reactions—always educate the patient about the side effects of drug-induced hepatitis (fever, nausea, vomiting, abdominal pain, jaundice) and instruct them to come to the emergency room if any such symptoms persist—continued therapy could prove life-threatening.
- **Contact public health in all suspect cases:** California state law (Gotch Bill) *requires* TB control approval prior to hospital discharge for all suspect or confirmed cases of tuberculosis. Contact the TB control nurse (ext. 4590) with any suspect case and obtain permission prior to discharge.

Miliary Tuberculosis—Clinical findings and diagnosis

Although the incidence of pulmonary tuberculosis has decreased dramatically in the industrialized world, miliary tuberculosis remains a persistent—though uncommon—problem. Those with past exposure to tuberculosis may reactivate infection following the decline in immune function associated with aging or immunocompromised states.

Miliary tuberculosis remains an important cause of fever of unknown origin (FUO) accounting for up to 30% of cases in some clinical series. Be on the lookout for miliary TB in immigrants from regions with a high incidence of tuberculosis—especially in elderly patients or those with underlying immunocompromised states (alcohol abuse, diabetes, AIDS, chemotherapy, renal failure, cancer).

Clinical presentation of military TB:

- **"Non-specific" findings common:** The clinical presentation of miliary tuberculosis is often non-specific—while fever and pulmonary findings are present in over 90% of cases, other "classic" findings (hepatosplenomegaly, lymphadenopathy) are frequently absent.
- **Occasional normal CXR:** Although the chest film usually demonstrates a miliary pattern (disseminated small nodules), up to 10% of patients will have a normal chest radiograph.
- **Laboratory findings** are generally non-specific; however, the presence of hyponatremia, elevated alkaline phosphatase or hematological abnormalities (anemia, lymphopenia, monocytosis) are clues supporting the diagnosis.

Table 1: Signs and symptoms of miliary tuberculosis

Symptom	% cases
Constitutional symptoms (fever, wgt loss, malaise)	90
Median symptom duration	4 wks (1-52 wks)
Cough	70
Abdominal pain	20
Headache	20
Sign	
Fever	90
Hepatomegaly	50
Splenomegaly	15
Chest signs (crackles)	70
Lymphadenopathy (local)	20
Serositis	40
Choroidal tubercles	<10
+ PPD	60-80

Based on Maartens et al. Am J Med 1990;89:291-96.

Table 2: Laboratory/radiographic findings

Laboratory value	% cases
Hyponatremia	75
Hyperbilirubinemia	15
Elevated Alk phos	80
Anemia	50
Leukopenia	15
Leukocytosis	15
Lymphopenia	85
Monocytosis	5
Thrombocytopenia	25
Thrombocytosis	25
Pancytopenia	5
Elevated ESR	>80
Radiographic findings	
Miliary CXR pattern	70+
Non-miliary CXR abn (effusion, infiltrate)	20
Normal CXR	10

Based on 109 pts described in Maartens et al. Am J Med 1990;89:291-6

Older patients with **cryptic miliary TB** represent a special diagnostic challenge—the diagnosis is frequently missed and often made at autopsy. Individuals with the condition typically present with non-specific signs of weight loss and "failure to thrive"; they may be afebrile or have only intermittent fever. They usually lack the characteristic chest radiograph findings of miliary tuberculosis and often have a normal chest film or one with non-specific pulmonary infiltrates. Hematologic abnormalities are common and patients are sometimes falsely labeled as having a "myelodysplastic" syndrome such as aplastic anemia or an associated underlying hematological malignancy.

Miliary tuberculosis—diagnostic testing:

Definitive diagnosis of miliary tuberculosis requires culture or demonstration of the organism in tissue or body fluid samples (Table 3). Although patients have a "disseminated" form of the disease, the organism load is relatively low and sputum smears are frequently negative—*only about a third of patients with chest radiograph abnormalities have positive sputum AFB smears*. The yield is higher on transbronchial biopsy—over 60% of cases demonstrate granuloma on pathological specimens. Bone marrow biopsy reveals granuloma in up to 80% of cases with hematological abnormalities[1] and liver biopsy is positive in between 66 and 100% of cases depending upon the series [2,3]; both tests can be quite helpful in those unable to undergo transbronchial biopsy. Whenever you suspect miliary TB, make an aggressive effort to obtain sputum samples or a transbronchial biopsy; although the smears may be negative, a positive culture 4-8 weeks later will confirm the diagnosis.

Table 3: Miliary tuberculosis— diagnostic procedures

Specimen type	%	Specimen type	%
Sputum (+AFB smear)	33	Bone marrow granuloma	50-100
Sputum (+AFB culture)	66	Bone marrow caseation	~ 25
Urine (+smear or culture)	10	+ Bone marrow AFB smear	~ 25
CSF (+smear or culture)	10	Liver Bx granuloma	75-100
TBBx (+ granuloma)	66	Liver Bx caseation	~ 45
TBBx (+ AFB smear)	25	Liver Bx AFB smear	~ 40

Abbreviation: TBBX: transbronchial biopsy
Table modified from Maartens. AJM 1990; 89:291-6.

Miliary TB "mimics": The following conditions may have a clinical presentation or chest radiograph picture that mimics miliary tuberculosis...

- **Disseminated fungal disease**
- **Metastatic carcinoma with lymphangitic spread**
- **Sarcoidosis**
- **Occupational or interstitial lung disease**

If you suspect miliary tuberculosis...

- ❑ **Question** the patient and family about past tuberculous exposure and PPD status.
- ❑ **Examine the patient** carefully for lymph nodes that can be biopsied.
- ❑ **Perform a dilated eye examination** looking for choroidal tubercles (found in 10% of cases).
- ❑ **Review the chest radiograph** looking for signs of a miliary pattern or old granulomatous disease (Ghon complex, calcified nodes, apical thickening, diaphragmatic blunting). A high-resolution chest CT scan may reveal miliary lesions earlier in suspected cases.
- ❑ **Check a PPD and anergy panel** (Remember, the PPD may be negative in up to 30% of cases!)
- ❑ **Obtain induced sputums** as well as AFB cultures from other sites (urine, CSF, gastric lavage).
- ❑ **Request bronchoscopy with transbronchial biopsy**—especially in those with characteristic radiographic findings.
- ❑ **Perform a liver or bone marrow biopsy** in those unable to undergo bronchoscopy.
- ❑ **Consider a trial of anti-tuberculous chemotherapy**—especially in those with serious disease experiencing signs of clinical deterioration.

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[1] Leibinger R, Guerin J-M. When Should We Perform Bone Marrow Biopsy in Patients with Miliary Tuberculosis? Chest 1995; 108:292-3.
[2] Munt PW. Miliary tuberculosis in the chemotherapy era: With a clinical review in 69 American adults. Medicine (Balt) 1972;51:139-55.
[3] Maartens G, Willcox PA, Benatar SR. Miliary Tuberculosis: Rapid Diagnosis, Hematologic Abnormalities, and Outcome in 109 Treated Adults. Am J Med 1990;89:291-6.

Thwarting a "MAC" attack— *MAI* complex lung infection

Pulmonary MAC (*Mycobacterium avium-intracellulare* complex) infection in non-HIV patients remains a problematic diagnostic and therapeutic dilemma. Most commonly seen in males with underlying COPD or bronchiectasis, recent recognition of the disease in older women (Lady Windemere's syndrome) suggest that the incidence of the condition is increasing.

Clinical presentation and diagnosis of pulmonary MAC infection

Patients with pulmonary MAC infection typically present with a history of persistent cough and sputum production, sometimes accompanied by intermittent fever, night sweats and weight loss. While sputum smears may be positive, definitive diagnosis of the condition requires isolation of MAC from the sputum, BAL or lung biopsy. Be careful about a single positive sputum culture, diagnosis of pulmonary MAC infection is based on specific criteria (see Table 1) emphasizing the importance of real infection considering the need for prolonged antibiotic therapy.

Table 1: Clinical and microbiologic criteria for diagnosing non-MTB mycobacterial lung disease

Clinical (both required)
1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules
and
2. Appropriate exclusion of other diagnoses
Microbiologic (one required)
1. Positive culture results from at least two separate expectorated sputum samples. If the results from (1) are nondiagnostic, consider repeat sputum AFB smears and cultures.
or
2. Positive culture result from at least one bronchial wash or lavage
or
3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.
Also keep in mind the following... • Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination. • Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded. • Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients.
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Treatment of MAC infection—Recommended regimens

Treatment of MAC infection is problematic—patients require prolonged therapy with a multi-drug regimen (Table 2), sometimes associated with significant side effects and a relatively high failure rate. Once a diagnosis of MAC infection is made, subsequent therapy is based on the "stage" or severity of the disease (e.g. "Mild" nodular or bronchiectatic disease vs. "severe" nodular or bronchiectactic disease).

When deciding to treat pulmonary MAC infection, keep the following in mind...

- ✓ There are no randomized comparative trials of Rx of pulmonary disease in non-HIV patients
- ✓ Prior to advent of macrolides, combined treatment with INH, RIF, ETM was successful in 50-70% of cases but there was a 30% relapse rate

- ✓ In non-HIV patients, clarithromycin monotherapy (500 mg BID) often results in "negative" sputums (60% sputum negative in 4 months) but is associated with a high rate of relapse and resistance.
- ✓ Susceptibility testing for macrolides is recommended; however, there are is no proven value for testing of other agents.

Table 2: 2007 ATS/IDSA Guidelines for management of non-HIV pulmonary MAC infection

MAC nodular or bronchiectatic pulmonary disease
Clarithromycin (1000 mg three times per week) or azithromycin (500 mg three times per week) PLUS Rifampin (600 mg three times per week) or rifabutin (300 mg three times per week) PLUS Ethambutol (25 mg/kg three times per week)
Fibrocavitary MAC lung disease or severe nodular or bronchiectatic disease
Clarithromycin (500 to 1000 mg daily) or azithromycin (250 mg daily) PLUS Rifampin (600 mg daily) or rifabutin (150 to 300 mg daily) PLUS Ethambutol (15 mg/kg daily)
Note: In patients with fibrocavitary MAC lung disease or severe nodular or bronchiectatic disease, consideration should also be given to streptomycin or amikacin (both 10 to 15 mg/kg three times per week) as a fourth agent for the first eight weeks. The dose should be lowered to 6 to 8 mg/kg two to three times weekly for in patients who are older than 50 years of age, whose weight is <50 kg, or who require parenteral therapy for longer than two to three months.

Treatment caveats:

1. **Dosing in older patients (> 60 yrs):** Use lower doses of clarithromycin (500 mg PO qday) in older patients with low body mas or reduced creatinine clearance—standard dosing may lead to more drug toxicity in this population.
2. **Use of streptomycin** is particularly useful in patients who have a substantial burden of extracellular organisms, against which streptomycin is highly active. Consider adding this agent in patients with radiographically extensive or cavitary disease, especially those with strongly positive smears.
3. **Intermittent dosing:** In patients with milder disease, intermittent dosing may be as effective as daily therapy and better tolerated. Nevertheless, data suggests that intermittent medication dosing is not effective for patients with severe or cavitary disease or those who have failed previous therapy. Clarithromycin interacts with rifabutin to increase rifabutin levels, while azithromycin does not.
4. **Macrolide-resistance**: Consider use of parenteral therapy (streptomycin or amikacin) in patients whose isolates become macrolide-resistant. Other agents such as fluoroquinolones, clofazimine, cycloserine and ethionamide are sometimes used but are of unproven value. Macrolide-resistant MAC lung disease is associated with a very poor prognosis in general—data suggests that successful therapy of this condition requires use of both parenteral drugs and surgical resection of involved lung tissue.
5. **Duration of therapy**: Treatment should be continued until sputum cultures are consecutively negative for at least one year.
6. **Long term sputum conversion rates:** Long-term sputum conversion rates up to 90 percent may be expected in patients without previous history of treatment failure who are able to tolerate all three oral drugs. Patients who have failed previous therapy are less likely to respond to subsequent therapeutic efforts, even in those with macrolide susceptible MAC isolates

What to do in a patient with suspected MAC pulmonary infection…

Pulmonary infection with MAC remains a significant diagnostic and therapeutic challenge—evaluate the patient carefully and avoid overtreatment based on a single "positive" culture. As you evaluate a suspect case, keep the following in mind:

- ❑ **Rule out MTB:** In a patient with clinical symptoms and a "positive" AFB smear—order a PPD and consider the possibility of underlying MTB infection. If uncertain, start anti-tuberculous chemotherapy (RIPE) until culture results are available.
- ❑ **Review cultures and diagnostic criteria:** Be cautious about starting therapy based on single smear or culture—*Mycobacterium avium* is found in water supplies and sometimes lead to "contaminated" sputum samples. If uncertain, obtain additional smears/cultures and consider an invasive procedure for more definitive testing.
- ❑ **"Stage" the patient:** Using results of radiographs (e.g. CT scan) and clinical presentation, "stage" the patient based on the severity of the disease—more severe disease requires more intensive (daily) and prolonged therapy.
- ❑ **Start antimicrobial therapy:** If you have a strong suspicion of underlying pulmonary MAC infection, consider starting therapy with a three drug regimen (e.g. macrolide + rifampin + ethambutol) based on recommendations in Table 2. Consider parenteral therapy (e.g. streptomycin or amikacin) in patients with large organism loads and severe disease.
- ❑ **Watch out for drug side effects:** Therapy for MAC infection is frequently associated with medication side effects. In addition to "standard" complaints (e.g. allergy; GI distress), keep in mind the following adverse effects…
  - ✓ **Clarithromycin:** This drug is metabolized via the CYP450 system and has significant interactions with multiple drugs. Be especially careful with agents that prolong the QT interval—clarithromycin has rarely been associated with ventricular arrhythmias.
  - ✓ **Ethambutol:** In patients receiving hi-dose therapy (25 mg/kg/day), patients may develop progressive vision loss due to a painless optic neuritis. When using this agent, obtain initial vision tests and encourage the patient to report any changes in vision.
  - ✓ **Rifampin:** This drug also has significant interactions with other drugs due to CYP450 effects. An "allergic" systemic reaction—fever, rash, renal insufficiency—is more common in patients receiving hi-dose intermittent therapy.

Source: Up to Date; Treatment of nontuberculous lung disease in non-HIV patients Accessed: 2/15/11

The Amphotericin B User's Manual

Despite the proliferation of new anti-fungal agents, amphotericin B remains the gold standard for treatment of many severe, life-threatening fungal infections. Here are some recommendations for treating patients with standard amphotericin B desoxycholate (ABD) including recommendations on managing side effects:

1. **Saline load:** Administer 500 cc to 1 liter 0.9% NS prior to amphotericin B infusion

   Although there is conflicting evidence, some studies suggest that daily saline loading (0.5-1.0 litre 0.9% NS) prior to amphotericin helps reduce nephrotoxicity[1]

2. **IV Amphotericin B in D5W**—run over 3-4 hours

   Patient with moderate-severe invasive fungal disease or febrile neutropenia: :

   Day #1: 0.25 mg/kg (Start with 0.5 mg/kg in severe, life-threatening infection)
   Day #2: 0.5 mg/kg
   Day #3: 0.5-1 mg/kg depending upon severity of illness

   Febrile neutropenia—no evidence of invasive fungal infection: 0.5 mg/kg
   Evidence of invasive aspergillosis (e.g pulmonary infiltrates): 0.75-1 mg/kg

   Test dose: Although many clinicians dispense with the standard "test" dose, serious reactions to amphotericin (hypotension, anaphylaxis, arrhythmias) do occur and some form of observation during the initial infusion is recommended. One suggested regimen is to give 5 mg of the initial calculated dose over 30 minutes—if the patient tolerates the drug (no allergic reaction or evidence of severe, symptomatic hypotension), administer the remainder of the dose over 3-4 hours.[2] Do not confuse an infusion-related event (fever, mild hypotension) with anaphylaxis—true allergy to amphotericin B is extremely rare.

3. **IREs (Infusion-related events):** Fever, chills and rigors are seen in the majority of patients who receive the drug. For symptomatic patients, consider the following strategies to reduce toxicity:

Adverse reaction	Treatment
Fever	Acetominophen (325-650 mg PO) 1 hour prior to infusion; repeat after 4-6 hours Diphenydramine (25-50 mg PO/IV) prior to infusion
Chills/Rigors	Meperidine (25-50 mg IV) before or at time of event; repeat q 4-6 hours PRN
Nausea/vomiting	Prochlorperazine (5-10 mg PO/IM/IV prior to dose); repeat as necessary
Peripheral phlebitis	Add heparin (1000 units) to infusion

4. **Nephrotoxicity:** The initial administration of Amphotericin B can cause renal vasoconstriction leading to modest rises in serum creatinine (2.0-3.0 mg/dL). This usually stabilizes with continued treatment and returns to normal following completion of therapy—long-term renal insufficiency is rarely seen in those receiving cumulative doses less than 4.0 grams.

   Risk factors for nephrotoxicity include preexisting underlying renal disease, diabetes, dehydration and co-administration of other nephrotoxic agents. When the patient's creatinine begins to rise (1.5-2.5 mg/dL), keep in mind the following strategies to help limit toxicity…

   - **Saline loading:** Although there is conflicting evidence, some studies suggest that daily saline loading (0.5-1.0 litre 0.9% NS) prior to amphotericin helps reduce nephrotoxicity[3].

- **Dose reduction:** When the serum creatinine reaches 2.5 mg/dL, reduce (by 5-10 mg) or hold the next dose of amphotericin; some experts will wait 24 hours and restart the drug at half the previous dose.
- **Continuous infusion:** Although some believe that more rapid infusion regiments have superior efficacy[1], a recent report suggests that continuous, 24 hour infusions are less nephrotoxic and as efficacious as the standard 4-hour dosing regimens[4].
- **Avoid other nephrotoxic agents:** If possible, avoid—or dose-reduce—other nephrotoxic drugs such as cyclosporine, aminoglycosides, NSAIDs, or chemotherapeutic agents.
- **Switch to liposomal amphotericin:** Consider switching to a liposomal amphotericin product— especially in those with creatinine levels above 2.5 mg/dL or preexisting renal disease. Although liposomal products are generally less nephrotoxic, they *do not* prevent electrolyte abnormalities (e.g. hypokalemia, hypomagnesemia) stemming from renal tubular dysfunction.

5. **Electrolyte abnormalities:** The renal tubular toxicity of amphotericin B leads to renal tubular acidosis with electrolyte abnormalities such as hypokalemia, hypomagnesemia and hypocalcemia. Follow serum electrolytes closely (daily or every-other-day depending upon response) and replace documented deficits as needed via intravenous or oral routes.

   - **Hypokalemia:** This can be treated with a combination of oral supplements (mild hypokalemia) and intravenous supplementation (moderate-severe hypokalemia). For IV supplementation, add KCL (20-30 mEq per liter) to normal saline load—be careful not to administer IV KCl at rates greater than 10 mEq per hour because of the danger of arrhythmias. Oral amiloride (10 mg/day) or spironolactone may be helpful in patients with severe potassium wasting.
   - **Hypomagnesemia:** Treat with oral magnesium supplements or add magnesium sulfate (48 mEq/liter) to IV saline load.
   - **Hypocalcemia:** Administer PO (oral calcium carbonate) or IV (10% calcium gluconate—60 ml in 500 5% d5/W at 0.5-2 mg/kg/hr).

6. Other considerations:

- **Anemia:** A normochromic-normocytic anemia is common with prolonged amphotericin therapy—most patients stabilize at a hemoglobin between 7.5-10 gm/dL and do not require transfusion.
- **Rapid infusion:** Avoid rapid infusion regimens (infusion over 30-60 minutes) in those with underlying cardiopulmonary disease or central venous catheters—there is an increased risk of infusion-related events (fever, rigors), *hyperkalemia* and cardiac arrhythmias.
- **Renal/hepatic failure:** No dose adjustments are necessary in dialysis patients or those with liver disease since the drug is highly protein bound and not excreted via the liver or kidney.

7. Total (cumulative) dose:

The total (cumulative) dose depends upon the specific pathogen and severity of the illness (see following table). In the febile neutropenic patient receiving empiric therapy, amphotericin B is usually continued until the patient's absolute neutrophil count is above 500 cells/mm3. In patients with documented infection, total dose depends upon the nature of the pathogen and severity of the disease. For example, patients with *Candida* infections—which tend to be easier to treat—usually respond to a total dose of 0.5 to 1.0 grams of drug.

Patients infected with the "geographic" fungi (histoplasmosis, blastomycosis and coccidioidomycosis) usually require between 1.0 to 2.5 grams of drug depending upon severity of the infection. *Aspergillus* and *Mucor* infections are the most difficult-to-treat—patients often require a total cumulative dose of 2.0 to 2.5 grams for successful cure. These doses are recommendations—patients responding to an initial course of amphotericin can often be switched to an oral azole

depending upon susceptibility of the underlying pathogen.

Table 2: Recommended "standard" Amphotericin B (AmBD)dosing

Condition	Daily Target AmBD dose*	Total (cumulative) dose†
Esophageal candidiasis	0.3 mg/kg/day	500 mg
Disseminated candidiasis	0.5 mg/kg/day	0.5 gm—1.0 gm
Blastomycosis Disseminated histoplasmosis Extracutaneous sporotrichosis	0.5 mg/kg/day	1.0—1.5 gm.
Cryptococcal meningitis	0.6—0.8 mg/kg/day	1.0—1.5 gm
Coccidioidomycosis	1.0 mg/kg/day	1.5—2.0 gm
Mucormycosis Invasive aspergillosis	1.0—1.5 mg/kg/day	2.0—2.5 gm
Neutropenic host (empiric therapy)	0.5—1.0 mg/kg/day	1.0—1.5 gm

* Recommended target daily dose for Amphotericin B desoxocholate—dosing may vary depending upon severity of illness

† Recommended cumulative dose—may vary depending upon patient response and ability to switch to azole agent

Table based on Stevens DA, Bennett JE, Chap 35: Antifungal Agents in ed. Mandell, Principles and Practice of Infectious Diseases (5th ed) Churchill-Livingston, 2000, pp. 452-4.

Note: All doses refer to Amphotericin B desoxycholate

[1] Anderson C. Sodium Chloride Treatment of Amphotericin B Nephrotoxicity—Standard of Care?. West J Med 1995;162:313-7.
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The lipid "solution"—Using liposomal amphotericin B

Problems with toxicity related to amphotericin B deoxycholate—the standard preparation of the drug—led to the development of several "liposomal" products with the hope that the new products would have lower toxicity and greater clinical efficacy. While the newer products have lower nephrotoxicity, the higher cost and difficulty in proving a substantial clinical benefit have served to limit their use. What follows is a brief overview and comparison of standard amphotericin B (AMBd) and the various lipid-based preparations currently available (ABCD,ABLC, L-AMB)[1,2]:

Formulation	Amphotericin B deoxycholate (AMBd)	Amphotericin B Colloidal Dispersion (ABCD)	Amphotericin B Lipid Complex (ABLC)	Liposomal Amphotericin (L-AMB)
Preparation	Bile salt complex	Lipid-based discs	Lipid-based ribbons	Liposomes
Dose*	0.7-1.0 mg/kg	3-6 mg/kg	5 mg/kg	3-5 mg/kg
Cmax (Peak serum concentration)	1.7 ug/ml (1.0 mg/kg dose)	3.1 ug/ml (5.0 mg/kg dose)	1.7 ug/kg	83 ug/kg
Cost (Average daily wholesale price)	$24	$330-$660	$570	$1300
Adverse Events				
Nephrotoxicity	+++ (30-40%)	+	++	+
Infusion-related events (fever, chills, hypotension,hypoxia)	++++ (80%)	++++	++++	+ (<5%)
Abnormal LFTs	+	+ (↑Tbil, AP)	+ (↑ Tbil,AP)	+ (rare ↑ ALT/AST)

* Recommended initial dose for serious fungal infection

Careful review of this table and supporting literature suggest several important points:

- **Dosing:** In comparison to amphotericin B desoxycholate, the lower toxicity of the lipid-based products permits much higher dosing; there is no need to gradually increase the dose as is sometimes done with standard amphotericin B (AMBd).
- **Tissue concentration:** The clinical relevance of the high serum concentration (Cmax) of L-AMB is unclear; lipid-based products are concentrated within tissue (especially the liver and spleen). The achievable tissue concentrations may be a greater predictor of efficacy.
- **Less nephrotoxicity:** All the lipid-based products are less nephrotoxic than AMBd; when toxicity is present with these compounds, it is generally mild and resolves when the drug is stopped.
- **Infusion related events:** L-AMB appears to have a much lower rate of infusion-related adverse events (IRAEs) than other formulations of amphotericin B.
- **Cost $$$:** The average daily cost of all lipid-based products is 10 to 50X the cost of regular amphotericin B (AMBd).
- **? Improved efficacy:** Aside from the lower toxicity, controlled trials have yet to show that lipid-based amphotericin products are more effective [3]. Anecdotal studies suggest that L-AMB may be more effective in certain types of CNS fungal infection; however, this may be due to the higher dosing permitted by the lower toxicity.

What patients are candidates for treatment with lipid-based amphotericin B products?

Because of the cost of lipid-based amphotericin B, most clinicians limit usage of the drug to the following situations:

- **Baseline renal insufficiency:** Patients with abnormal renal function as evidenced by an abnormal creatinine or elevated creatinine clearance.
- **Amphotericin-induced nephrotoxicity:** Patients who develop renal insufficiency (creatinine > 2.0 mg/dl) while receiving standard amphotericin B.
- **Risk factors for nephrotoxicity:** Individuals with *multiple* risk factors (elderly, other nephrotoxic drugs, hypotension, diabetes) likely to lead to amphotericin nephrotoxicity.
- **Poor response to regular amphotericin B:** Patients failing to respond to regular amphotericin B—especially immunocompromised patients with invasive aspergillosis and/or central nervous system infection.

Are there any contraindications to using lipid-based amphotericin products?

While toxicity with lipid-based products appears to be lower than that seen with regular amphoterin B, severe infusion related toxicities have been reported with all the lipid-based formulations [4]. This includes reports of anaphylaxis, cardiac toxicity and respiratory failure—life-threatening syndromes sometimes seen with other liposomal products and possibly related to the lipid component of the drugs.

The high cost of these formulations are also a drawback—without a clear indication that they are more efficacious than standard amphotericin B desoxycholate, it is hard to recommend them for most cases requiring antifungal therapy. While amphotericin is likely to be the "gold standard" of anti-fungal therapy, new classes of anti-fungal agents (azoles, echinocandins) permit efficacious and less toxic therapy of a widening number of pathogens.

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Does your patient have invasive candidiasis?

- Persistent fever and leukocytosis despite broad-spectrum antibiotics?
- Hospitalized for weeks following bowel surgery, immunosuppression or chemotherapyinduced neutropenia?
- *Candida* species growing from one or more sites?

Sound familiar? Your patient could have invasive candidiasis, a growing problem in hospitalized patients saddled by complex medical conditions and widespread use of broad-spectrum antibiotics. A definitive diagnosis of invasive candidiasis is often difficult—only 50% of invasive candidiasis (demonstrated at autopsy) had positive blood cultures. Early clinical diagnosis requires an appreciation of the risk factors for candidiasis as well as a careful physical examination for subtle clues that suggest the condition.

When faced with a febrile patient with suspected candidiasis, ask yourself the following questions:

1. Does the patient have risk factors for candidiasis?

While no single risk factor predicts invasive candidiasis, patients with the following risk factors are more likely to develop the condition…

- **History of immunosuppressive therapy** (corticosteroids), chemotherapy induced neutropenia or diabetes
- **Disruption of gastrointestinal tract integrity:** recent GI surgery, mucositis, diarrhea
- **Total parenteral hyperalimentation** with high calorie feedings
- **Presence of a central venous catheter**
- **History of intravenous drug use**
- **Broad spectrum antibiotic use** (Luria's rule… "3 antibiotics = 1 fungal infection")

2. Is the patient colonized with *Candida* species?

Colonization with *Candida* species at various sites (oral cavity, sputum, urine, vagina, skin) is a risk factor for invasive disease, with some studies suggests an increasing risk when multiple sites are involved. *Absence* of colonization does not rule out invasive candidiasis but certainly reduces the likely risk. Nevertheless, while colonization is common, true "invasion" is rare—the presence of colonization at a peripheral site does not predict invasive disease unless a clinical syndrome compatible with invasive candidiasis is present.

3. Is the clinical syndrome compatible with invasive candidiasis?

As noted above, persistent fever and/or leukocytosis in a patient on broad-spectrum antibiotics is the most common clinical presentation of invasive candidiasis. Unfortunately, the diagnosis is not simple since the symptoms are often non-specific and mimicked by other conditions in the hospitalized patient. When evaluating a patient for candidiasis, see if the patient fits one of the following syndromes…

- **Acute disseminated candidiasis**: Patients present with persistent fever on antibiotics, pulmonary infiltrates and—in 50% of cases—positive blood cultures. Mortality is 30-60% depending on underlying host status and response to treatment.
- **IV catheter associated candidemia**: This often responds to prompt removal of the catheter. Although such patients often defervesce following catheter removal, treatment with 7-10 days of an anti-fungal compound is appropriate to prevent seeding and distant infection in other organs.
- **Hepatosplenic candidiasis**: Look for this in immunocompromised patients following prolonged periods of neutropenic and systemic antibiotics. Patients present with chronic fever, RUQ pain and hepatosplenomegaly. UTZ or CT scan of the liver may demonstrate characteristic focal lesions. Blood cultures are usually negative-liver bx is required for definitive diagnosis.
- **Candida endopthalmitis**: Although sometimes seen following opthalmologic surgery, it most commonly

liver bx is required for definitive diagnosis.

- **Candida endopthalmitis**: Although sometimes seen following opthalmologic surgery, it most commonly results from fungemia with subsequent seeding to the retina.
- **Candida endocarditis**: Seen in intravenous drug users and patients with prolonged central venous catheterization (tricuspid endocarditis). Almost always requires valve replacement although rare cases have been controlled with high-dose anti-fungal therapy alone.
- **Genitourinary candidiasis**: Usually a problem of hospitalized patients with indwelling foley catheters. Dx by presence of + urinary Candida cultures and associated pyuria. Check renal UTZ for presence of "fungal balls" in renal pelvis that might require surgical removal.

A snapshot of the bugs involved...

A multicentered trial comparing amphotericin B and fluconazole in several hundred cases of fungemia gives an idea of the spectrum of *Candida* species likely to be encountered...

Candida species	% Infections	Fluconazole MIC_{50}* (ug/ml)
C. albicans	56	0.25
C. tropicalis	17	1.0
C. parapsilosis	10	1.0
C. glabrata	13	16†
C. krusei	2	32†

*Concentration required to kill 50% of strains
† Resistance; Fluconazole mean level of 6.7 ug/ml following 200 mg IV
Adapted from Rex et al.

4. What is appropriate therapy for suspected invasive candidiasis?

If the patient has a clinical syndrome consistent with invasive candidiasis, consider empiric therapy. In the hospitalized patient, use the following guidelines to choose the appropriate treatment:

- **Recent hospitalization**, no previous anti-fungal therapy, patient clinically stable → IV/PO fluconazole
- **Prolonged hospitalization**, "septic" patient → micafungin or IV amphotericin B
- **Prolonged hospitalization**, previous anti-fungal therapy (fluconazole) → Micafungin or IV amphotericin B
- **? Renal insufficiency** → IV fluconazole, micafungin or liposomal amphotericin B
- **? Risk for fluconazole-resistant organisms** (previous fluconazole; non *C. albicans* species) → micafungin or IV amphotericin B

During therapy, remember the following principles:

- ✓ **Response to therapy:** Start treatment and look for a clinical response—patient's treated for invasive candidiasis often defervesce within 48-72 hours following initiation of appropriate therapy.
- ✓ **Total dose:** Simple fungemia or disseminated disease usually requires 500 mg—1.0 gram amphotericin B.
- ✓ **Line infections:** For simple line-associated fungemia, 10-14 days of therapy (fluconazole or amphotericin B) are usually adequate if the line is removed. Other clinical syndromes (hepatosplenic candidiasis, *Candida* endophthalmitis, endocarditis, genitourinary candidiasis) may require more prolonged therapy.
- ✓ **Colonization:** Try to avoid treating simple colonization and "afebrile" patients—this is usually of little value

What should you do if you suspect invasive candidiasis...

- **Suspect the condition:** Invasive candidiasis is usually seen in certain clinical scenarios—hospitalized patients with indwelling lines who have received previous courses of antibiotics. Be especially watchful in patients with persistent fever despite "appropriate" antibacterial therapy—they might be colonized with *Candida* and have invasive fungal disease.
- **Check for skin involvement:** Characteristic erythematous nodules of invasive candidiasis are seen in 10% of cases—examine the skin carefully and biopsy any suspicious nodules.
- **Eye examination:** Fundiscopic findings (the white "fungal balls") are common in patients with disseminated candidiasis—perform a careful, dilated fundiscopic exam looking for the characteristic lesions. If necessary, obtain an ophthalmology consult—an "indirect" exam by an ophthalmologist is more likely to identify the characteristic lesions.
- **Culture and pull intravenous catheters if possible:** While not always immediately convenient, try to pull and culture all intravenous catheters in patients with suspected invasive candidiasis Chronic indwelling central lines appear to be have the highest risk.
- **Obtain fungal cultures:** Obtain "fungal" blood cultures and culture any accessible site (sputum; urine) for fungi—in a patient with a typical syndrome, presence of *Candida* at any of these sites is a clue to disseminated candidiasis in the "at risk" patient.
- **Start empiric anti-fungal therapy** in patients with a typical clinical presentation. Don't automatically treat a "positive" screening culture (e.g wound, urine, sputum) if the patient is afebrile—most patients with such cultures do not have invasive candidiasis. Whenever possible, remove catheters (intravenous; foley catheter) in those with positive cultures—sometimes removal will resolve simple colonization.
- **Consider the possibility of resistant *Candida*:** Keep in mind the possibility of azole resistance in patients who have received previous fluconazole or in those with non-*albicans Candida* species—in these cases, administer an echinocandin (e.g. micafungin) or amphotericin B until the isolate can be speciated. In select cases, formal susceptibility testing may be required.
- **Watch for a response:** In most cases of invasive candidiasis, patients will become afebrile within 48-72 hours following effective therapy. Patients with an infected line—or fungal endocarditis—may violate this rule and remain persistently fungemic. In a patient with fungemia, always try to pull an infected line and—in cases of suspected endocarditis—obtain an echocardiogram for further evaluation.

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Making the diagnosis of histoplasmosis

Table 1 shows the various tests available for the diagnosis of histoplasmosis and their utility in various clinical syndromes:

Histopathology: Pathology may be quite helpful in the rapid diagnosis of suspected histoplasmosis—especially in patients with disseminated histoplasmosis (DH) and high organism loads. One study of AIDS patients in a non-endemic area demonstrated the presence of the organism in 69% of cases via transbronchial biopsy specimens [i]. Likewise, in immuncompromised patients with DH, a "buffy coat smear" can detect the characteristic intracellular organism in over 50% of patients (don't forget to request a PAS [Periodic acid-Schiff] or GMS [Gomori methenamine silver] buffy coat stain in patients with suspected disseminated histoplasmosis[ii]).

Culture: In "normal" hosts with pulmonary disease, sputum cultures are frequently negative and cannot be relied on to "rule-out" histoplasmosis. Culture based testing is more likely to be positive in immunocompromised patients with acute disseminated histoplasmosis. In one case series of DH in AIDS patients, blood and bone marrow cultures were positive in over 90% of patients [iii]. This recovery rate reflects the use of more careful culture techniques—if you suspect DH, make sure your laboratory uses lysis-centrifugation culture techniques (Dupont ISOLATOR) to increase yield from tissue specimens.

Serology: In proper hands, serological testing can be quite helpful in suggesting the diagnosis of histoplasmosis (see Table). Two tests are available—an immunodiffusion test (ID) that detects antibody to M and H antigens—and a complement fixation (CF) test; both tests have a sensitivity of approximately 80% and are more likely to be positive after several weeks of illness. Be careful in interpreting the test in non-endemic areas—false positive tests may be seen in patients infected with other fungal pathogens.

Antigen testing: In patients with disseminated histoplasmosis, urine or serum antigen testing is generally quite helpful in confirming the diagnosis, especially in immunocompromised patients with disseminated histoplasmosis; in this situation, the tests are positive in over 80% of cases. Urine testing is more sensitive than the serum assay—in most cases, there is usually no need to send serum levels. Antigen testing of other sterile fluids (pericardial fluid, cerebrospinal fluid) may be helpful in selected cases. Antigen testing is also helpful in guiding histoplasmosis therapy—urine antigen levels should drop following successful treatment of the infection.

Table 1: Laboratory Diagnosis of Selected Histoplasmosis Syndromes

Clinical Tests	Acute Pulmonary	Chronic Pulmonary	Disseminated		
			"Normal" host	Immunosuppressed	AIDS
Histology	N/A	N/A	40-60%	60%	40-60%
Fungal stain[1]	10%	40%			
Sputum/BAL[2]	< 25%	50-85%	50-70%	N/A	N/A
Serology	25-85%[3]	100%	85-100%	80%	70%
Urinary Antigen	25-75%[4]	15%	80%	80%	95%

[1] Sputum KOH and cytopathology
[2] Includes both culture and histopathology
[3] Likelihood of positive serology depends on both intensity of exposure (low inoculum vs. high inoculum) and timing of blood sample (acute vs. convalescent)
[4] High frequency (75%) more common following high-inoculum exposure prior (<4 wks) to appearance of antibodies. Patients with low-inoculum exposure rarely have positive urine antigen.
Table contains data extracted from Wheat LJ, Sem in Resp Dis 2001;16:131-40.[iv]

The challenge of coccidioidomycosis meningitis

Almost always fatal if untreated [1], coccidioidomycosis meningitis (CM) remains a condition with significant morbidity and mortality despite recent advances in antifungal therapy. Coccidioidomycosis meningitis is a *basilar* meningitis—complications ensue from meningeal inflammation with local entrapment of blood vessels and cranial nerves at the base of the brain. When faced with a case of suspected or proven coccidioidomycosis meningitis, keep in mind the following questions:

1. What is the recommended antifungal therapy?

Until recently, intrathecal amphoterin B was the mainstay of treatment for coccidioidomycosis meningitis—patients received periodic treatment courses in an attempt to keep the condition under control. The introduction of azole drugs in the late 1980s has offered a more convenient therapeutic option for patients with milder forms of the disease[2]. In many situations, high-dose fluconazole is the initial "drug of choice" with intrathecal amphotericin B reserved for patients failing to respond to azoles or those with particularly severe forms of CM.

- **Fluconazole:** The drug's in vitro activity against coccidoidomycosis and excellent CSF penetration (CSF levels = 90% serum levels) make it the azole of choice for treatment of coccidioidal meningitis. In patients with moderate-severe disease (high fever, neurological abnormalities), start with intravenous fluconazole and switch to an oral regimen following response to treatment.

  Mild disease: Although IDSA recommendations suggest 400 mg PO daily, most ID experts start with fluconazole 800 mg PO daily with switch to IV drug in those failing to respond.

  Moderate-severe disease: In patients with high fever, altered mental status or neurological abnormalities, start with IV fluconazole (800 mg daily). In those failing therapy, increase the dose of fluconazole (up to 2 gm/day) or add intrathecal amphotericin B.

  Although itraconzole has poorer CSF penetration, at least one study suggests that oral itraconazole (400-600 mg daily) compares favorably to oral fluconazole for treatment of CM[3]. Recent case reports suggest that voriconazole may have some benefit in patients who fail to respond to fluconazole. Whatever agent is chosen, patients with almost always require lifelong suppressive therapy to limit the likelihood of relapse.

- **Amphotericin B:** Amphotericin B has poor CSF penetration—intravenous amphotericin alone is inadequate for treatment of coccidioidomyocosis meningitis. Intrathecal amphotericin B is indicated for those with severe CM or in patients failing to respond to a reasonable trial of intravenous fluconazole[4].

  Intrathecal amphotericin B: Intrathecal amphotericin B can be given by direct injection into the lumbar space or basilar cisterns. Although useful in an acute situation, intralumbar therapy is associated with arachnoiditis and meningeal scarring—this limits long term use of this route since drug delivery to diseased areas at the base of the brain is frequently impaired. Intracisternal injection remains the preferred route of treatment utilized by most experts in the field. Practitioners begin with a low dose of intrathecal amphotericin (0.1 mg) followed by gradual daily increases of the dose to between 1 and 1.5 mg per treatment. Significant side effects include posttreatment headache—which is to be expected—and neurological abnormalities such as weakness and paralysis related to toxic effects on the brainstem (these symptoms may sometimes respond to high-dose corticosteroids).

  As with intralumbar therapy, long term intracisternal administration of amphotericin B may lead to arachnoiditis and basilar scarring that limit its' usefulness in some cases. Those responding to intrathecal therapy demonstrate a clinical response (decreased fever, meningismus, amelioration of neurological symptoms) along with improvement in CSF parameters (decreased cell count and complement fixation titers; gradual rise in CSF glucose). Patients undergoing intrathecal therapy

usually require daily or thrice weekly cisternal taps by a practitioner trained in the technique. Administration of drug via a CNS cather is an attractive option but frequently complicated by infection, catheter blockage and the anatomic constraints of the disease. Use of a standard ventricular Omaya reservoir is unlikely to be effective since it delivers drug to the lateral ventricle rather than the base of the brain where most disease resides. Implantation of a catheter into the basilar cistern (with injection of drug into a subcutaneous reservoir) has been used by some practitioners but is technically complicated and rarely utilized in practice.

- **Combination therapy:** Combination therapy (intrathecal amphotericin B + PO/IV fluconazole) is frequently used—especially in those with disseminated disease outside the central nervous system. Those responding to an initial course of intrathecal therapy may be converted to and maintained on fluconazole in order to minimize the need for cisternal taps[5]. Patients with particularly severe extra-CNS disease are often given concomitant high-dose IV amphotericin B despite its' poor CNS penetration. A recent animal study suggests that high-dose liposomal amphotericin B might be useful in the management of CM although no human clinical trials are available.

2. Does the patient have hydrocephalus?

Hydrocephalus is a serious complication of CM that is seen in over 50% of cases in some series[6]. Most patients have a communicating hydrocephalus and require placement of a ventriculo-peritoneal (VP) shunt for relief of increased intracranial pressure. Carefully monitor all patients with CM—those who experience increased headache or neurological deterioration should undergo brain imaging and be sent for neurosurgical shunting if significant hydrocephalus is detected. Although placement of a VP shunt may be lifesaving, patients run the risk of shunt infection or obstruction and not infrequently require shunt replacement or revision in the future.

3. Should the patient receive a trial of corticosteroids?

The basilar meningitis seen in CM often results in a "vasculitis" of blood vessels supplying the base of the brain[7]. Studies performed in animal models and anecdotal case reports suggest that patients may benefit from a course of corticosteroids to minimize basilar inflammation. Consider conticosteroids in those who deteriorate on therapy or present with clinical signs of stroke or cranial nerve abnormalities. Start with prednisone (1mg/kg/day)—or an equivalent steroid—and taper the dose gradually over 8-12 weeks depending upon the patient's clinical response. Make sure the patient is receiving systemic anti-fungal therapy so disease is not reactivated in another extra-CNS location.

Coccidioidomycosis meningitis remains an extremely challenging management problem—patients with severe disease may deteriorate rapidly despite recommended therapy. Because it is a relatively rare disease, there are few controlled trials and the "optimal" therapeutic regimen is still debated by experts in the field. Most practitioners start with high-dose intravenous or oral fluconazole and reserve intrathecal amphotericin B for those failing to respond to initial therapy or patients with particularly severe disease. In any chronic meningitis patient who deteriorates on therapy, be alert to the possibility of hydrocephalus and don't hesitate to obtain a CT scan of the head to see if a VP shunt is necessary. Patients with coccidioidomycosis meningitis generally require life-long therapy—almost all patients will relapse if antifungal therapy is discontinued.

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How to treat suspected Malaria ? ... Ask the Five questions.

1. What is the species and parasite load on peripheral smear?

A trained observer is often able to identify the organism based on morphological appearance on the peripheral smear. *Plasmodium falciparum* is the species most likely to cause life-threatening malaria. Non-falciparum species (*P. vivax, P. ovale, P. malariae*) are likely to be sensitive to chloroquine. In falciparum malaria, the degree of parasite load is an important predictor of severity of illness and prognosis—patients with high parasite loads (>5%) are more likely to have a poor outcome and should be managed in the hospital. —a patient with falciparum malaria should be thought of as a medical emergency.

2. Where did the patient acquire malaria?

Knowledge of where the patient acquired malaria helps with both identification and decisions about drug therapy. The geographic ranges of the various species overlap considerably. *P. falciparum* is found thorughout the tropics but is especially a problem in Southeast Asia, Africa , South America, Oceania and Haiti. *P. vivax* is more common in Central America and the Indian subcontinent. *P. ovale* is found almost exclusively in Africa. *P. malariae* is present throughout the tropics but is especially common in Africa. Keep in mind that patients may have dual infections with more than one species.

3. Is the infection chloroquine-sensitive?

Unfortunately, in many parts of the world falciparum malaria is resistant to chloroquine; assume that travelers returning from these regions (Southeast Asia, Africa, Indian subcontinent, South America) are infected with chloroquine-resistant organisms. As of this writing, several areas (Central America west of the Panama Canal; Mexico; Middle East, North Africa, China) still have choroquine-sensitive *P. falciparum*. Keep in mind that this is a fluid situation—always obtain the most up-to-date susceptibility information from the traveler's page at the CDC website (. The benign malarias (*P.vivax, P.ovale, P. malariae*) remain susceptible to chloroquine (An exception to this rule is the more recent emergence of chloroquine-resistant *P.vivax* in New Guinea, Indonesia and Guyana).

4. How sick is the patient—do they require parenteral therapy?

Patients who have nausea/vomiting or are unable to take oral medications require parenteral therapy. Falciparum malaria is fatal in up to 30% of non-immune individuals who contract the infection—never underestimate the severity of illness and be alert for clinical features that predict a poor outcome.

Table 1: Features Indicating a Poor Prognosis in Severe Malaria

Clinical features
Impaired consciousness *(the deeper the coma, the worse the prognosis)* *Repeated convulsions (≥ 3 in 24 hr),* *Respiratory distress (rapid, deep, labored, stertorous breathing)* *Substantial bleeding or shock*
Biochemical features
Renal impairment (serum creatinine, >3 mg/dl) *Acidosis (plasma bicarbonate ,15 mmol/liter);* *Jaundice (serum total bilirubin, >2.5 mg/dl)* *Hyperlactatemia (venous lactate, >45 mg/dl)* *Hypoglycemia (blood glucose, <40 mg/dl)* *Elevated aminotransferase levels (>3 times normal)*
Hematologic features
Parasitemia (>5-15%) *≥ 5% of neutrophils contain malarial pigment*

Table from White, NEJM; 1996:335:800-6

5. What is the recommended therapy?

The therapy of malaria is constantly changing as chloroquine resistance spreads and new medications are introduced. In any individual case, don't hesitate to check with an infectious disease/tropical medicine expert or government source (CDC) to obtain the most up-to-date treatment recommendations. The following table gives general guidelines for the management of malaria:

Table 2: Drug therapy of malaria

Chloroquine-resistant *P. falciparum* (including chloroquine resistant *P. vivax*)	
Oral therapy	Quinine sulfate (650 mg salt PO q 8hr x 3-7 days*) + Doxycycline (100 mg PO BID) [or clindamycin 450mg TID)
Alternatives	Atovaquone/proguanil (Malarone-4 adult tabs PO daily x 3 days) or Mefloquine (750 mg salt followed by 500 mg 6-12 hours later) † or Artesunate (4 mg/kg/d x 3 day) + mefloquine (1250 mg once)
Parenteral therapy	Quinidine gluconate 10 mg/ kg salt load in saline (max: 600 mg) over 1-2 hr, followed by continuous infusion of .02 mg/kg/min until oral therapy started
Alternative	Artesunate 2.4 mg/kg IV q day
Chloroquine-sensitive *P. falciparum, P. vivax, P. ovale and P. malariae*¶	
Oral therapy	Chloroquine phosphate (1gm [600 mg base], then 500 mg [300 mg base] 6 hr later, then 500 mg [300 mg base] at 24 and 48 hr.
Parenteral therapy	Quinidine gluconate as above

* Quinine rx should continue for 7 days for infections acquired in SE Asia and for 3 days for infections acquired in Africa or South America
† Mefloquine is associated with a higer rate of severe neuropsychiatric reactions when used at treatment doses.
¶ Chloroquine remains drug of choice for *P. malariae* infections since no widespread evidence of chlorquine resistance in *P. malariae*; *P. vivax and P. ovale* require followup treatment with agent (primaquine) to prevent relapse from liver phase (hypozoites).

What to do if you suspect malaria...

- **Consider the possibility** of malaria in travelers (or immigrants) from endemic regions. The first rule of travel medicine is to *assume the possibility of malaria in the febrile traveler.*
- **Examine the peripheral smear:** Review the peripheral smear with a knowledgeable person. Try to speciate the parasite and get a general estimate of the parasite load
- **How sick is the patient?** This is critical in determining the route of therapy—patients with poor prognostic factors (see above table) or those unable to take medication due to nausea and vomiting should receive parenteral therapy until able to take by mouth. Severely ill patients should be managed in an intensive care unit.
- **Choose appropriate therapy** based on the likely organism (travel history and review of peripheral smear) and the severity of illness (parenteral therapy for severely ill patients or those unable to take PO). Consider **exchange transfusion** in individuals with severe illness and high parasite loads (>15-20%).
- **Monitor response to therapy:** Repeat peripheral smear within 12-24 hours to ascertain response to therapy; should see gradual drop in parasitemia over several days along with clinical improvement.
- **Call an expert:** Managing severe falciparum malaria can be a daunting challenge—the mortality rate is significant (up to 30% in non-immune individuals) and there is little room for error. If you are uncertain about therapy, do not hesitate to call a local expert or personnel at the CDC to obtain the most up-to-date information. (CDC Malaria Hotline: 770-488-7788 M-F, 8am-4:30pm, eastern time; Emergency consultation after hours, call: 770-488-7100 and request to speak with a CDC Malaria Branch clinician).
- **Avoid the pitfalls:** Keep in mind the following pitfalls when managing malaria...
  - ✓ **Failure to recognize** a case of malaria due to a poor travel history or "atypical" symptoms. Remember that malaria may present with abdominal pain, diarrhea, headache, back pain and coma (cerebral malaria).
  - ✓ **False negative smears:** Don't exclude malaria because of a "negative" peripheral smear—in all suspect cases, repeat the smear in every 6-12 hours until the diagnosis is ruled our or another is apparent. In critically ill patients, start empiric therapy if you have a high index of suspicion for malaria.
  - ✓ **Inappropriate therapy**, especially if a patient is given chloroquine for possible chloroquine-resistant malaria. Attempts to give oral therapy in severely ill patients or those with nausea/vomiting are also dangerous—when in doubt it is better to give the initial doses via a parenteral route.

ID Checklist: A Malaria Identification Primer for Houseofficers

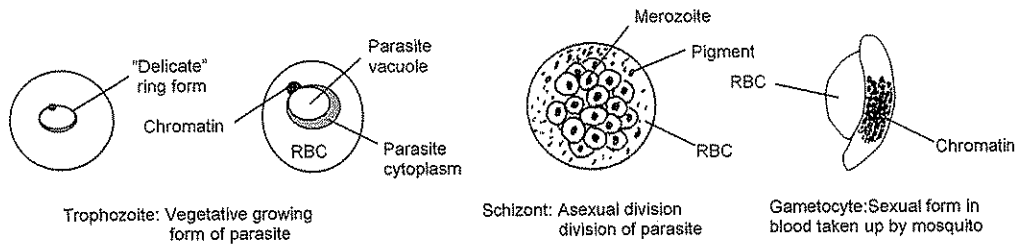
(What you need to know in the middle of the night!)

1. Thick and thin smears—what should you order? It is necessary to order both a thin and thick smear—although the thick smear will be delayed 24 hours, it allows the examiner to detect a lower parasite load. The thin smear (a standard peripheral blood smear) has a lower sensitivity but is better for species determination since one can see the RBC morphology of infected cells. Here are some of the pros and cons of the two preparations:

Thick smear: A drop of blood on a slide is allowed to dry and then stained 24 hours later (after RBCs lyse)
More likely to see parasites (especially ring forms) but it is difficult to speciate organisms
Best test for low-grade parasitemia but requires some degree of expertise for interpretation.

Thin smear: This is a regular Giemsa or Wright stain of a peripheral blood smear
Lower sensitivity than thick smear but better for parasite species determination.
Should check 300-500 fields (100x oil immersion) before calling it a "negative" smear.
If initial smear negative, repeat smear in 6 hours in suspect cases.
(Remember: A single negative thin smear does not rule out malaria)

Talk like a parasitologist: *Plasmodium* anatomy

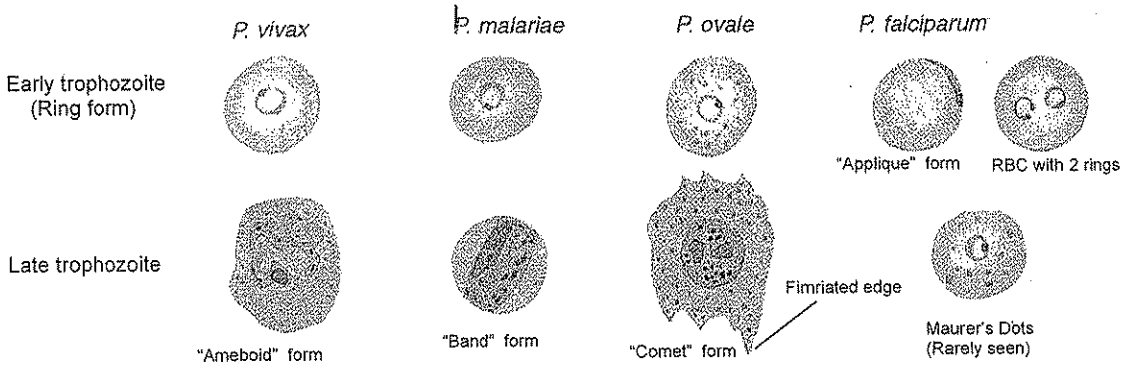


Trophozoite: Vegetative growing form of parasite

Schizont: Asexual division division of parasite

Gametocyte:Sexual form in blood taken up by mosquito

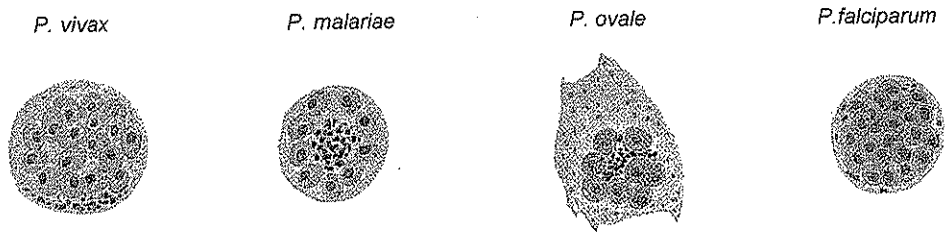
2. Look for "rings" and examine the RBC: The "ring" or trophozoite form is the most likely form that will be spotted by the examiner. Although these early forms may appear similar, morphological differences become apparent as the trophozoite matures and permit speciation. The size and shape of the RBC—and the presence of pigment in the infected cells offer important clues to the identity of the organism:



Trophozoite morphology	Early: Delicate ring Later: Develops pseudopods "ameboid" form Single chromatin dot	Sturdy (thick) cytoplasm" with large single chromatin dot Late trophozoite shows occasional "band" form c brown pigment	Sturdy cytoplasm with large chromatin dot "Comet" form of RBC with compact parasite and fimbriated RBC Occ pigment in parasite cytoplasm (later stage)	Delicate (thin) cytoplasm surrounding vacuole 1-2 chromatin dots (stereo headphones) Applique form plastered against RBC membrane
RBC morphology	Size: 1.5 –2 x nl RBC Schüffner's dots: + RBC cytoplasm pigment	Size: Nl- 3/4 x nl RBC (No cytoplasm pigment)	Size: Oval RBC 1.5-2 x nl + Schüffner's dots	Size: Normal RBC Multiple parasites/RBC Maurer's dots (rare)

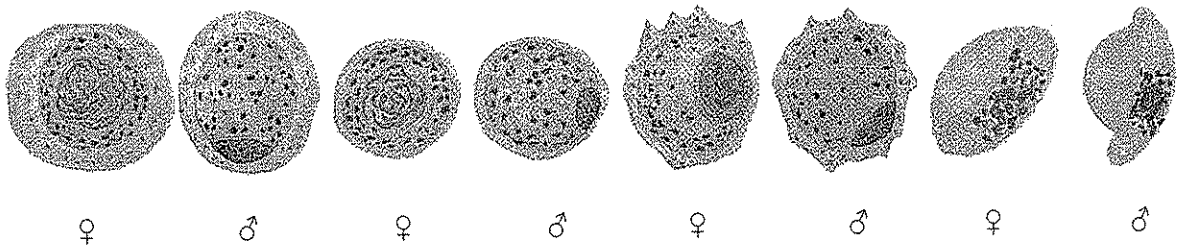
3. Are there any ancillary forms? The presence of asexual schizonts or sexual forms (male or female microgametocytes) provides valuable clues about the identity of the infecting organism. This is especially important for *P vivax* identification--careful examination of the peripheral smear usually shows parasites in multiple stages of development. When present, the number of merozoites in the schizont helps to differentiate between species. Although less commonly seen in "recent" infections (The gametocyte requires 4 weeks to develop following initial infection), the presence of a "banana-shaped" gametocyte is diagnostic of infection with *P. falciparum*.

Schizonts:



P. vivax	P. malariae	P. ovale	P. falciparum
Size: 1.5-2 x nl RBC 12-24 merozoites c yellow-brown pigment Fine Schüffner's dots in cytoplasm of RBC	Size: Normal to .75 RBC 6-12 merozoites clustered around mass of coarse, dark-brown pigment "Daisy head" appearance Occasionally forms rosettes	Size: Nl- 1.25 nl RBC 6-14 merozoites clustered around dark brown pigment Round-oval RBC (some fimbriated)	Size: Normal RBC 8-24 small merozoites c dark pigment clumped in one mass **Rarely seen on peripheral blood smear**

Gametocytes:



Note: Gametocyte forms generally larger than schizont or trophozoite forms
Chromatin more compact (often eccentric) in male (macrogametocyte) forms—more diffuse in female (microgametocyte) forms
Distinctive "banana-shaped" form of P. falciparum

4. What percentage of cells are infected? Count approximately 300-500 RBCs and make note of the number of infected cells—a simple formula ([infected RBCs/total RBCs] x 100) will give the percentage of infected cells. Parasite loads greater than 2-3% raise concerns of a severe infection; consider exchange transfusion in seriously ill patients with parasitemia greater than 10-20%.

5. Beware the pitfalls!

- **Delays in processing:** Delayed preparation (> 1hr) of smears may lead to alteration in parasite morphology with loss of Schüffner's dots in *P. vivax* and exflagellation of ookinites from gametocyte forms. Always make sure the blood is delivered immediately to the laboratory with prompt preparation of peripheral smears.
- **Negative smears** can occur with low parasite loads or in cases of severe malaria when the organisms are trapped in central capillaries. You should examine between 100-300 fields (100x oil immersion) before calling a slide "negative". In suspect cases, repeat the smears at 6 hour intervals until a positive smear is obtained. **Remember—a single negative smear does not rule out malaria!**
- **Multiple infections:** Patients may rarely be infected with multiple species—keep this in mind when the parasite morphology suggests two populations of organisms.
- **Malaria look-alikes:** In addition to laboratory artifacts (debris on slide or contaminated stains), blood elements (platelets) may mimic malaria as well other blood parasites (e.g. babesiosis).

"Terrible typhoid"—enteric fever syndromes

"Enteric fever" is a clinical syndrome characterized by fever, headache and abdominal pain. Although classically due to *Salmonella typhi* (typhoid fever), the syndrome is also caused by non-*typhi Salmonella* strains (paratyphoid fever) and may follow infection with several other closely related intestinal pathogens.

1. What is the clinical presentation of typhoid fever?

"Classical" typhoid fever is a condition characterized by the following features (see Table 1):

- **Fever:** Often insidious onset with stepwise increase (initially remittent) to sustained fever of 39-40° C by end of 1st week.
- **Abdominal pain:** A cardinal feature in most cases, often accompanied by abdominal distension, tenderness and hypotonic bowel sounds.
- **Constipation/diarrhea:** Patients may have brief episode of diarrhea following ingestion of agent—subsequent constipation is common but patients may develop diarrhea (often bloody) later in illness following involvement of Peyer's patches.
- **Headache:** This is quite common in enteric fever; some patients may develop severe confusion, obtundation suggesting underlying encephalitis, meningitis or neuropsychiatric disturbance.
- **Relative bradycardia:** Although not seen in all patients, relative bradycardia (high temperature/normal pulse) is an important clue to the possibility of typhoid fever.
- **Rose spots:** Scattered 2-4 mm erythematous maculopapular lesions that blanch on pressure; typically appear in crops of 10 on upper abdomen and resolve within hours/days; less visible on darkly pigmented patients.

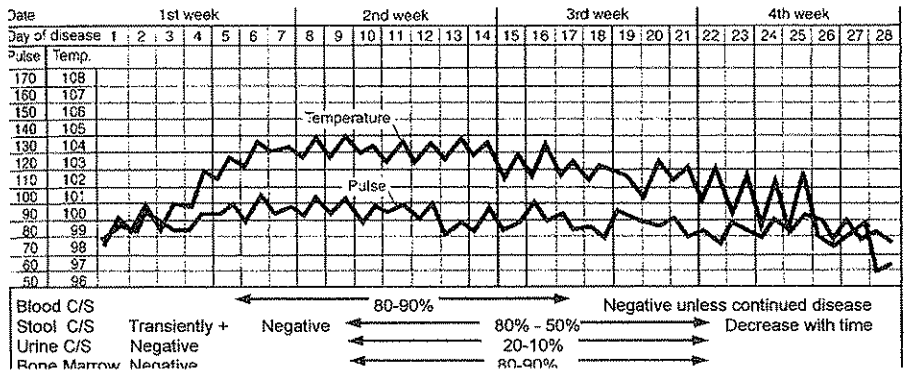
Table 1: Frequency of symptoms and signs in enteric fever (typhoid fever)

Symptoms	(%)	Physical findings	(%)
Fever	39-100	Fever	98-100
Headache	43-90	Abd tenderness	33-84
Nausea	23-36	Splenomegaly	23-65
Vomiting	24-35	Hepatomegaly	15-52
Abdominal cramps	8-52	Relative bradycardia	17-50
Diarrhea	30-57	Rose spots	2-46
Constipation	10-79	Rales/ronchi	4-84
Cough	11-86	Epistaxis	1-21
		Meningismus	1-12

Source: Table from Mandell: Infectious Diseases 5th ed. p. 1276

Epidemiological factors are important clues to the possibility of typhoid fever. Although typhoid fever may be acquired in the United States, most cases occur in travelers or immigrants from endemic areas such as Mexico, Peru, Chile or the Indian subcontinent. The incubation period depends upon the size of the inoculum but is generally between 3 and 21 days following exposure.

Table 2: Course of typhoid fever with culture/serology findings



2. What laboratory and diagnostic procedures are appropriate in suspected cases?

The gold standard for diagnosis of typhoid fever is confirmation by culture. Presence of positive cultures depends upon the site and stage of disease (Table 2)—blood cultures are usually positive early in disease (by week 1) but positive stool and urine cultures are usually delayed until later in the illness (week 2 and later).

Bone marrow cultures have a high yield in typhoid fever and may be positive in up to 90% of patients despite administration of prior antibiotics. The utility of serology (Widal test) is debated—in industrialized countries, exposure to non-*typhi Salmonella* commonly cause false positive tests; in the right clinical context, an acute serum—with subsequent 4-fold rise in titer—may be helpful in confirming the diagnosis.

Laboratory studies:

- ✓ **Anemia** develops rapidly and reaches a nadir during 3rd week of illness
- ✓ **Leukocytosis** may be seen in early disease but most patients develop leukopenia or have normal WBC
- ✓ **Liver tests:** Transient elevations of liver tests (AST, ALT, AP, LDH) are common during acute illness but jaundice is rare
- ✓ **DIC:** Signs of Disseminated Intravascular Coagulation (DIC) associated with GNR sepsis (↑ D-dimer, ↑ PT/PTT, ↓ plate) are seen in over 50% of patients

3. What conditions mimic typhoid fever?

The differential diagnosis of enteric fever is extensive; however, the following table lists some of the more common conditions along with pertinent diagnostic clues:

Causes of enteric fever	Clinical clues
Yersinia infection	Chronic liver disease; arthritis, erythema nodosum; older adults± pet exposure
Campylobacter	Stigmata of chronic liver disease; occ. Phlebitis; older adults± farm or small animal contact
Brucellosis	Headache; back pain; orchitis; hx of animal contact or raw cheese/milk ingestion
Typhoidal tularemia	Severe prostration; splenomegaly common; Dx via serology
Enteric fever "mimics"	
Leptospirosis	Relative bradycardia; conjunctival suffusion; liver/renal involvement; Dx via serology
Tuberculosis	Ileocecal mass (GI TB) or peritoneal thickeningon CT scan; CXR abnl in 50% of pts
Legionellosis	Pneumonia; Abnl LFT; pyuria or ↑ creatinine;
Viral hepatitis	Presence of jaundice (uncommon in typhoid)
Dengue fever	Hx of travel to endemic area; relative bradycardia; conjunctival suffusion; rash; Dx via serology
Infectious mononucleosis	Pharyngitis; lymphadenopathy; splenomegaly; atypical lymphs on blood smear; Dx via serology
Malaria	Hx of travel to endemica area; characterisitic fever pattern; splenomegaly; √ blood smear
Amebic liver abscess	RUQ pain c tenderness; √ RUQ ultrasound; Dx via amebic serology
Lymphoma	Presence of adenopathy (uncommon in typhoid fever); high LDH; severe anemia
Hematophagocytic syndrome	Fever, pancytopenia; ↑ LDH and serum ferritin; abnormal bone marrow confirms Dx

For more complete differential see Mandell: Infectious Diseases; Sixth edition P 1274-5.

4. What is the appropriate antibiotic therapy for typhoid fever?

The following table lists current recommendations for antibiotic therapy in typhoid (enteric) fever:

Antibiotic (preferred RX)	**Comments**
Any quinolones (PO or IV) x 10-14 days	Drug of choice with lowest relapse rate
TMP-SMX 5 mg/kg (IV/PO) q 6 hr x 10-14 days	May be 20% resistance to TMP/SMX
Antibiotic (alternate Rx)	
3rd generation cephalosporin (IV or PO) x 10-14 days	
Chloramphenicol 500 mg (IV or PO) q 6 hr x 10-14 days	Increasing resistance worldwide but excellent agent

- ✓ **Quinolones** have excellent intracellular penetration and are the drugs of choice in Rx of typhoid fever
- ✓ **Increasing antimicrobial resistance** (= 20%) to TMP/SMX, ampicillin, doxycycline and chloramphenicol
- ✓ **High dose corticosteroids** (e.g. dexamethasone 3 mg/kg load followed by 1 mg/kg q 6 hr x 48 hr) may improve survival in severe, life-threatening typhoid fever
- ✓ **Avoid aspirin therapy** in typhoid fever—this drug may precipitate acute hypotension.
- ✓ **Response to therapy** is generally slow with gradual defervescence over 3-5 days.

5. What are the complications of typhoid fever?

Once you suspect the diagnosis, be on the lookout for the following complications of typhoid:

- **Intestinal perforation/hemorrhage:** In pre-antibiotic era, these complications had a significant mortality and occurred in approximately 2-5% of patients, generally during 2nd or 3rd week of illness. In a patient with typhoid, suspect intestinal perforation in those with a sudden increase in abdominal pain/tenderness accompanied by leukocytosis and recurrence of fever. Intestinal perforation may be conservatively managed (e.g. no surgery) but more recent studies suggest improved survival with laparotomy and resection of involved bowel followed by primary closure.
- **Focal lesions:** As with other *Salmonella* serotypes, focal infection including endocarditis, meningitis, pneumonia, empyema, splenic/liver abscess, osteomyelitis and septic arthritis may rarely be seen with typhoid fever.
- **Chronic carrier state:** By definition, a chronic carrier has persistent infection in stool or urine lasting longer than one year. The chronic carrier state is more common in patients with underlying gallstones or nephrolithiasis; however, up to two thirds of patients have no history of previous typhoid fever.

Management of Neurocysticercosis

Neurocysticercosis (NCC) is a common problem in immigrants from Mexico/Central America and one of the most frequent causes of new onset seizure at Olive View. The diagnosis is usually confirmed by the presence of characteristic lesions on head CT scan (e.g. calcified nodule/cyst; viable cysts c scolex).

Principles of Neurocysticercosis therapy

- **Treat initial seizures:** Along with headache, a focal or generalized seizure may be the initial presentation for NCC (NCC is the most common cause of "new onset" seizure in the OVMC ER!). Prophylactic anti-seizure therapy is indicated in those with a high risk for seizure, especially symptomatic patients with multiple parenchymal lesions.
- **Anti-inflammatory therapy (Corticosteroids):** Initial corticosteroid therapy is indicated in patients with symptomatic disease (except for those presenting with seizure alone and "single calcified nodule) and should be administered *prior* to treatment with antiparasitic therapy (e.g. albendazole). Methotrexate may be used as a "steroid sparing" agent in selected cases.

Corticosteroid agent	Dosing
Prednisone	1 mg/kg x 5-10 days, followed by slow taper (can split dose and give BID)
Dexamethasone	0.1 mg/kg/day x 5-10 days , in divided doses followed by slow taper (Example: 2mg IV/PO q 6-8 hr)

- **Anti-parasitic therapy:** Controlled trials suggest that anti-parasitic therapy reduces the long term incidence of seizure in NCC. Except for patients with a "single calcified nodule", such therapy is potentially helpful (with important precautions) in most forms of NCC. Most experts recommend **albendazole** as initial therapy for NCC, with praziquantel reserved for those who fail to respond to the initial regimen.

Agent	Dosage	Comments
Albendazole	400 mg/kg PO BID Available in 400 mg tablets	Drug of choice for most patients Levels may increase c corticosteroid or anti-seizure medications Duration of therapy depends on severity of disease (1-4 weeks) Side effects: GI disturbance; N/V/Abd pain; hepatitis (1%) CNS complaints common in NCC
Praziquantel	50-100 mg /kg/day in 3 divided dailydoses Available in 600 mg tablets	Second line agent in most cases Serum levels reduced by cytochrome P-450 induction (e.g. corticosteroids; phenytoin; carbamazepine; phenobarbital) Increased levels with grapefruit juice; cimetidine; fatty/Hi CHO meals Side effects: N/V/ abd pain common; hepatitis: 25% CNS complaints common in NCC

Potential Risks of therapy: Antiparasitic therapy (APT) is not without risks—killing of cysts may lead to a life threatening "**CSF reaction**" characterized by cerebral edema, altered mental status and possible cerebral herniation. Avoid APT in patients with multiple cysts and significant cerebral edema (cysticercal encephalitis)—in these patients, treat with corticosteroid first and decide (on a case by case basis) on APT later. Do not give APT in patients with hydrocephalus or intraventricular cysts unless patient is evaluated for ventriculostomy by neurosurgeon.

- **Neurosurgery indications:** Neurosurgical consultation is indicated in the following situations:
  - ✓ **Hydrocephalus:** Patients with increased intracranial pressure (ICP) may require VP shunt

- ✓ **Intraventricular cysts:** These cysts are usually removed via neuroendoscopic surgery. In some cases, cysts may be treated medically, but only after placement of ventriculostomy to prevent hydrocephalus.
- ✓ **Subarachnoid cysts:** Neurosurgery removal may be indicated in patients with subarachnoid cysts that do not respond to anti-parasitic therapy.
- ✓ **Ocular cysts:** Intraocular (retinal) cysts are generally removed via vitriol-retinal surgery.

Neurocysticercosis—recommendations for therapy

The following table gives a quick overview of the recommended treatments for various forms of NCC:

NCC stage	Clinical presentation	Treatment
Single calcified, inactive nodule	Seizure +/- headache	Anti-seizure medications Corticosteroids indicated if headache Anti-parasitic therapy generally not necessary
Single parenchymal lesion **Viable or degenerating cysts**	Headache; seizure; focal signs	Corticosteroids Albendazole 400 mg PO BID x 7 days
Multiple parenchymal lesions (Cysticeral encephalitis: Diffuse edema secondary to degenerating cysts)	Headache; seizures Altered mental status Cerebral edema	Corticosteroids Albendazole 400 mg PO BID x 7 days Anti-seizure medication (prophylaxis) Consider ventricular shunt (cerebral edema)
Subarachnoid cyst Giant cysts: > 5 cm	Headache; seizure; focal signs	Corticosteroids Albendazole 400 mg PO BID x 14-28 days
Intraventricular cyst c hydrocephalus	Headache; N/V; ↑ ICP; hydrocephalus	Initial corticosteroids Neuroendoscopic surgery with removal ? medical therapy following ventriculostomy
Intraocular cysts	Visual abnormalities	Retinal surgery Avoid anti-parasitic meds

Checklist for Neurocysticercosis therapy…

Once you have made the diagnosis of NCC, use the following checklist as a guide for initiating therapy:

- ❑ **Treat initial seizures:** Use phenytoin, phenobarbital or gabapentin
  - ✓ Consider prophylactic anti-seizure meds in pts c multiple cysts and/or cerebral edema
- ❑ **Administer corticosteroids** for acute symptoms (Prednisone or dexamethasone)
  - ✓ Check PPD (or Quantiferon test), *Strongyloides* serology, Direct Eye exam (r/o retinal cyst)
- ❑ **Consider anti-parasitic therapy** (Albendazole 400 mg/BID or Praziquantel)
  - ✓ **Avoid immediate treatment** in patients with retinal cysts, multiple cysts (c cerebral edema) and patients with intraventricular cysts (with possible hydrocephalus)
- ❑ **Consult neurosurgery** in the following situations…
  - ✓ **Hydrocephalus** (Ventriculostomy or VP shunt often required)
  - ✓ **Multiple cysts** and cerebral edema (Ventriculostomy or VP shunt may be needed in selected cases)
  - ✓ **Subarachnoid cysts** that fail to respond to anti-parasitic therapy
  - ✓ **Intraventricular cysts** (Removal via neuroendoscopic surgery)
  - ✓ **Ocular cysticercosis** (need for surgical excision in patients with retinal cysts)

Source: UptoDate Accessed: 1/21/11; Emedicine: Accessed 1/22/11

ID Checklist: Travel Recommendations

It happens to all physicians—one week prior to travel, a patient, family member or friend calls you up and asks if they should take any "special precautions" before their river-rafting trip in New Guinea. Even if you haven't thought about tropical diseases since medical school, here's a checklist to get you up to speed on the risks they face and ways to avoid them…

- **Travel destination:** The risks involved in a safari in East Africa are different than a week in Paris—once you know the destination, check it out at the CDC Travel Health Web site (www.cdc.gov). This is the CDC's "Yellow Book" for traveler's health—an updated summary of travel risks according to region. You'll be able to obtain updated info on malaria risks, local outbreaks and recommended vaccines and prophylaxis measures.

- **Traveler's diarrhea:** Diarrheal illness is the most common medical illness encountered by the traveler. Most parts of the developing world represent a high risk for diarrheal disease. Warn the traveler about the dangers of raw food, hotel tap water, street vendors and the ice in their drinks (It may be tempting on hot day but the bacteria survive freezing!).

  Despite the precautionary measures, even the most meticulous traveler runs the risk of an "adverse event". For patients with significant diarrhea (> 24 hours of loose stools), quinolones (ciprofloxacin 500 BID or levofloxacin 500 mg x 1-3 days) are generally the treatment of choice in adults. Anti-motility agents (Immodium, Lomotil) can be quite helpful—especially if you have to endure that bus ride to the Pyramids!—but should be avoided in patients with true dysentery syndromes (+ risk of toxic megacolon). Typhoid vaccine is recommended for travelers going outside the usual tourist routes in areas where typhoid is endemic (Latin America, Asia).

- **Malaria risk:** For the majority of tropical travelers, malaria represents the most deadly risk likely to be encountered. See if the destination has chloroquine-resistant malaria and make sure your patient has the appropriate prophylaxis (Malarone [atovaquone/proguanil] is the drug of choice in most locations with chloroquine-resistant falciparum malaria).

- **Mosquito avoidance:** Don't rely completely on malaria chemoprophylaxis regimens—they're not 100% effective and can't prevent other mosquito-borne diseases such as dengue fever. Counsel your patient to avoid nighttime walks during high-risk periods (early evening). Patients should bring and use mosquito repellants (Look for preparations containing 15-20% DEET) and use mosquito nets when sleeping out in the open.

- **? Hepatitis risk:** Areas that have a high risk for traveler's diarrhea—most of the developing world—also represent a risk for Hepatitis A. The old approach to this problem—IM gamma globulin—is rarely used because of the availability of several recombinant Hepatitis A vaccines. For best results, the vaccines should be given at least one month prior to travel although partial protection may be provided even when given within a week of travel.

- **Miscellaneous vaccines:** The CDC website will outline regional risks such as Yellow Fever (Africa, South America) and Japanese Encephalitis (rural Asia). Make sure your patient has updated their polio and tetanus status—especially in those traveling to rural areas where health care is less available and sanitation is likely to be non-existent or marginal. Warn patients about the dangers of rabies in many parts of the developing world—rabies control is non-existent in some countries and represents a real risk to the unwary traveler.

For potentially complicated travel situations (e.g the pregnant traveler), it's best to ask for expert help—don't be afraid to contact a travel medicine specialist with the most up-to-date information.

HIV Physical Exam—Bedside Clues to a Clever Killer

Aside from careful questioning about HIV risk factors, your initial physical examination can provide clues to underlying HIV infection. The following clinical and laboratory findings—while sometimes non-specific—suggest impaired immunity and an early warning that HIV may be at the bottom of your patient's problems…

- ❑ **Face:** *Seborrheic dermatitis*—erythema with scaling of the paranasal areas and eyebrows—is common in the general population but also one of the earliest findings in HIV-infected patients. Be especially suspicious of HIV in at-risk patients with new-onset, recalcitrant seborrheic dermatitis.

- ❑ **Oral cavity:** *Oral hairy leukoplakia*—"corrugated" white patches on the side of the lateral aspect of the tongue—should always raise the possibility of HIV infection. An OHL lesion *can't* be scraped off with a tongue blade—a feature that differentiates it from the white lesions of *oral thrush* (candidiasis), another marker for HIV infection. Severe, unexplained *gingivitis* may also be seen in patients with underlying HIV.

- ❑ **Lymph nodes:** Unexplained, generalized *lymphadenopathy* should always raise the possibility of underlying HIV infection.

- ❑ **Skin:** In addition to the above lesions, there are additional skin findings that should suggest HIV infection…

  - **Herpes zoster:** Active, dermatomal herpes zoster should always raise the possibility of an underlying immunodeficiency such as HIV—leftover scarring or pigmentation from a previous episode in an at-risk patient is also a tip-off.
  - **Tinea pedis/onychomycosis:** *Tinea pedis* (athelete's foot) is very common—don't jump to the conclusion that your patient has HIV! Nevertheless, new-onset, recalcitrant tinea pedis—especially if it involves all 10 toes or responds poorly to therapy—could be the initial presentation of HIV infection. Look for the presence of proximal subungual *onychomycosis* (deformity and white discoloration of the *proximal* nail) since this condition is seen almost exclusively in patients with significant underlying immunodeficiency.
  - **Molluscum contagiosum:** *Molluscum contagiosum*—a papular skin eruption due to a sexually transmitted poxvirus—may worsen as the patient's immune system begins to fail.
  - **Kaposi's Sarcoma (KS):** Named after a Hungarian dermatologist, KS is now most commonly seen in advanced HIV infection. Nevertheless, the discrete, purple, non-blanching lesions may be the initial presentation for HIV infection; always check for their presence in the oral cavity since this may be a common site of asymptomatic lesions.

- ❑ **Genital:** Any signs of sexually transmitted genital tract disease—*urethritis, chancres, ulcerations, penile warts*—should raise the possibility of coinfection with HIV. Women with persistent vaginal discharge, or difficult-to-treat, recalcitrant *vaginal thrush* or *herpes* should be tested for HIV.

- ❑ **Anorectal:** *Anorectal warts* are more common in homosexual males and should be considered a marker for possible underlying HIV infection. As the immune system fails, proliferation of the warts often occurs—don't forget that HIV-infected patients have a higher incidence of anorectal squamous cell carcinoma—a neoplasm believed related to underlying papillomavirus infection.

- ❑ **Lymphopenia:** While not a finding on physical examination, the presence of *lymphopenia* on the patient's blood count could be a sign of HIV-induced immunodeficiency. Always be suspicious of HIV in patients with unexplained neutropenia or lymphopenia.

Identifying Primary HIV infection (PHI)

Physicians usually confirm HIV infection after a patient presents with an AIDS-related opportunistic infection or after the virus has been detected during routine HIV screening in an at-risk patient—in these situations patients have already had HIV for a number of years. How can HIV be detected at the earliest possible stage—when patients have just recently been exposed to the virus and are in the state of HIV seroconversion or "primary HIV infection"? An early diagnosis is especially important in order to block subsequent transmission of the virus to other at-risk partners.

What is the clinical syndrome of primary HIV infection?

Over 80% of individuals who experience primary HIV seroconversion are symptomatic (see Table 1)—unfortunately, many of these symptoms are non-specific and often overlooked by the average physician. In many respects, primary HIV infection is very similar to the "mono"-type syndromes seen with Epstein-barr virus (EBV) and cytomegalovirus (CMV). Despite the non-specific nature of primary HIV infection, a number of features should suggest the diagnosis:

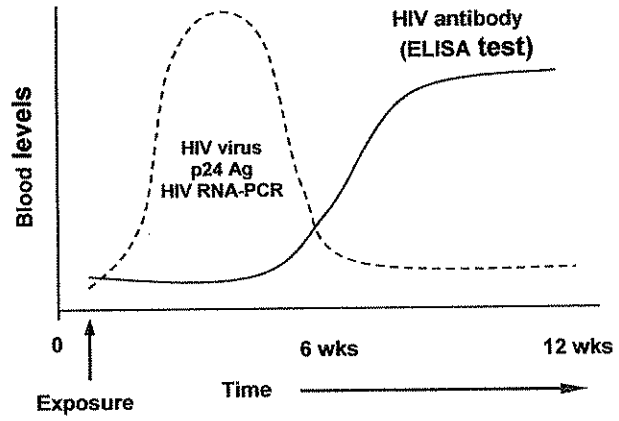
- **Fever/myalgias/malaise:** Almost all patients have fever (90%) and associated systemic symptoms (malaise, myalgias). Gastrointestinal symptoms such as nausea, vomiting and diarrhea are also common, sometimes leading to a false diagnosis of primary gastroenteritis.
- **Rash:** A truncal, maculopapular rash (erythematous macules, papules) that may mimic syphilis pityriasis rosea is quite common in patients with primary HIV infection (60% of patients). On rare occasions, patients may develop urticarial or vesicular eruptions.
- **Pharyngitis:** An erythematous pharyngitis is quite common in primary HIV infection (40% of pts); although less common, the presence of pharyngeal ulceration (8%) is a specific clue to the possibility of underlying HIV seroconversion.
- **Lymphadenopathy:** As with other viral syndromes (EBV, CMV), lymphadenopathy is common in primary HIV infection (37%). Although generalized lymphadenopathy may be seen, the nodes are especially prominent in the neck, occipital and axilla.

Other findings: In addition to this "mononucleosis" type syndrome, patients may present with other findings, especially neurological syndromes such as aseptic meningitis or encephalitis (see Table 2).

Table 1: Primary HIV infection—Clinical features

Symptom/sign	% of patients
Fever	87.5
Malaise	72.5
Rash	57.5
Headache	55.0
Night sweats	50.0
Sore throat	42.5
Lymphadenopathy	37.5
Arthralgia	27.5
Nasal congestion	17.5
Oral ulcers	7.5
Thrush	5.0

Source: [1]



What laboratory tests document primary HIV seroconversion?

As can be seen from the graph (above right), the standard HIV antibody tests (ELISA) used to "screen" for HIV are typically negative during the first few weeks of primary seroconversion—this can lead to a false

sense of security with regard to the presence of HIV infection. Tests designed to detect the actual presence of the virus—the p24 antigen test or viral load test (HIV RNA-PCR)—are required to diagnose infection during the first 6-12 weeks ("window period") following the initial exposure. Additional laboratory abnormalities seen during PHI include anemia, leukopenia, "atypical" lymphocytosis, thrombocytopenia and hepatitis.

What are some of the pitfalls in the diagnosis of HIV seroconversion?

When presented with a syndrome compatible with primary HIV seroconversion, keep in mind the following "pitfalls" which can lead to an overdiagnosis (false positive) or failure to make the diagnosis.

- ✓ **Missing the "window":** Failure to obtain specific viral test (p24 antigen or HIV RNA-PCR) during "window" period of seroconversion when HIV serology is negative.
- ✓ **False positive viral loads:** False positive HIV RNA-PCR test in patient *without* HIV seroconversion—in these cases the viral load is usually in levels less than 5000 copies/ml[3] and patients will fail to develop a + HIV-ELISA test.
- ✓ **Coinfections:** Concomitant seroconversion for another pathogen (EBV, CMV, HHV-6, Syphilis) acquired at the time of primary HIV seroconversion.

What other syndromes are associated with primary HIV infection?

In addition to the standard "mononucleosis" presentation of PHI, a number of other organ systems have been associated with HIV seroconversion including neurologic, cardiac and gastrointestinal syndromes (see Table 2)...

- **Neurological disease:** Primary HIV infection may present with any one of several neurological syndromes that might mislead the clinician. These include muscle (rhadomyolysis), neuropathies (Guillain-barre syndrome; facial palsy, brachial neuritis), CNS disease (aseptic meningitis; encephalitis) and spinal cord disease (myelopathy).
- **Gastrointestinal syndromes:** Gastrointestinal symptoms such as diarrhea and abdominal pain are common during PHI. In addition, small numbers of patients may develop oral thrush or oral hairy leukoplakia, syndromes generally associated with more advanced HIV infection.
- **Other conditions:** Other conditions seen with primary HIV infection include myocarditis, haemophagocytic syndrome and pancreatitis. Pelvic inflammatory disease (PID) suggests viral acquisition via a genital route; these patients may have prolonged, persistent pelvic pain that fails to respond to standard PID regimens.

Table 2: Syndromes associated with primary HIV seroconversion:

Acute rhabdomyolysis[1]	Facial palsy
Acute disseminated encephalomyelitis[2]	Guillain-Barré syndrome
Acute neurogenic urinary retention[3]	Haemophagocytic syndrome[6]
Aseptic meningitis	Myelopathy[7]
Brachial neuritis	Myocarditis[8]
Encephalopathy[4]	Lymphocytic alveolitis[9]
Esophageal candidiasis	Pancreatitis[10]
Esophageal ulcers[5]	Pelvic Inflammatory Disease (PID)

What is the treatment for primary HIV seroconversion?

This remains an unanswered question. Most patients with PHI will recover with development of some degree of HIV immunity associated with resolution of symptoms. Laboratory data will show a drop in HIV

viral load accompanied by a rise in CD4 T-cell counts to near normal levels. The utility of antiretroviral therapy in this population is uncertain and there is some evidence that early drug treatment may impair the development of immune response.

Nevertheless, there are some patients who appear to develop progressive HIV infection following primary HIV seroconversion. In these individuals, HIV viral loads will remain elevated and CD4 T-lymphocyte counts will continue to drop. A strong case can be made for intervention with administration of anti-retroviral therapy in this group. When a patient with PHI is identified, consult an HIV expert for the most up-to-date guidance on management of the syndrome—the patient may be a candidate for clinical trials designed to provide a definitive answer to questions concerning therapy of this condition.

What to do if you suspect primary HIV infection...

- ❑ **Consider the diagnosis:** Primary HIV is relatively non-specific and frequently missed by the primary care physician. Think about it in sexually active patients with a "mono" type syndrome accompanied by fever, rash or oral ulcers. Keep in mind that PHI may present with atypical neurological or gastrointestinal syndromes.
- ❑ **Ask about risk factors:** Always ask patients about risk behavior for HIV, especially unprotected sexual contact or needle use. Ask about previous HIV screening and try to question patients in a non-judgmental fashion with questions such as: "Do you have sex with men or women—or both? " "Do you inject drugs or share needles with others?"
- ❑ **Order the correct testing:** Remember that the standard HIV serology (antibody) may not be positive for 6-12 weeks (rarely even longer)—order a test (HIV viral load; p24 antigen) that permits detection of active virus during the initial "window".
- ❑ **Don't forget about coinfections:** Remember that other viruses/bacteria may be passed at the time of HIV transmission—consider the possibility of other viral infections (EBV; CMV; HHV-6) and other sexually transmitted pathogens (e.g. syphilis; GC; chlamydia). This is especially important in individuals with symptoms that might be less common with PHI (e.g. uveitis in secondary syphilis).
- ❑ **Consider the need for anti-viral therapy:** This is generally not a decision that needs to be made on an immediate basis—once you have confirmed the diagnosis consult with an HIV expert for additional advice.

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Outpatient management of HIV infection (2011)

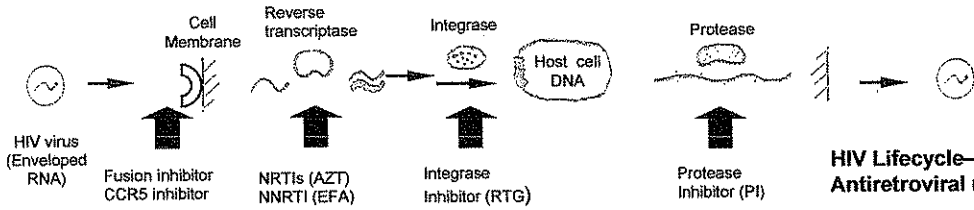
The following represents a brief outline of HIV management including a description of available drugs as well as a checklist for the patient's clinic visit:

Goals of therapy in HIV management:

- Suppress virus to "undetectable" levels (< 50 copies/ml)
- Raise T-cell (CD4) levels to "normal" (> 500 cells/mm^3)
- Minimize the risk of opportunistic infection (e.g. PCP, MAC) in patients with low T-cell counts.
- Manage the potential complications of drug therapy and long-term HIV infection (e.g. lipodystrophy)
- Deal with the psychosocial problems including depression, homelessness and substance abuse
- Reduce risk of transmission to other individuals

When should you start antiretroviral therapy?

- Patient is symptomatic due to HIV infection *or*
- CD4 <350 cells/mm3 (Some experts recommend starting at CD4<500 cells/mm3) *or*
- Viral load > 100,000 (RT-PCR assay)



HIV Lifecycle—Actions of Antiretroviral medications

What drugs are available for treatment of HIV infection?

Class	Drug (Generic)	Brand Name	Dose	Main Side Effects
Nucleoside Reverse Transcriptase Inhib. (NRTIs)	AZT (Zidovudine)	Retrovir	300 mg BID	N+V (50%); headache (60%); anemia, neutropenia
	ABA (Abacavir)	Ziagen	300 mg BID	Hypersensitivity syndrome (5%): malaise, fever, abdominal pain, rash (Caution: fatal on rechallenge)
	3TC (Lamivudine)	Epivir	150 mg BID	Neuropathy; anemia/N+V in combo with AZT
	FTC (Emtricitabine)	Emtriva	200 mg daily	Mild headache; GI disturbances
	DDI (Didanosine)	Videx	200 mg BID	Pancreatitis:6% neuropathy:20%;↑ LFT diarrhea:25%
	D4T (Stavudine)	Zerit	40 mg BID	Neuropathy (20%); rare pancreatitis; lactic acidosis
Nucleotide RTI	Tenofovir (TFV)	Viread	300 mg daily	N/V (10%); rare lactic acidosis; renal insufficiency
Combination Drugs	Abacavir/3TC	Epzicom	1 tab Q day	See individual drugs
	AZT/ 3TC	Combivir	1 tab BID	See individual drugs
	AZT/ 3TC/Abacavir	Trizivir	1 tab BID	See individual drugs
	Tenofovir/FTC	Truvada	1 tab Q day	See individual drugs
	TFV/FTC/EFA	Atripla	1 tab Q day	See individual drugs
Non-nucleoside RTIs (NNRTIs)	Efavirenz (EFA)-	Sustiva	600 mg QHS	CNS effects (depression,nightmares,insomnia); Rash-18%; ? teratogenic—do not use in pregnancy
	Etravirine	Intellence	200 mg BID	Rash-9%; Hepatitis (avoid in Hep B/C)
	Nevirapine	Virammune	200 mg BID	Hepatitis (caution in pt with underlying liver disease); Rash in up to 35% (rare Stevens-Johnson syndrome)
Protease Inhibitors (PIs)	Atazanavir*	Reyataz	300 mg daily	Asymp ↑ indirect bili; RIT: 100 Qday
	Darunavir*	Prezista	600 mg BID	Hepatitis; Rare SJ syndrome; RIT: 100 mg BID
	Fosamprenavir*	Lexiva	700 mg BID	N/V (40-75%); diarrhea; rash-28%; RIT: 100 BID
* Require ritonavir boost	Indinavir*	Crixivan	800 mg BID	Kidney stones; ↑ indirect bili (10-15%); RIT: 100 BID
	Saquinavir*	Fortavase	1000 mg BID	GI disturbance; RIT: 100 mg BID
	Tipranavir*	Aptivus	500 mg BID	GI disturb; ↑ lipids; hepatitis; RIT: 200 BID
				RIT: Ritonavir boosting
	Lopinavir/ritonavir	Kaletra	2 tabs BID	N+V/diarrhea; hyperlipidemia; rare pancreatitis
	Nelfinavir	Viracept	1250 mg BID	Diarrhea (up to 50%); No ritonavir boost
CCR5 Inhibitor	Maraviroc	Selzentry	300 mg BID	↑ LFTs; Need CCR5 receptor test
Integrase Inhibitor	Raltegravir (RTG)	Isentress	400 mg BID	Diarrhea, nausea, fatigue, headache, and itching
Fusion inhibitor	Enfuvirtide (T-20)	Fuzeon	90 mg sc BID	Local injection site rxn; rare (<1%) hypersensitivity

Anti-retroviral Regimens Recommended for Treatment-Naïve Patients*

NRTI Backbone

Tenofovir/FTC
(Truvada 1 tab Qday)

Or

AZT/3TC
(Combivir 1 tab BID)

+

NNRTI (Efavirenz†)
Tenofovir/FTC/Efavirenz (Atripla 1 tab Qday)

Or

Protease Inhibitor
Atazanavir (300 mg Qday) + Ritonavir (100mg Qday)
Darunavir (600 mg BID) + Ritonavir (100mg BID)

Or

Integrase inhibitor
Raltegravir (400 mg BID)

†Use efavirenz with caution in patients with history of depression or psychiatric disease. Do not use in pregnancy
* Preferred regimen for pregnant women: Lopinivir/ritonavir (2 tabs BID) + AZT/3TC (1 tab BID) DHHS Guidelines: Dec 1, 2009

When seeing a patient in clinic, make sure to check the following ...

- ❑ **HIV medications:** Record the patient's medications and ask about possible side effects. Question the patient about medication compliance—poor adherence to therapy is the #1 cause of drug failure!

- ❑ **T-cell count and viral load:** Record the most recent T-cell count and viral load. In a patient on a stable regimen, monitor the T-cell count and viral load every 3 months—look for a viral load < 400 copies/ml and a rising T-cell count. In a patient on a new regimen, check these parameters after one month of therapy—if not undetectable, the viral load should at least be lower than value prior to change in therapy.

- ❑ **Opportunistic infection (OI) prophylaxis:** Based on the patient's clinical history and T-cell count, make sure the patient is receiving appropriate prophylaxis to prevent new-onset (primary prophylaxis) or recurrent (secondary prophylaxis) opportunistic infections. Consider stopping OI prophylaxis in patients with sustained response to HIV anti-viral meds (e.g. CD4 > 300; viral load-undetectable).

  - **PCP** (CD4<200): TMP-SMX—1 DS tab QD (or MWF); dapsone—100 mg PO QD; atovaquone 1500 mg PO QD
  - **MAI** (CD4<75): Azithromycin 1250 mg (5 x 250 mg tab) PO q week
  - **TB** (+PPD): Isoniazid 300 mg PO QD x 1 year
  - **Cryptococcal meningitis** (Secondary prophylaxis): Fluconazole 200 mg PO QD
  - **CMV retinitis** (Secondary prophylaxis): Valganciclovir 900 mg PO QD
  - **Recurrent HSV infection**: Acyclovir 400 mg PO BID

- ❑ **Metabolic complications of HIV infection/drug therapy:**

  - **Lipodystrophy syndrome:** √ "Buffalo" hump, lipoatrophy in cheeks and extremities, + abdominal fat
  - **Hyperlipidemia:** √ fasting trigylcerides and cholesterol twice yearly
  - **Diabetes:** √ $HgBA_1C$ yearly

- ❑ **Other STDs and screening tests:** Ask patient about unprotected sexual contacts and stress the importance of condom use

  - **Chlamydia/Gonorrhea:** √ urine chlamydia/GC test yearly in asymptomatic pt
  - **Syphilis:** √ RPR twice a year
  - **PPD:** √ yearly
  - **Pap smear:** √ on yearly basis (HIV+ women have a higher rate of invasive cervical carcinoma)

- ❑ **Is the patient depressed, homeless or abusing drugs?**

  Ask patient about the above psychosocial stressors and document patient response in chart—if necessary, refer patient to psychiatrist or social worker.

Fever of Unknown Origin (FUO) in the AIDS patient

1. **Know the definition of "FUO" in AIDS patients:** "FUO" has a specific definition and includes the following features…

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

   With the above criteria, consider the following conditions:

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

Etiology	# Pts (%)	Etiology	# Pts (%)
Infection		Neoplasia	
MAI	22 (31)	Lymphoma	5 (7)
PCP	10 (13)	Kaposi's Sarcoma	1 (1)
CMV	8 (11)		
Histoplasmosis	5 (7)	Miscellaneous	
Viral (not CMV)*	5 (7)	Drug fever	2 (3)
Bacterial	4 (5)	Castleman's disease	1 (1)
MTB	4 (5)		
Parasitic†	2 (3)		

* HepC/B;adenovirus pneumo; HSV esophagitis; v zoster enceph.

† Cerebral toxoplasmosis; disseminated cryptosporidiosis

Source: 72 fever episodes Armstrong et al., CID 1999;28:341-5

2. **What is the T-cell count?** This is a key piece of information in weighing the probability of various infections—the standard opportunistic infections associated with AIDS (e.g. PCP, cryptococcus, CMV MAI) are much more common in patients with CD4 counts less than 200 cells mm3. Patients with higher counts are more likely to have infection with "standard" pathogens seen in the general population. The T-cell count also conditions the clinical presentation. For example, patients with tuberculosis and low CD4 counts (< 200) are more likely to have disseminated infection with atypical pulmonary infiltrates; TB patients with higher counts generally present with radiographic patterns (e.g. upper lobe infiltrates/cavitation) traditionally associated with TB.

3. **Is the patient receiving PCP prophylaxis?** If the patient has been given PCP prophylaxis (e.g. TMP/SMX, dapsone, atovaquone)—and is actually taking the medicine—the likelihood of PCP is much lower. Likewise, patients taking MAI prophylaxis (e.g. azithromycin 1200 mg q 21 wks) are far less likely to develop disseminated MAI infection.

4. **What are the patient's symptoms?** See if the patient's clinical presentation fits any of the following "patterns":

   - **Headache/CNS:** Think cryptococcus, toxoplasmosis and CNS lymphoma. Obtain a CT scan (c contrast) and lumbar puncture.

   - **Pulmonary:** Focal pulmonary infiltrates→bacterial pneumonia
     Diffuse pulmonary infiltrates→PCP,cryptococcus,MTB, histoplasmosis
     Diffuse pulmonary nodules (miliary nodules)→TB, histoplasmosis, coxy
     Hilar adenopathy: TB, fungal, lymphoma

   - **Gastrointestinal:**
     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: Consider cryptosporidium and microsporidium; less likely

to have fever; need to order specific O+P
Post-antibiotic: *C. difficile*
Hepatosplenomegaly: May be seen with HIV alone; however, think disseminated TB, histoplasmosis, lymphoma or bacillary angiomatosis

- **Neuropathy:** May be due to HIV, vit def (B12) or meds (DDI, D4T) but think CMV in pts with low CD4 counts
- **Anemia:** Think lymphoma, parvovirus B19, histoplasmosis and drug toxicity (AZT, TMP/SMX)
- **Effusions:** (pleural, pericardial, abdominal): Primary body cavity lymphoma (+HHV8); crypto; TB; histo

5. Are there any exposure or geographic factors? Ask about the following risk factors…

- **Central America/Midwest US:** Histoplasmosis (usually has HS megaly c lymphadenopathy)
- **Hx of TB exposure:** Immigrants from TB endemic areas; ask about previous PPD or family TB hx
- **Travel to Southwest** (e.g. Las Vegas, Palm Springs, Lancaster, Bakersfield): risk for coxy
- **SE 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)
- **Hx of IVDU:** Consider *S. aureus* endocarditis or bacteremia

6. Is this immune reconstitution (IRIS) or drug fever?

- **IRIS:** Inflammatory syndrome that occurs within 3-4 months after starting effective HIV Rx
  May be associated with underlying OI such as MAI, cryptococcus or CMV

- **Drug fever:**
  TMP/SMX or dapsone: Maculopapular rash
  Anemia c hemolytic anemia: G6PD def due to sulfa drugs or dapsone
  Abacavir: Fever, rash, abd pain—usually within 12 weeks of starting Rx
  Chance of fatality with rechallenge
  Nevirapine: MP rash after starting drug in 25% of patients

What you need to do in an HIV/AIDS patient c persistent fever:

- ❑ **H+P:** Careful physical examination and history
- ❑ **Eye examination** (Dilated funduscopic exam—look for subclinical CMV retinitis)
- ❑ **CXR:** Look for focal pneumonitis, diffuse infiltrates and hilar adenopathy (see above)
  PCP induction and sputum AFB/fungi in pts with infiltrates; √ PPD in all patients
- ❑ **√ LFTs:** ↑ Alk PO4 may be clue to disseminated infection (e.g. TB, histo) or lymphoma
- ❑ **√ HgB and LDH:** High LDH in pt with low HgB suggests lymphoma (Consider bone marrow Bx)
- ❑ **Abdominal CT scan:** Look for HSmegaly/adenopathy (MAI, MTB, lymphoma), focal liver lesions (Bacillary angiomatosis), colitis (CMV, *C. difficile*)
- ❑ **Serology:** √ Serum cryptococcal antigen, urine histo antigen (in at risk pts), RPR, CMV IgG, toxo
- ❑ **Miscellaneous tests:** Serum cortisol (r/o adrenal insufficiency); Giemsa stain of buffy coat to r/o histo
- ❑ **Biopsy:** FNA any large node to r/o lymphoma, granulomatous disease
  Colonoscopy/biopsy in pts with evidence of colitis or heme+ stools
- ❑ **Antibiotic trial:** May be indicated in selected patients
  Pneumonia→trial of TMP/SMX and 3rd generation cephalosporin (e.g. ceftriaxone)
  Diarrhea→ consider PO ciprofloxacin (check stool cultures first)
  Low CD4 ct→ consider trial of MAI rx (clarithromycin + ethambutol) after blood AFB cultures
- ❑ **? Corticosteroid trial:** In patients with possible IRIS (But first rule out active infection!)

Malignant Otitis Externa (MOE) in diabetes

Your diabetic patient is afebrile but has a persistent severe earache accompanied by ear drainage— this clinical scenario should suggest malignant otitis externa (MOE), a serious, potentially life-threatening infection of the temporal bone and surrounding soft-tissue structures.

1. An "Evil Earache"—Clinical presentation of Malignant Otitis Externa

Although most common in older patients with non-insulin dependent diabetes, MOE can also develop in immunocompromised patients with underlying neutropenia or AIDS. When considering the possibility of MOE, keep the following in mind the following clinical features…

- ✓ **Persistent severe ear pain** is a hallmark of the disease and helps to differentiate it from other more benign conditions such as external otitis. Presence of trismus or pain in the temporal mandibular joint (TMJ) suggests extension to subtemporal tissues and raises the possibility of underlying MOE.
- ✓ **Lack of fever:** Most patients lack fever except those with extensive, late-stage disease or patients with pyogenic complications.
- ✓ **Physical examination** almost always demonstrates abnormalities of the external auditory canal such as erythema, swelling and drainage. Look especially for narrowing of the canal with evidence of inflamed granulation tissue at the bone-cartilage junction.
- ✓ **Delay in diagnosis:** Recent studies suggest significant delays in diagnosis of MOE due to "less extreme" symptoms—in patients with "ear infection", widespread use of short-course oral or topical (e.g. eardrops) quinolones therapy may have altered the clinical presentation [1].

2. Pseudomonas Alert!—the microbiology of MOE

Pathogenic organisms enter the mastoid and skull base through the fissures of Santorini, tiny crevices that occur in the cartilage lining the external auditory meatus. Underlying microvascular disease also plays a predisposing role; this may account for the fact that the condition is more common in older diabetics.

Although other bacterial pathogens may be seen, almost most all cases of MOE in diabetics (95%+) are due to infection with *Pseudomonas aeruginosa.* This organism is not a normal inhabitant of the external ear; however, the organism is found in water and two thirds of MOE cases are associated with antecedent ear irrigation. In rare cases, fungal pathogens (*Aspergillus*, *Scedosporium apiospermum, Candida* species) are associated with MOE, especially in immunocompromised patients with underlying AIDS or neutropenia.

3. Malignant otitis externa—confirming an oft-delayed diagnosis

The diagnosis of MOE is a clinical one—suspect the condition in any diabetic (or immunocompromised) patient with swelling/erythema of the external auditory canal accompanied by significant, persistent ear pain. When you suspect the possibility of MOE, order the following tests:

- **Laboratory studies:** An elevated **erythrocyte sedimentation rate** is seen in almost all patients with MOE and is helpful in differentiating the condition from more benign causes of "earache". In patients with ear drainage, obtain routine **bacterial and fungal cultures**, recognizing that these may be misleading and don't always represent the organism causing the underlying infection.
- **CT/MRI scans:** In patients with suspected MOE, obtain an initial CT scan, with special attention to the ear canal, temporal bone and surrounding soft tissue structures. While soft tissue abnormalities are quite common in this condition (see Table 1), bony erosion—signifying involvement of the underlying temporal bone—may not be seen till later stages of the infection. Although less sensitive for bony involvement, an MRI scan may allow detection of MOE at an earlier stage.

- **Radionuclide scanning:** Both technetium-99m labeled bone scanning and gallium scan are quite sensitive for MOE; however, they lack specificity and may be positive in other conditions such as malignancy. Gallium scan (but not bone scan) may be helpful in following clinical response to treatment.
- **Biopsy:** In patients with suspected MOE, consult an otolaryngologist as soon as possible for biopsy and culture of deeper tissues—the pathology will help confirm the diagnosis and cultures such as infected bone; this will confirm the diagnosis and provide more reliable culture results— important information considering the prolonged antibiotic therapy required.

Table 1: CT findings in MOE

Findings	% cases*
Abnormality of external auditory canal	100
Fluid in mastoid or middle ear	80
Disease around Eustachian tube	64
Mass effect in nasopharynx	54
Subtemporal extension	54
Parapharyngeal space involvement	54
Crossing of midline	36
Disease in masticator space	27
Clivus erosion	9
Intracranial extension	9

* reported in approximately 11 cases as described in Rubin et al. Radiology 1990;174:391-4.

Table 2: Antibiotic therapy in MOE

Organism	Therapy*
Pseudomonas aeruginosa	Severely ill, toxic patient Ciprofloxacin (IV) + cefepime or piperacillin Mild-moderately ill patient Ciprofloxacin (PO) Alternate therapy Aminoglycoside + cefepime or piperacillin
Aspergillus sp. Scedosporium sp.	Liposomal amphotericin B Voriconazole

* Treat for 8-12 weeks depending upon the clinical response. Fungal pathogens may require longer therapy in immunocompromised patients.

4. A quinolone "quantum leap"—antibiotic therapy for MOE

Prolonged, effective antibiotic therapy is the key to managing MOE. The availability of quinolones active against *Pseudomonas aeruginosa* has greatly improved therapy for this condition. Although surgical biopsy is important in confirming the diagnosis, since the advent of more effective antibiotics, surgical debridement of the underlying bone is no longer necessary in most. When choosing an appropriate antibiotic regimen, keep the following considerations in mind…

- ✓ **Seriously ill patients** should receive initial combination therapy intravenous quinolones in combination with a B-lactam agent until the patients is clinically stable. Quinolone resistance is now reported in up to 30% of *Pseudomonas* isolates [2]—if the patient has received previous quinolone therapy, always add an additional agent (e.g. carbapenem, aminoglycoside or cefepime) until culture results are available.
- ✓ **Quinolones** are well absorbed following oral adminstration—patients can be switched to PO therapy as soon as they are stable or in patients with mild-moderately severe disease. Since these patients have a deep-seated osteomyelitis of the temporal bone, most experts recommend prolonged therapy (8-12 weeks) in documented cases.
- ✓ **Aminoglycoside therapy** is now less commonly used due to potential ototoxic and nephrotoxic side effects; however, these agents may still be valuable in patients with quinolone resistant isolates.
- ✓ **Fungal infection:** In patients with suspected fungal infection, liposomal amphotericin B is the drug of choice for initial, empiric therapy. Although there is little clinical experience with voriconazole in this condition, the drug has excellent activity against a number of pertinent fungal pathogens, including *Scedosporium apiospermum,* an organism that is traditionally resistant to amphotericin B.

5. A wayward ear infection—complications of MOE

Most of the complications of MOE occur with extension of the infection into surrounding soft tissue structures. When confronted with a case of MOE, keep in mind the following complications:

- **Cranial nerve dysfunction:** Not surprisingly, involvement of local cranial nerves is one of the most common complications of MOE. Involvement of the VII (facial) nerve is the most common; look for evidence of facial palsy on physical examination. With petrous ridge involvement, patients may rarely have Vth nerve involvement (e.g. anterior facial pain) or VI nerve involvement (e.g. double vision). With involvement of the jugular foramen, rare patients may develop Villaret's syndrome—involvement of IX, X and XII cranial nerves as they exit the jugular foramen (Look for hoarseness, decreased gag reflex and inability to shrug the shoulder).
- **Local soft tissue infection:** In addition to cranial nerve dysfunction, keep in mind the effects infection extension to local soft tissues—patients may complain of trismus (e.g. masseter involvement) or TMJ involvement.
- **CNS infection:** On rare occasions this infection may extend intracranially with involvement of the brain or meninges. Local extension to the dura may lead to venous thrombosis of the sigmoid sinus; this presents with worsening of headache, often accompanied by evidence of increased intracranial pressure (e.g. papilledema).

What to do if you suspect a case of malignant otitis externa...

- ❑ **Consider the diagnosis**, especially in older diabetic patients with persistent ear pain and drainage. Remember that patients with previous quinolone or corticosteroid therapy (oral or topical) may have a less severe presentation.
- ❑ **Order radiographic imaging:** If you suspect MOE, order a head CT scan with special views of the temporal bone. While the CT scan permits better visualization of the bone, MRI scan may be able to detect suggestive soft tissue involvement at an earlier stage.
- ❑ **Obtain a bone biopsy/culture:** While culture of ear drainage may sometimes demonstrate the pathogen, it is better to confirm the diagnosis with biopsy and culture of the underlying infected bone. Request an ENT consult for evaluation and diagnostic biopsy; make sure that any culture material is handled properly, including cultures for mycobacteria and fungi. Although the yield is low, obtain blood cultures in toxic, febrile patients.
- ❑ **Start antibiotic therapy:** In seriously ill patients, start with parenteral quinolone and B-lactam (e.g. cefepime or piperacillin/tazobactam). Subsequent therapy depends upon culture results and antimicrobial susceptibilities.
- ❑ **Follow the patient:** Once a patient appears to have responded, switch the patient to oral quinolones and treat for 8-12 weeks depending upon the clinical response (e.g. clinical improvement; reduction of ESR). In addition to clinical parameters (e.g. improvement in symptoms and physical examination), obtain a repeat CT (or MRI) scan and ESR to help document resolution.
- ❑ **Watch out for complications:** Remember the close proximity of this infection to vital structures in the brain and surrounding tissues—be on the lookout for cranial nerve dysfunction, especially involvement of CN VII (facial palsy), XI, X, XII (Villaret's syndrome) and VI (Abducen's palsy). Rare patients may develop venous sinus thrombosis, meningitis or brain abscess.
- ❑ **Counsel the patient:** In patients with underlying diabetes, avoid vigorous ear irrigation non-sterile water; use sterile water instead and encourage the patient to report any symptoms of ear pain as soon as possible. In at-risk patients, urge use of ear plugs when swimming or bathing whenever possible.

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[1] Grandis JR, Branstetter BF and Yu VL. The changing face of malignant (necrotizing) exteran otitis: clinical, radiological, and anatomic correlations. Lancet Infect Dis 2004; 4:34-9.

[2] Berenholz L, Katsenell U, Harell M. Evolving resistant pseudomonas to ciprofloxacin in malignant otitis externa. Laryngoscope 2002; 112: 1619-22.

Tips on managing Diabetic Foot Infection

Here are some recommendations on managing this common and potentially life-threatening condition:

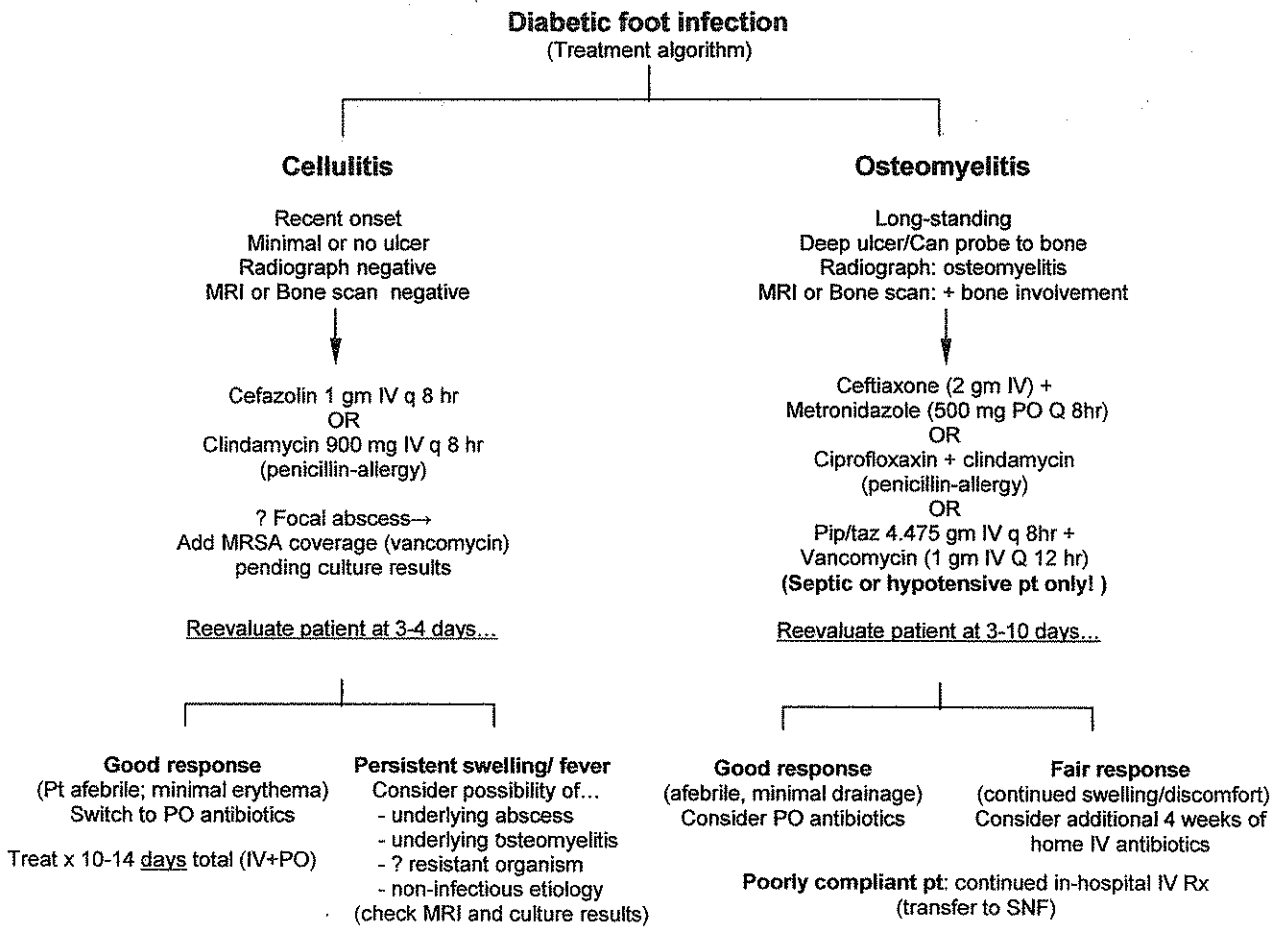
1. **Examine the foot** with special attention to the following diagnostic signs…
   - ✓ **If gangrene or soft-tissue air is present**, call a surgeon immediately—the patient may have gas gangrene and require immediate surgery.
   - ✓ **Is there a foul smell?** Anaerobes are likely to be present and require antibiotic coverage.
   - ✓ **Examine the toes** for evidence of tinea pedis or onychomycosis—these seemingly "harmless" infections may be the entry point for life-threatening bacterial infection of the foot.
   - ✓ **Measure and probe any ulcer**—osteomyelitis is likely present if a blunt probe can reach bone.
   - ✓ **Squeeze the affected area**—if you can express pus the patient will likely require surgical drainage of an underlying soft-tissue abscess suppurative tenosynovitis.
   - ✓ **Check the patient's peripheral sensation**—most patients with diabetic foot infection have some degree of peripheral neuropathy that may dull the pain of the infection.
   - ✓ **Check and record pulses in the lower extremity**—a poor blood supply will hamper healing and impair antibiotic delivery. In those with poor pulses, check an ankle-brachial index (ABI)—an ABI < 0.8 is abnormal and suggests the ulcer is unlikely to heal.

2. **Culture any drainage** from an ulcer; unroof any blisters and culture the fluid.
   - **Deep is best**: Most diabetic foot ulcers have mixed aerobic and anaerobic flora—the bugs on the surface may not always represent organisms causing infection of underlying bone. Try to get the surgeon to debride the wound in order to obtain cultures from deeper structures—such cultures more accurately reflect the true pathogens.
   - **A single bug?** The presence of a single organism—especially in those with *Staphylococcus aureus*—suggests the likely cause of the underlying osteomyelitis. Keep in mind the increasing incidence of resistant organisms such as MRSA—without a culture such patients may receive inappropriate therapy.
   - **? Blood cultures:** Obtain blood cultures in any patient with fever and toxicity.

3. **Obtain a radiograph of the foot:** Any patient with a foot ulcer should have plain radiographs looking for a fracture, foreign body, soft-tissue air or underlying osteomyelitis. Consider obtaining an **MRI of the foot** in the following circumstances:
   - ✓ High suspicion of underlying osteomyelitis (e.g. patient with deep ulcer) despite a negative plain radiograph.
   - ✓ Patients with a poor clinical response to appropriate antibiotics.
   - ✓ Possibility of a deep, soft-tissue abscess or tenosynovitis.
   - ✓ Uncertainty about the extent of infection (the "tip of the iceberg" phenomenon).

4. **Consider the possibility of a cellulitis "mimic":** Don't forget that several syndromes can mimic diabetic foot infection…
   - **Charcot's foot:** Seen in patients with "good' blood supply (bounding pulses) and peripheral neuropathy—may completely mimic cellulitis/osteomyelitis with swelling and erythema. More common in "midfoot" region and likely to cause "rocker bottom" foot deformity (loss of longitudinal and transverse arch).

- **Gout:** Check a uric acid level and look for evidence of 1st metatarsophalangeal (podagra) involvement—patients develop pain, erythema and swelling that mimic cellulitis. May need to tap joint to look for crystals.
- **Ischemia:** Dry gangrene may be present though there is a high risk of secondary infection ("wet" gangrene"). Calciphylaxis is a form of ischemia seen in end stage renal disease patients with secondary hyperparathyroidism and calcified vessels.
- **Deep venous thrombosis:** Check venous duplex in suspect cases.



Choose oral therapy based on culture results and likely pathogens:		
Oral therapy regimens	**Dose***	**Comment**
Amoxicillin/clavulanic acid	875 mg BID	Use in mixed (aerobe + anaerobe) infection
Cephalexin	500 mg q 6 hr	Good for uncomplicated cellulitis (Grp A strep or *S. aureus*)
Ciprofloxacin	500 mg BID	Use for GNR infection
Clindamycin	600 mg q 6 hr	Use in combination with cipro for mixed infection
Metronidazole	500 mg q 12 hr	Use in combination with cipro for mixed infection
Rifampin	600 mg q day	Use in combination with cipro for tmp/smx for *S. aureus*
TMP/SMX (Bactrim DS)	2 tabs BID	Use in combo with rifampin for MRSA infection
* Dosing for 70 kg pt with normal renal function		

5. **Obtain a surgical consult as soon as possible** for …

   - Debridement of devitalized tissue or drainage of underlying soft tissue abscess.
   - Patients with poor vascular supply (decreased pulses or ABI < 0.8)
   - Patients with gangrene or possible necrotizing fasciitis.

6. **Control the serum glucose**—tight control of serum glucose allows for better control of infection.

7. **Call ID fellow in any case of suspected osteomyelitis**

8. **Call Continuity of Care nurse (Ext. 3352) to help arrange home IV antibiotics**

A murderous mold—Rhinocerebral mucormycosis

A diabetic patient presents with coma and diabetic ketoacidosis. Despite aggressive control of the diabetes, his mental status remains altered and he develops unilateral facial swelling with apparent opthalmoplegia—what's the problem? Your patient could have **rhinocerebral mucormycosis** (RCM), a rare but life-threatening condition seen in patients with diabetic ketoacidosis. RCM is most often due to fungi of the order *Mucorales,* a common bread mold that includes the genuses of *Absidia, Rhizopus* and *Mucor*. The devastating nature of this infection should not be underestimated—in some studies, despite treatment, the mortality may be over 50%.

1. The clinical presentation of rhinocerebral mucormycosis

Common predisposing factors for this infection are listed in Table 1—although diabetic ketoacidosis remains the most common associated condition, there is an increasing incidence of RCM in immunocompromised patients, especially in patients receiving high-dose corticosteroids or those with prolonged neutropenia. While some patients present with the full-blown syndrome, the clinical presentation may be quite insidious and delays in recognition are common.

Table 2 shows the incidence of various clinical features in a series of 118 patients diagnosed with rhinocerebral mucormycosis. Rapid recognition of this infection is critical—early, aggressive treatment gives the patient the greatest chance of survival. Unfortunately, early clinical signs such as fever, headache and facial pain are relatively non-specific and mimic other conditions. Although still an uncommon condition, consider the possibility of RCM in any diabetic patient complaining of fever, headache and facial pain.

Table 1: Predisposing factors

Disease	#*	%
Diabetes	87	60
Renal disease	11	7
Renal transplant	10	7
Desferoxamine toxicity	9	6.2
Leukemia	8	5.5
Steroid therapy	6	4.2
Hematologic disorder	5	3.4
Other (9 disorders)	11	9

* n=145 Adapted from Yohai et al and Hendrickson et al

Table 2: Clinical presentation of RCM

Sign/symptom	%	Sign/symptom	%
Fever	44	Leukocytosis	19
Nasal necrosis/ulceration	38	Nasal discharge	18
Facial/periorbital swelling	34	Nasal stuffiness	17
Decreased vision	30	Corneal anesthesia	17
Opthalmoplegia	29	Palatal/gingival necrosis	14
Sinusitis	26	Afferent papillary defect	13
Headache	25	CN VII palsy	11
Facial pain	22	Periorbital pain	11
Altered Mental Status	22		

Table adapted from Youhai et al.

When seeing a patient with possible RCM, keep the following in mind...

- **Clinical presentation:** The clinical presentation of RCM can be quite non-specific—fever is often absent and initial findings relatively minimal. At the time of clinical presentation, less than half of the cases demonstrate more specific signs such as facial swelling, ophthalmoplegia and nasalpalatal necrosis) at the time of presentation.
- **Specific findings:** More specific findings such as nasal necrosis/ulceration, ophthalmoplegia and palatal necrosis suggest advanced disease with a higher risk of serious complications and mortality. Look for these findings on physical examination.
- **Diabetic ketoacidosis:** DKA is a specific risk factor for rhinocerebral mucormycosis—be especially suspicious of RCM in DKA patients who present with coma or fail to "wake up" following correction of the metabolic defect.

2. "At risk" brain and vision--complications of RCM

Rhinocerebral mucormycosis follows localized fungal sinus infection with subsequent invasion of adjacent cranial structures. The organism has a propensity invade blood vessels causing tissue infarction and necrosis. The disease begins with sinus involvement and spreads along vascular pathways to involve the orbit and structures behind the facial bones. In a patient with suspected RCM, look for the following complications, all signs of potentially life-threatening disease:

√ **Orbital cellulitis:** Involvement of orbital structures with eye/orbital pain, limitation of eye movement and proptosis.

√ **Orbital apex syndrome:** Involvement of structures at orbital apex with external ophthalmoplegia (paralysis of extraocular muscles), loss of vision (compression of CN II) and ptosis.

√ **Cavernous sinus thrombosis:** Thrombosis of cavernous sinus with external opthalmoplegia (CN III, IV, VI), corneal anesthesia and loss of facial sensation (CN V), proptosis, conjunctival injection and retinal hemorrhage.

√ **Cerebral invasion:** Direct cerebral involvement with frontal lobe abscess or infarction with hemiparesis or neurological complaints.

3. RCM—making an early diagnosis of a deadly infection

Although a characteristic clinical picture is often enough to suspect the condition, definitive management requires tissue biopsy for documentation of infection. In an RCM suspect, look for the following:

- **Perform a careful physical examination** of the nasal turbinates and soft palate. Look for ulceration, bloody discharge and evidence of tissue infarction and gangrene.
- **Obtain radiographic imaging of the face and sinuses:** Although a CT scan is sometimes negative in early phases of the disease, it will usually show sinusitis and often demonstrates bony destruction in later stages. If possible, obtain an MRI—this modality is better at imaging the soft tissues and may allow you to pick up complications such as cavernous sinus thrombosis at an earlier stage.
- **Biopsy the affected tissues:** Obtain a biopsy of any tissue that appears to be involved. Send the sample to the laboratory for both pathology and culture. Instruct the microbiology laboratory to avoid grinding up the specimen—the fungus is quite fragile and it is more likely to survive if they "mince" the tissue prior to inoculation of fungal media.

  On pathology, look for the broad, non-septate hyphae (that branch at right angles) which characterize Mucor species. Aspergillosis infection may also "mimic" RCM; however, the organism looks different on tissue pathology—it demonstrates narrow, septate hyphae that branch at an acute (30-60° angle).

4. Fighting a fatal fungus—therapy for rhinocerebral mucormycosis

Proper therapy of rhinocerebral mucormycosis requires a combination of anti-fungal therapy and aggressive surgical debridement of affected tissues. The molds responsible for RCM are sensitive to amphotericin B but generally resistant to other agents including azoles (e.g. fluconazole, voriconazole) and caspofungin. Proper therapy requires high-dose amphotericin B, best administered as a liposomal compound to minimize toxicity. When confronted by a patient with suspect RCM, utilize the following:

- **Anti-fungal therapy:** Because of the relative resistance of fungal isolates, start high-dose amphotericin B (0.75-1.0 mg/kg/day) with rapid escalation to maximal dosing; the total cumulative dose may be as high as 2-3 grams (over 3-4 weeks) depending upon response to therapy. Because of the nephrotoxicity of this drug, many experts prefer a liposomal amphotericin B product (Ambisome)

and start the drug at 5 – 7.5 mg/kg/day; duration of therapy is usually 3-4 weeks but may be longer in established cases.

- **Request surgical evaluation:** A surgical consultant (ENT) should evaluate a suspected case as soon as possible to assist with diagnostic procedures and plan any subsequent surgical debridement. Aggressive surgery is often critical to patient survival—especially in advanced cases where there is extensive tissue infarction and possibly brain involvement. Such an approach may include radical procedures such as orbital exeneration or surgical excision of affected bony structures (partial or total maxillectomy); successful treatment may leave the patient with significant facial deformity or loss of vision following enucleation of the eye. Neurosurgical procedures may be required if there is any evidence of brain or meningeal involvement.
- **Treat diabetes and reduce immunosuppression.** Aggressive management of the underlying diabetes is a key factor in managing a patient with RCM. In those receiving corticosteroids or other agents, if possible, try to minimize immunosuppression by reducing the doses of the offending agents.
- **Consider adjunctive treatments:** Although not proven in randomized controlled trials, hyperbaric oxygen therapy has shown anecdotal benefit in some clinical series. Recent reports suggest that granulocyte-monocyte colony stimulating factor (GM-CSF) may be beneficial, even in patients who are not neutropenic. None of these adjunctive measures should replace aggressive antifungal and surgical treatments.

5. A guarded prognosis—will the patient survive?

The prognosis in rhinocerebral mucormycosis is somewhat guarded—studies suggest that the mortality is between 25 to 50% of cases, despite appropriate therapy. Patients with "early" disease limited to one sinus have a better prognosis; individuals with bilateral sinus involvement or more extensive disease clearly have a higher mortality.

Involvement of the central nervous system is a particularly poor prognostic factor—although some may survive following aggressive treatment, patients with hemiparesis, brain or cavernous sinus thrombosis have a high mortality rate. The patient's underlying disease also plays a role in disease prognosis—those with underlying leukemia, renal disease or desferoxamine therapy have particularly poor outcomes [i]. As with many fatal diseases, early identification is likely to lead to a better chance of survival.

In suspected RCM, take the following measures...

- ❑ **Carefully examine the patient** and look for clues to underlying RCM, especially unilateral facial edema (sinusitis), nasal or palatal eschar (tissue infarction) and evidence of eye involvement (proptosis, ophthalmoplegia); check for presence of corneal anesthesia suggesting CN V compromise.
- ❑ **Start anti-fungal therapy:** Because of the relative resistance of fungal isolates and the need for high levels of potentially toxic drug, most experts initiate therapy with high-dose liposomal amphotericin B (dose at 5.0-7.5 mg/kg/day). Although echinocandins have relatively little in vitro activity against *Mucor* species, recent animal studies suggest that caspofungin may have synergistic when used in combination with amphotericin B.
- ❑ **Obtain radiographic imaging:** Order a CT scan or MRI of the head and sinuses—if available, the MRI is more sensitive to the early, soft tissue involvement seen in the condition.
- ❑ **Request surgical evaluation:** A surgical consultant should evaluate a suspected case as soon as possible in order to help obtain tissue specimens for definitive diagnosis as well as help plan any subsequent surgical debridement. Studies suggest that patients who have early, definitive surgery have a better survival compared to patients where surgery is delayed.
- ❑ **Treat diabetes and reduce immunosuppression:** Aggressive management of the underlying diabetes is a key factor in managing a patient with RCM. In patients receiving

corticosteroids or immunosuppressive agents, if possible try to minimize immunosuppression by reducing the doses of the offending agents.

- **Consider adjunctive treatments:** Although not proven in randomized controlled trials, hyperbaric oxygen therapy has shown anecdotal benefit in some clinical series. Recent reports suggest that granulocyte-monocyte colony-stimulating factor (GM-CSF) may be beneficial, even in patients who are not neutropenic. None of these adjunctive measures should replace aggressive antifungal and surgical treatments.

[i] Yohai RA, Bullock JD, Azia AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. Surv Opthalmol 1994; 39:3.

ID Miscellany

A compendium of additional ID topics

"Possum Fever"—Murine Typhus in Los Angeles

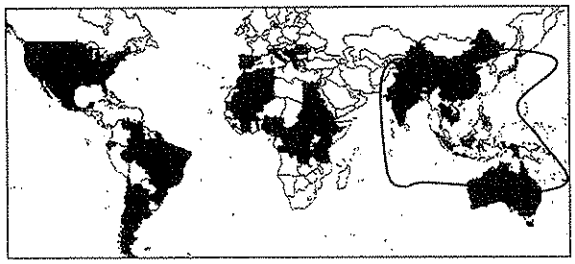
Fever, headache and rash—the first consideration should be meningococcal disease; don't forget the possibility of murine typhus—our local, homegrown rickettsial disease. What follows is a brief guide to diagnosis and management of this uncommon—but important—infection in Los Angeles.

1. What is the cause and epidemiology of murine typhus?

The syndrome of murine typhus is caused by one of two species of rickettsia—*Rickettsia typhi* and *Rickettsia felis.* These species have slightly different epidemiological circumstances—*R typhi* is associated with a rat-flea-human cycle, *R. felis* is linked to a opossum-cat-flea-human cycle. In Los Angeles, *R. felis* predominates with most human cases associated with exposure to cat fleas (X. felis) acting as a vector to transmit the agent from local wild animal populations. In addition to the clinical presentation, several epidemiological facts are important in estimating the likelihood of murine typhus in any individual patient:

- **Worldwide distribution:** Murine typhus is found in temperate and subtropical regions throughout the world; while it may be seen in rural areas, areas near coasts (seaports) with large rat populations represent specific risk locales. In the United States, recent outbreaks have occurred in South Texas (Corpus Christi area), Los Angeles and the Hawaiin islands.
- **Season:** Most cases occur in the summer/fall although cases have been reported year round in warm climates.
- **LA epidemiology:** In Los Angeles, the majority of cases occur in a region northwest of downtown in the communities of Pasadena, Glendale and Mount Washington.

Table 1: Worldwide distribution of murine typhus*



*Map based on case reports and serological surveys in both animal and human populations. Distribution is likely to be highly variable in any one country and depends on climate, control and exposure to rodent populations. Outlined area shows range of scrub typhus—a clinical illness that often mimics murine typhus.

Table 2: Signs and symptoms in murine typhus*

Sign or symptom	Cumulative course (%)	At presentation (%)
Fever	98	96
Headache	75	45
Chills	66	44
Rash	54	18
Myalgia	46	33
Nausea/vomiting	45	30
Diarrhea	26	18
Abdominal pain	23	18
Cough	35	16
Arthralgia	23	9
Confusion	8	5

* Based on 80 pts reported in JAMA 1991;266:1365-70

2. What is the typical clinical presentation of murine typhus?

As with most rickettisial illnesses, murine typhus is associated with an abrupt onset of fever, headache and myalgias; rash is seen in up to 50% of patients but may not be apparent until several days into the illness. In addition to the epidemiological clues, there are several clinical features that should suggest the disease:

- ✓ **Fever:** Patients experience an abrupt onset of fever (often up to 40° C) with an appropriate tachycardia.
- ✓ **Rash:** Although a key feature in diagnosis, only 18% of patients have rash on clinical presentation and up to 50% of patients never develop a rash. When present, the rash is an erythematous maculopapular rash that begins on the trunk and spreads to the extremities (centrifugal spread). It may first occur on the inner aspect of the arms and in the axilla. Petechial eruptions are seen in 10% of patients; rash on palms/soles is quite uncommon but has been reported. Because of the delayed presentation, the rash may be mistaken for an allergic reaction if the patient has received antibiotics.
- ✓ **Conjunctival injection:** A common, but important clue to the possibility of murine typhus—is also seen in leptospirosis and dengue fever.

- ✓ **Leukopenia/thrombocytopenia:** Although leukocytosis may appear later in the illness (2nd week), patients often have neutropenia or a normal leukocyte count early in the illness. Thrombocytopenia may be seen during the second week of illness and is a clue to the possibility of rickettisial disease as well as viral illness such as dengue fever.
- ✓ **Abnormal LFTs:** Although jaundice is quite uncommon, almost all patients have some abnormalities of liver function tests (e.g. AST, ALT, alkaline phosphatase) which serve as important clues to the possibility of murine typhus.

Although considered a "milder" rickettsial disease, mortality can occur (1-2%) and patients may rarely develop severe manifestations such as meningoencephalitis , acute renal failure, acute congestive heart failure and gastrointestinal bleeding.

3. Laboratory diagnosis of murine typhus: Serological testing is the mainstay for diagnosis of murine typhus. Don't be mislead by a "negative" serum titer—only 20% of patients will have a high-positive titer at clinical presentation so that definitive diagnosis depends upon demonstrating a 4-fold rise in titer over 3-4 weeks. The following tests are available for diagnosis of murine typhus:

- **Microimmunoflourescence titer for *R. typhi* :** This is the most specific serological test for murine typhus with titers designed to detect a specific rickettisial species.
- **Weil-Felix test:** This is the classical test for rickettisial diseases where serum is tested against a battery of *Proteus* antigens (murine typhus demonstrates a rise in *Proteus* OX-19, *Proteus* OX-K antigens). There is greater overlap with other rickettisial diseases, some of which have different patterns of antibody reactivity.
- **Additional testing:** Additional tests available through research laboratories include nucleic acid based testing (e.g. PCR), immunohistochemical staining of formalin-fixed tissues and cell culture techniques.

> **Note:** Do not wait for positive serology before starting therapy in suspected cases—although serology may be positive at clinical presentation, seroconversion may be delayed several weeks in the majority of cases.

4. Diseases that "mimic" murine typhus: The following conditions are often considered in patients with murine typhus:

Condition	Comments
Typhoid fever	Insidious onset; relative bradycardia (e.g. high fever, low pulse); rash is different (Rose spots are erythematous macules/papules on abdomen)
Leptospirosis	Conjunctival injection but relative bradycardia (high fever, low pulse) on exam; presence of jaundice and renal function abnormalities far less common in murine typhus
Dengue fever	Travel to endemic region (Mexico, Carribean, SE Asia, Pacific); Transient erythematous rash with development of petechiae in later stages.
Malaria	Hx of travel to endemic area; √ peripheral smear

5. What is the treatment for murine typhus? Tetracyclines (e.g. doxycycline) and chloramphenicol are the "drugs of choice" for treatment of murine typhus. With doxycycline, studies suggest the "time to defervescence" is 4-5 days though patients usually start feeling better within 24-48 hours of start of therapy. Chloramphenicol is an excellent drug for rickettisial disease but is generally reserved for patients unable to take tetracyclines. Quinolones have in vitro activity against rickettsia; there are studies suggesting that quinolones are effective in treatment of murine typhus although recent case reports indicate that quinolones are less effective than tetracycline.

What to do if you suspect murine typhus:

- **Take a careful history** and specifically ask about exposure to rats, oppossums, cats and flea bites. Epidemiological clues are particularly important—murine typhus needs to be considered in certain geographic areas and knowledge of the local conditions is vital. Although most cases are acquired in the immediate area, travelers can contract murine typhus in certain foreign countries.
- **Look for clues** to the possibility of murine typhus, especially the abrupt onset of fever accompanied by headaches and myalgias. Although not always on admission, the development of the characteristic rash is an important clue though present in only 50% of patients. On laboratory examination, leukopenia and abnormal liver tests support the diagnosis and help rule out other considerations.
- **Order serologies** on all suspected cases but keep in mind that only 20% of patients have a positive titer (MIF= 1:128) at clinical presentation. Request both acute and convalescent (3-4 weeks later) titers in order to document seroconversion.
- **Start empiric therapy**—oral doxycycline in patients able to take PO; IV doxycycline in individuals requiring parenteral therapy.

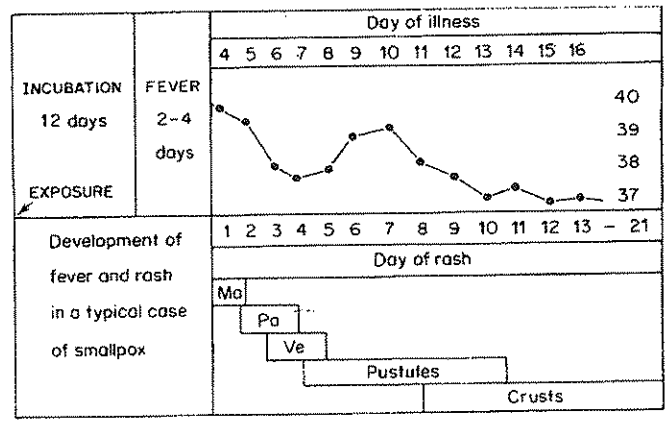
Smallpox vs. chickenpox—differential diagnosis

Most physicians have never seen a case of smallpox and would have difficulty differentiating it from other causes of vesicular/bullous skin disease. Chicken pox—now becoming less common because of the availability of a new live, attentuated vaccine—is the disease most likely to be confused with smallpox. Although differentiation may be difficult, in most cases the two diseases demonstrate characteristic features that permit clinical differentiation…

1. Differential features of rash: smallpox vs. chickenpox

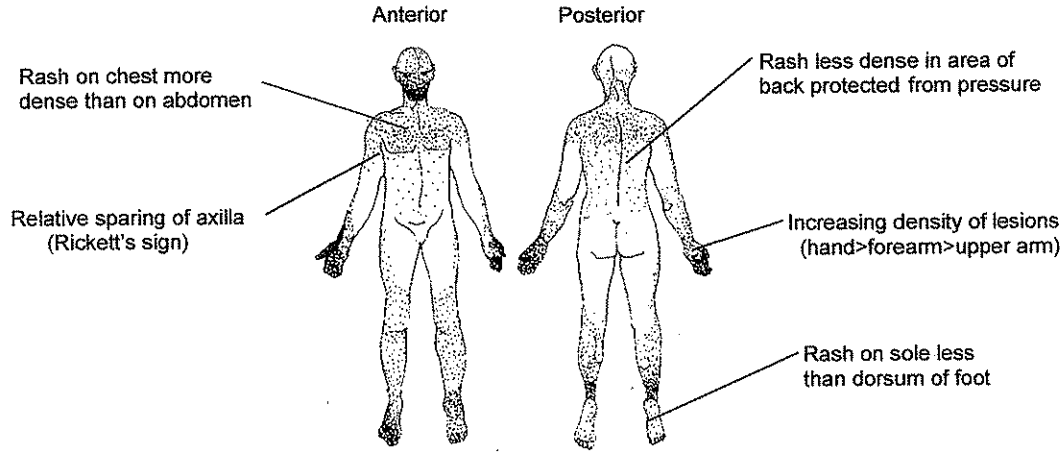
Feature	Smallpox	Chickenpox
Onset	2-3 days fever, malaise prior to onset of rash	Rash onset with fever
Distribution	Centrifugal (starts on extremities)	Centripital (Scalp,face trunk)
Evolution	Slow (days) evolution of rash from macular to papular to vesicular	Rapid evolution of rash—evolution from macular lesion to pustule within 24 hours
Flexural regions (axilla)	Relative sparing of axilla	Equal density in axilla
Palms/soles	Frequent involvement hands and feet (Dorsal surface > ventral surface)	Rare involvement of hands and feet
Timing	Lesions at same stage of development	"Crops" of lesions at different stages of development

2. Development of fever and rash in a typical case of smallpox



Ma=macules; Pa=papules; Ve=vesicles. *(From D. Baxby, 1991, 'Poxviruses'*, in Textbook of Human Virology, *(ed. R.B. Belshe).*

3. Distribution of lesions in smallpox



The "cold" reality of hepatitis C complications

Although it has significant effects on the development of cirrhosis, hepatitis C is a systemic illness with significant extrahepatic complications—these are especially common in patients with hepatitis C-associated mixed cryoglobulinemia. In your patients with hepatitis C, be on the lookout for the following associated conditions/complications:

- **Mixed cryoglobulinemia (MC):** Approximately 50% of patients with hepatitis C have detectable cryoglobulinemia although less than 10% actually develop clinical symptoms associated with the complication. Hepatitis C is most closely associated with MC Type II (Polyclonal IgG + monoclonal IgA,IgM or IgG) and MC type III (Polyclonal IgG + monoclonal IgM, IgG or IgA) although selected studies suggest an additional association with MC Type 1(isolated monoclonal IgG, IgM with lymphoproliferative disease.

  Common clinical manifestations include palpable purpura (cutaneous vasculitis), peripheral neuropathy, glomerular disease and arthritis/arthralgias (see below). Although the long term benefit is unclear, recent trials suggest that interferon based regimens (e.g. interferon + corticosteroids; interferon + ribavirin) can decrease cryoglobulin levels and lead to clinical improvement.

- **Cryoglobulinemic vasculitis:** Patients with cryoglobulinemia may develop a cutaeous vasculitis, usually characterized by palpable purpura, papules and ulceration in the lower extremities; these lesions are frequently painful or itchy. Skin biopsy demonstrates "leukocytoclastic vascultis"—a manifestation of immune complex vascultitis with small vessel involvement and mononuclear cell infiltrate.

- **Porphyria cutanea tarda (PCT):** This condition is characterized by the presence of vesicles and bullae (sometime hemorrhagic) on sun exposed areas, especially the dorsal aspect of the hands. In addition to the photosensitivity, patients develop hyper- and hypopigmentation, hirsuitism (usually on the face) and skin thickening similar to scleroderma. PCT is seen with increased frequency in patients with underlying cirrhosis. While only a small percentage of hepatitis C patients develop PCT (< 5%), there seems to be an epidemiological link between PCT and hepatitis C, especially in Southern European populations—in some studies, up to 50% of patients with PCT have underlying hepatitis C. Although phlebotomy is the traditional treatment for PCT, at least one case documented disappearance of PCT following interferon therapy[1].

- **Membranoproliferative glomerulonephritis (MPGN):** This syndrome—characterized by renal insufficiency and nephrotic range proteinuria (> 3 g/24 hr) is the most common renal manifestation of hepatitis C. Most of these cases have underlying mixed cryoglobulinemia and hypocomplementemia. Although signs and symptoms of liver disease may not be present, up to 50% of these cases have some evidence of liver cirrhosis on liver biopsy. Interferon based treatment regimens (interferon + corticosteroids) may provide short term benefit with reductions of proteinuria although there is generally minimal improvement in renal function and the proteinuria tends to recur with completion of therapy.

- **Sjögren syndrome/lymphocytic sialoadenitis:** Patients with hepatitis C may develop a lymphocytic sialoadenitis that is resembles a milder form of idiopathic Sjögren syndrome. Of these individuals, only about 10% develop "sicca" symptoms (e.g. xerophthalmia: dry eyes; xerostomia: dry mouth) and most generally lack the laboratory abnormalities (anti-SSA/Ro, anti-SSB/La antibodies) seen with classic Sjögren syndrome. As of yet, there are no clinical trials investigating the effect of interferon based therapies on this complication.

- **Lymphoproliferative disorders:** Approximately 10% of patients with mixed cryoglobulinemia and hepatitis C will develop a B-cell malignancy, most commonly a follicular lymphoma or lymphoplasmacytoid/immunocytoma (Lp/Ic) subtype. Compared with other patient populations, hepatitis C patients with lymphoma have a particularly high incidence of extranodal involvement in the liver and salivary glands [2]. There is also an association between hepatitis C infection and mucosa-associated lymphoid tissue lymphoma (MALT) [3].

Interferon-based therapies may be beneficial in hepatitis C patients with low grade lymphomas—clearance of HCV may lead to regression of the tumor [4]. Patients with high-grade lymphoma associated with HCV still require intensive, systemic chemotherapy. Studies suggest that patients with low-grade lymphomas associated with hepatitis C may experience regression following treatment with interferon and HCV clearance; patients with high-grade lymphoma still require systemic chemotherapy.

- **HCV-related neuropathy:** Patients with HCV-associated mixed cryoglobulinemia may develop an associated neuropathy ranging from mononeuritis multiplex to a painful, symmetric polyneuropathy. There are also cases of polyarteritis nodosa associated with HCV—these individuals typically develop an asymmetric polyneuritis with prominent motor symptoms. In general, HCV-related neuropathies respond poorly to interferon therapy; however, a combination of interferon and plasmapheresis may be quite effective in management of HCV-associated polyarteritis nodosa [5].

- **Other conditions associated with HCV infection:** In addition to the above syndromes, there are additional conditions associated with HCV infection. Some of these are autoimmune phenomenon that follow treatment of HCV with interferon-based regimens. In your patients with HCV, be on the lookout for the following syndromes:

Condition	Comments
Mooren ulcer[6]	A progressive ulcerated keratitis that responds to interferon Rx
Lichen planus	Extremely pruritic, flattop, purple papules—there may be a link with HCV, especially in patients with underlying HCV-associated cirrhosis.
Osteosclerosis[7]	Rare bone disorder with increased bone mass, increased bone turnover and painful extremities during active disease.
Arthritis	HCV associated with oligoarticular or polyarticular non-erosive arthritis that mimics rheumatoid arthritis.
Thyroid disease	HCV patients—especially women—have a higher incidence of thyroid disorders (e.g. hypothyroidism); however, interferon therapy may unmask autoimmune thyroiditis with subsequent Grave's disease, Hashimoto's thyroiditis and hypothyrodism.
Interferon-induced retinopathy	Most common in patients with underlying hypertension or diabetes—seen in 60% of HCV patients receiving interferon.

Source: Ali A, Zein NN. Hepatitis C infection: A systemic disease with extrahepatic manifestations. Clev Clinic J Med 2005;72:1005-19.

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Osteomyelitis—clinical clues to optimize therapy

Chronic osteomyelitis is a potentially debilitating infection that generally requires prolonged antibiotic therapy combined with aggressive surgical management. When called to see such a patient, use this checklist to evaluate the case and help determine the best approach to treatment and monitoring:

- ☐ **Review previous antibiotic therapy and culture results.** The identity of the organism is critical in determining optimal therapy. If possible, hold off on antibiotic therapy till there is an attempt to get a representative specimen for culture. Isolates from deep bone biopsy or blood culture are the most reliable—positive cultures from draining sinuses or superficial wounds may be helpful but must be interpreted with caution. In these cases, a single organism is more likely to be significant—mixed infection (with multiple bacteria) could be misleading since all these isolates may not represent the true bone pathogen (this is a situation where deep debridement/biopsy might be helpful prior to committing a patient to a long course of treatment). Likewise, review the antibiotic history—failure to respond to a prolonged course of antibiotics suggests 1) the wrong diagnosis 2) inadequate surgical debridement 3) poor drug delivery [inadequate absorption or poor vascular supply] 4) immunocompromised patient or 5) poor patient compliance.

- ☐ **What is the source?** While the source may be obvious in an individual case (e.g. *Staph aureus* bacteremia in an intravenous drug user), keep in mind the possibility of bacteremia from a distant site. On physical examination, check for underlying dental disease (? gingivitis, dental abscess), endocarditis (? Heart murmur), gastrointestinal disease (? heme + stool; ? diverticular or perirectal abscess) and genitourinary disease (? UTI, prostatitis). In patients with recent surgery/hospitalization, consider the possibility of infection from intravenous lines or post-operative infection. In special situations, look for the following clues:

- ☐ **Consider the patient and underlying disease:** The presence of comorbidities (e.g. diabetes, HIV, immunosuppressive agents) may alter response to therapy. Although there are no clear guidelines, such conditions often require more prolonged antibiotic therapy and closer followup. The presence of significant immunosuppression suggests the possibility of "exotic" pathogens such as fungi or mycobacteria.

- ☐ **Could this be an unusual organism?** A poor response to previous therapy might suggest an "exotic" organism not covered by the current antibiotic treatment. Take a careful history and specifically ask about the following risk/historical factors:
  - **History of TB exposure:** ? family history of TB; hx of immigration or overseas travel; previous PPD status
  - **Travel/residence history:** Obtain a detailed travel and residence history—consider the possibility of coccidioidomycosis (SW USA), histoplasmosis (Midwest, Central America) and blastomycosis (Mississippi Valley)
  - **Hx of hospitalization:** In patients with recent hospitalization, don't forget nosocomial pathogens related to IV lines (staphylococci; *Candida* sp.), genitourinary (GNRs; enterococcus, *Candida* sp) and wound infection.
  - **Animal/pet exposure:** Ask about animal bites, pets at home and farm exposure
  - **Food history:** Specifically ask about raw milk/cheese (e.g brucellosis, *Salmonella* sp.)
  - **Prolonged hospitalization** (? *Candida* species), travel, pets (*Pasteurella* species) and unusual food ingestion (raw milk/cheese: ? *Brucellosis, Salmonella* species)

- ☐ **Is this an osteomyelitis mimic?** Bone tumors (primary and metastatic), bone infarction (e.g. sickle cell anemia), metabolic disorders (Diabetes with Charcot's joint) and rheumatologic diseases (gout; reflex sympathetic dystrophy) may mimic osteomyelitis—don't automatically assume the bone/joint is infected.

- **Review the radiograph:** Review the patient's radiographs with attention to the following features:
  - **Progression of radiographic findings** and corresponding time course: With osteomyelitis, one usually sees progressive bone destruction when serial radiographs are compared.
  - **Presence of sequestrum and foreign bodies:** This is critical for subsequent therapy—such lesions require debridement/excision for cure of the underlying infection. Sequestra are segments of necrotic bone separated from surrounding bone by granulation tissue. Retained—or implanted— foreign bodies are especially important in post-traumatic osteomyelitis—cure will be close to impossible unless such fragments are removed.
  - **Presence of vascular calcification:** Suggests poor blood supply with impaired antibiotic delivery
  - **Proximity to soft tissue ulcer:** Suggest "contiguous" osteomyelitis—deep culture of the ulcer may reveal the putative pathogen.
  - **? Involvement of adjacent joint or soft tissue structures (MRI):** In rare cases, osteomyelitis may spread to adjacent joints via penetration of the joint capsule—in this case, cure will require surgical drainage of the affected joint.

  The utility of radiographic studies depends upon the timing of the osteomyelitis (early vs late) and the nature of the radiographic study. Plain film radiographs are a good initial study—a positive film (+ bone erosion, osteolysis) is strongly supportive of osteomyelitis in the right clinical setting. Remember; however, that it takes 10-14 days before such findings are apparent on plain radiographs. Other studies (e.g. bone scan, leukocyte scan, MRI) are more sensitive and may pick up signs of osteomyelitis at an earlier stage. Unfortunately, in some situations, some of these studies may be too sensitive—don't automatically assume osteomyelitis based on a positive scan unless the clinical situation is supportive and other findings point to osteomyelitis.

Imaging technique	*Sensitivity (%) in pt with osteomyelitis*	*Specificity (%) in patient with osteomyelitis*
Plain-film radiography	62 ± 9.7 *	64 ± 11.8
Tc-99m bone scintigraphy	86 ± 5.9	45 ± 8.9
Indium In 111-labeled leukocyte scan	89 ± 7.3	79 ± 9.0
Magnetic resonance imaging	99†	81

* Values (except for MRI) are mean ± standard deviation
† For MRI, values represent best case (sensitivity) and worst case (specificity)
Adapted from Eckman MH et al. JAMA 1995;273:712-20

- **Is there a need for surgical intervention?** In addition to antibiotic therapy, surgical debridement is frequently necessary, especially in patients with post-traumatic osteomyelitis (e.g. presence of sequestrum) or those with osteomyelitis associated with peripheral vascular disease (e.g. excision of necrotic bone or gangrenous tissue). In patients with infected "hardware", removal of the foreign body is usually necessary for cure—antibiotics "alone" are likely to be ineffective in this situation.

- **Remember the principles of antibiotic therapy:**
  - **Choose the right drug** based on available culture results. If possible, avoid scattershot "empiric" therapy without an attempt to obtain an appropriate culture.
  - **"Bone friendly" antibiotics:** Among antibiotics, penetration into bone is variable. Animal models of bone infection suggest that most B-lactam agents (penicillins and cephalosporins) have reasonable bone penetration and are relatively non-toxic to bone. Quinolones have excellent oral absorption and bone penetration; however, some studies suggest they may interfere with bone regrowth—some experts avoid quinolones unless other agents are not active. Tetracyclines

(minocycline, doxycycline) have excellent (>70%) bone penetration and may be appropriate for MRSA infection. Clindamycin and TMP/SMX are well absorbed and generally appropriate for osteomyelitis due to sensitive organisms. Addition of rifampin to the treatment of staphylococcal osteomyelitis is useful since it may help eradicate persistent, "latent" organisms in bone osteoblasts. In general, animal models have shown a higher failure rate with vancomycin (a large molecule with poor bone penetration) and linezolide.

- **Oral versus parenteral treatment:** Febrile, acutely ill patients generally require initial parenteral therapy to adequate antibiotic at the infection site. Once the patient is afebrile and clinically stable, a switch can be made to oral antibiotics, provided that the organism is susceptible and the drug well absorbed.
- **How long to treat patients?** Most animal studies suggest that at least 4-8 weeks of antibiotic therapy is required for cure of acute osteomyelitis. Treatment may need to be longer in immunocompromised patients, individuals with underlying vascular disease or patients with selected pathogens (e.g. tuberculous osteomyelitis may require 18-24 months of therapy). Treatment longer than 4-6 weeks depends on the clinical response (see below) and the underlying host.

❑ **Is the patient responding to therapy?** While there are no rigid rules, use the following parameters to judge clinical response to therapy:

✓ **Patient clinical response:** Decreased fever, decreased pain and bone tenderness (be patient, this takes time). Local pain and erythema should decrease with gradual healing of overlying ulcers. A persistent sinus tract (with drainage) is a bad sign and suggests continued underlying infection.

✓ **Radiographic changes:** With acute osteomyelitis, demineralized areas of bone may gradual remineralize (although this may take time); patients are often left with some evidence of previous infection including increased bone thickening and periosteal elevation. Although helpful with initial diagnosis, bone scans may remain positive for some time—even after cure of the infection—and are not generally helpful in following response to therapy. Indium labeled leukocyte scans may be helpful in judging response to therapy—activity should decrease on scans obtained following effective therapy. On MRI, reduced contrast enhancement (on T1 scans) and decreased signal (on T2 scans) suggest clinical improvement although residual signal may remain despite clinical cure.

✓ **Erythrocyte sedimentation rate:** Check the ESR at the beginning of therapy with serial determinations at therapy proceeds—a response to therapy is usually accompanied by a decrease in sedimentation rate. Some experts recommend use of C-reactive protein (CRP) in addition to ESR—CRP demonstrates a more rapid response to effective treatment.

Vertebral Osteomyelitis—evaluation and management

Persistent back pain accompanied by fever and elevated erythrocyte sedimentation rate should raise the possibility of vertebral osteomyelitis. Patients with advanced infection almost invariably have changes on routine radiographs—early infection is most readily diagnosed with spinal MRI imaging. Once you suspect the diagnosis of pyogenic vertebral osteomyelitis (PVO), evaluate the patient using the following checklist:

1. **History and physical examination:** This is often the key to ferreting out the cause of an unexplained PVO—pay particular attention to the following:

   - **Skin infection/IVDU:** *Staphylococcus aureus* is the most common cause of PVO—inquire about recent skin infections (paronychia, boils, impetigo)—no matter how trivial—and ask the patient about any history recent hospitalization, intravenous catheters or IVDU. Examine the *entire* body surface for a potential "point of entry" or sign of localized skin infection. In addition to *Staph aureus,* IVDUs are at special risk for gram-negative pathogens (*Pseudomonas aeruginosa*) and *Candida albicans*.

   - **Endocarditis:** Examine the patient carefully for signs of endocarditis—PVO may be the initial presentation of subacute bacterial endocarditis; if necessary, obtain an echocardiogram. Also ask the patient about recent dental work and perform a careful examination of the oral cavity—occult dental infection with transient bacteremia may lead to vertebral osteomyelitis.

   - **Spine:** Use the "thumb test" in checking the spine for osteomyelitis—press on the suspect area with your thumb looking for pain or tenderness; most patients with PVO will have definite tenderness on firm palpation.

   - **Neurologic examination:** Do a careful neurological examination to rule out spinal cord or root involvement—epidural abscess is a common complication of PVO and can lead to cord compression if not promptly treated. The most dangerous lesions are in the cervical and thoracic spine since abscesses in these sites directly overlay the spinal cord.

   - **Genitourinary examination:** Question the patient about episodes of recent urinary tract infection—in older males, vertebral osteomyelitis is often due to occult urinary tract infection with the typical gram negative urinary tract pathogens (*E. coli, Klebsiella, Proteus*). In these patients carefully examine the epididymis and prostate—a prostatic abscess may be surprisingly occult.

   - **TB and fungal disease:** Pott's disease—vertebral osteomyelitis due to *Mycobacterium tuberculosis*—is one of the most common causes of PVO worldwide; ask the patient about previous tuberculosis exposure or skin tests. All the geographic fungi (coccidioidomycosis, histoplasmosis, blastomycosis) have been associated with vertebral osteomyelitis—question the patient carefully about recent or remote travel and obtain appropriate serology in selected cases.

   - **Additional history:** In addition to the above features, look for the following associations:
     - ✓ **Hemodialysis:** PVO may mimic renal osteodystrophy—*S. aureus* and *S. epidermidis* are common pathogens.
     - ✓ **Sickle cell anemia:** + association with *Salmonella* osteomyelitis
     - ✓ **Foodborne pathogens:** Ask about ingestion of raw eggs/milk products (*Salmonella*), "deli" products (*Listeria, Campylobacter, Salmonella*) and unpasteurized milk/cheese (*Brucellosis*).
     - ✓ **Animal exposure:** Domestic farm animals (*Brucellosis*), parturient cats (*Coxiella burnettii*).
     - ✓ **Immunocompromised patients:** In addition to the above pathogens, immunocompromised patients are at risk for a host of unusual pathogens—renal

transplant/febrile neutropenia (*Aspergillosis, Candida*), AIDS (*Mycobacterium avium-intracellulare, Cryptococcus*).

2. **Laboratory:** Obtain blood and urine cultures on all patients with suspected PVO; although 50% of patients are afebrile, a positive culture may reveal a suspect pathogen or point towards an underlying endocarditis. A baseline erythrocyte sedimentation rate is helpful both for diagnosis and monitoring of response to therapy. Avoid scattershot serological testing; however, specific serologies—especially for fungal pathogens—may be quite helpful in selected cases.

3. **Radiology:** Obtain a spinal MRI (with contrast) and personally review it with a neuroradiologist—there is a specific radiographic pattern (disc lesion with involvement of adjacent vertebrae) that is characteristic of spinal infection. Look carefully for any of the local complications of PVO, especially the presence of anterior (epidural abscess) or posterior (psoas abscess, aortic mycotic aneurysm) extension of the infection.

4. **Obtain a bone biopsy:** Definitive diagnosis and therapy of PVO depends upon isolation of an organism from bone biopsy or blood culture. Arrange a CT guided bone biopsy/needle aspiration with appropriate aerobic/anaerobic, mycobacterial and fungal cultures. If there is evidence of cord compression, cultures can be obtained at the time of surgical intervention.

5. **Surgery evaluation:** A surgeon with expertise in spinal disease (orthopedic surgeon or neurosurgeon) should evaluate *all* patients with suspected vertebral osteomyelitis. Indications for surgical intervention include:

   - **Pathogen unknown and failure to respond to antibiotic therapy:** While often helpful, a CT-guided bone biopsy may not always reveal a pathogen. A bone biopsy may be particularly helpful in immunocompromised patients with more exotic pathogens.
   - **Evidence of neurological compromise** (especially in cases of epidural abscess, impending cord compression and root involvement)
   - **Paravertebral abscess:** Diagnostic or therapeutic surgical drainage may be required in selected cases.
   - **"Unstable" spine:** External fixation often required to accelerate healing.

   There are several different surgical procedures available for managing PVO depending upon the extent of infection and local complications. *Percutaneous transpedicular débridement and diskectomy* with removal of infected bone may accelerate healing and stabilize the spine in early stages of vertebral osteomyelitis. More advanced cases—especially those with evidence of neurological compromise—may require open surgery with débridement and spinal fusion followed by placement of external rods/apparatus for spinal stabilization.

6. **Antibiotic therapy:** If possible, delay antibiotic therapy until cultures have been obtained—in clinically "stable" patients, try to obtain a bone biopsy prior to initiation of antibiotic treatment. For those with hemodynamic instability or neurologic compromise, start intravenous antibiotics as soon as possible after obtaining blood and urine cultures. Patients with PVO generally require prolonged antibiotic therapy (4-8 weeks) depending upon the underlying pathogen and host immunologic state. While there is no "gold standard" for cure, progressive clinical improvement with normalization of the ESR is a sign that the patient is responding to therapy. Some patients will continue to have back pain despite curative therapy; follow these individuals with serial ESRs and scans (MRI or Indium-labeled leukocyte scan) if you are concerned about recrudescence of the infection.

Recognition and management of Anaphylaxis

Studies suggest that penicillin and its' related derivatives are the most common cause of anaphylaxis in the hospital setting—early recognition and prompt therapy are critical since the condition has a mortality exceeding 10%. This handout will offer clues to the early diagnosis of anaphylaxis as well as outline a protocol for managing this deadly disorder.

1. Recognition of anaphylaxis and differential diagnosis

While full-blown anaphylaxis (Urticaria, facial edema, respiratory distress with wheezing, hypotension) is not difficult to recognize, diagnosis is often delayed when only part of the syndrome complex is present. Keep in mind that a number of conditions "mimic" anaphylaxis—consider the possibility of anaphylaxis when presented with any of the following conditions:

- **Acute asthmatic attack:** May mimic anaphylaxis with wheezing and respiratory difficulty; however, most patients present with hypertension and lack the cutaneous signs (urticaria, facial/lingual edema)of anaphylaxis .
- **Angioedema:** Hereditary angioedema is due to C1esterase inhibitor deficiency and causes attacks of acute abdominal pain and life-threatening laryngeal edema; in contradistinction to anaphyhlaxis, acute attacks do not respond to epinephrine. Angioedema is a side effect of ACE inhibitors; it is more common in patients with underlying renal disease.
- **Congestive heart failure:** Acute CHF may mimic anaphylaxis; however, patients lack urticaria/angioedema and usually have an S3 gallop on physical examination.
- **Panic attack (Acute vocal chord spasm):** Patient may have respiratory stridor that mimics acute airway obstruction; patients will not develop hypoxia and are usually normo- or hypertensive rather than hypotensive.
- **Procaine toxicity:** Occasionally seen following IM procaine penicillin injection, patients develop tachycardia, shortness of breath and CNS symptoms (anxiety, panic, hallucinations, seizures). While clinically similar to anaphylaxis, patients do not have facial/tongue swelling, hypotension and wheezing seen in the condiition.
- **Pulmonary embolism:** Pulmonary embolism may present with wheezing along with respiratory distress; patients do not develop urticaria, facial or lingual edema. .
- **Vasovagal reaction:** A simple faint or acute vasovagal reaction may follow a painful injection and mimic anaphylaxis with pallor, diaphoresis, hypotension and syncope. In contrast to anaphylaxis, patients usually have bradycardia and promptly improve when placed in a recumbent position
- **Other conditions:** Less common conditions mimicking anaphylaxis include **carcinoid syndrome** and **scromboid toxicity** (histamine toxicity following ingestion of contaminated fish).

2. Grading the severity of acute anaphylaxis

The following table is designed to assist in grading the severity of acute anaphylaxis. Keep in mind; however, that the onset and progression may not always be predictable. Patients may present with respiratory symptoms (dyspnea; wheezing) in the absence of skin manifestations. Selected cases may progress rapidly through the first three phases.—always treat every case as a potential medical emergency and don't delay therapy.

	Symptoms/Signs Increasing Severity →			
Organ	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Skin	Pruritus Flushing Urticaria Angioedema →			
Abdomen		Nausea Cramping	Vomiting Defecation/Diarrhea	
Respiratory Tract		Rhinorrhea Hoarseness Dyspnea	Laryngeal edema Bronchospasm Cyanosis	Respiratory arrest
Cardiovascular		Tachycardia	Hypotension Cardiac arrhythmias	Cardiac arrest

Emergency management of acute anaphylaxis...

Acute anaphylaxis is a medical emergency requiring immediate therapy—when confronted with a suspected case, use the following checklist to ensure rapid and appropriate treatment:

- ❑ **Stop the drug:** If the reaction occurs during parenteral administration, stop the infusion immediately. If a SC or IM injection is the cause of the reaction, consider placing a tourniquet above the affected site to delay absorption of the offending agent.
- ❑ **Administer oxygen:** Patients with acute anaphylaxis rapidly develop hypoxia due to bronchoconstriction and airway obstruction—administer high-flow nasal oxygen and consider emergency intubation or tracheostomy in those with upper airway obstruction (laryngeal edema).
- ❑ **Epinephrine:** Epinephrine is the drug of choice for treatment of acute anaphylaxis. The route depends upon clinical staging of the anaphylaxis—use SC therapy in patients with milder forms of anaphylaxis and IM therapy for more severe stages. Intravenous epinephrine is potentially dangerous—reserve this route for critically ill patients who fail to respond to SC or IM therapy. In an emergency, epinephrine can be given via sublingual injection or squirted down an endotracheal tube.

Epinephrine dosing:

SC: 0.3-0.5 mL of 1:1,000 aqueous solution (1mg/ml)
Repeat every 10-20 minutes x 3 if no response

IM: Same dose as SC—more reliable delivery in ill patients

IV: 1 to 3 ml of 1:10,000 (0.1 mg/ml) given over 10 minutes

Caution: Intravenous epinephrine may precipitate severe hypertension, cardiac arrhythmias and myocardial infarction—use only in critically ill patients failing to respond to other routes of administration.

- **IV Fluids:** Because of increased capillary permeability and peripheral vasodilation, most patients develop edema and hypotension--administer isotonic solutions (5% dextrose in 0.5N saline solution or lactated Ringer's solution) once a secure IV line is available.
- **Bronchodilators:** Used an inhaled beta$_2$ agonist (aluproterenol) in patients with wheezing—consider intravenous aminophyline in those with persistent bronchoconstriction failing to respond to initial therapy.
- **Antihistamines:** Diphenhydramine or hydroxyzine (25-50 mg IM or PO Q 6 hr) reduce urticaria and antagonize H_1 histamine effects on myocardium and peripheral vasculature. Although controversial, many experts recommend cimetadine (300 mg IV or PO q 6 hr) to block H_2 histamine activity.
- **Corticosteroids:** While less helpful in the acute situation, corticosteroids may block or reduce prolonged "late phase" reactions seen in some cases—administer methylprednisolone (125 mg IV) if available.
- **Vasopressors:** Administer continuous infusion norepinephrine (4 mg in 1 liter of D5W IV at a rate of 5-15 ug per minute) or dopamine in patients with persistent hypotension despite the above measures.

Pitfall: Anaphylaxis treatment in patient receiving β-blocker

The $ß_1ß_2$ antagonist actions of ß blockers interfere with the action of epinephrine—patients receiving epinephrine for anaphylaxis may fail to respond or develop serious side effects (hypertension, cardiac arrhythmias, myocardial infarct) related to unopposed α effects. Glucagon can stimulate intropic and chronotropic cardiac function despite ß blockade—consider IV glucagon in patients with refractory hypotension.

Glucagon: 1 mg IV bolus—repeat in 5 minutes if no response
Glucagon Infusion: 1 mg in 1 liter D5W IV at rate of 5-15 ug/min (5-15 ml/min)
Anti-emetic helpful in preventing nausea/vomiting side effect

"The Patient has a Rash"—is the antibiotic responsible?

Cutaneous reactions to antimicrobials represent one of the most common causes of in-hospital skin reactions. In a patient receiving multiple drugs, it may be difficult to determine if the antibiotic is the cause of a new skin eruption. When evaluating a patient with a new-onset skin rash, consider the possibility of faced with a new rash in a patient, keep in mind the following issues during your patient evaluation:

1. Recognizing the at-risk patient:

A previous history of antibiotic "allergy" is an important clue to the possibility of a drug reaction—review the chart and ask the patient (and family members) about previous reactions to antibiotics or other agents. In the world of ID, reaction to B-lactam agents (penicillins; cephalosporins) and sulfa drugs are especially common although almost all antibiotics have occasionally been linked to some form of drug allergy.

Keep in mind that drug allergy is more common in some patient populations. Drug eruptions are especially common in the following situations…

- **Previous history of drug allergy**:
- **Connective tissue disease:**
- **HIV/AIDS patients:**
- **Family history:**

When asking patients about previous "drug allergy", be careful to get an accurate history of the reaction—certain reactions such as GI upset (nausea/vomiting) may be a side effect rather than a true "drug allergy". If there is a history of "rash", ask the following questions…

√ **Timing of onset:** What is the specific timing of the eruption in relation to drug administration?

√ **Nature of the rash:** Was this a classic maculopapular rash, or did the patient have hives and wheezing suggesting an IgE mediated reaction? Was there mucous membrane involvement (sore throat; oral ulcers; conjunctivitis) suggesting possibility of an erythema multiforme eruption. Was there any connection to sun exposure (e.g. photosensitivity reaction)?

√ **Did it require hospitalization?** Serious rashes requiring hospitalization are always a concern—be especially careful about "rechallenging" patients with a drug in this situation.

√ **How was it treated?**

2. Dermal dilemmas—antibiotic reaction rates

Keep in mind that certain antibiotics are more commonly associated with skn eruption. A previous study found that antibiotics —especially B-lactam agents and sulfa drugs—were some of the most common causes of in-hospital drug eruptions (see Arch Derm 2001;137:765-70). Almost any agent may be associated with an allergic skin eruption; however, the following table (taken from various sources) lists the reaction rates associated with common antibiotics.

Table 1: Allergic cutaneous reactions to antimicrobial agents (Rate/100 patients)

High Risk (> 3%)		Moderate Risk (1-3%)		Low Risk (< 1%)	
Amoxicillin*	5.1	Acyclovir	2	Caspofungin	0.9
Ampicillin*	4.5	Aztreonam	1	Cefpodoxime	< 1
Amphotericin B	25	Cephalosporins†	1-2.4	Macrolides*	0.3
Ambisome	25	Dalfo/quinupristin	2.5	Nitrofurantoin	< 1
Abelcet	14.1	Fluconazole	1.8	Tetracyclines*	0.5
Amphotec	>5	Gentamicin*	1		
Cefaclor*	4.8	Imipenem	2.2		
Rifampin	5.8	Itraconazole	3		

High Risk (> 3%)		Moderate Risk (1-3%)		Low Risk (< 1%)
Rifater (INH/RIF/PZA)	7	Linezolide	2	
Rifabutin	11	Meropenem	1.4	
Sulfonamides	> 3	Penicillin G*	1.6	
TMP/SMX*	3.2	Piperacillin/tazo	1.3	
Voriconazole	5.8	Quinolones	1.6	

* Data extracted from tables in Arch Derm 2001;137:765-70
† Includes cefoperazone, cefotaxime, cefotetan, cefoxitan, cefprozil, ceftazidime and ceftriaxone
Remainder of rates obtained from Physicians Desk Reference (2004)—most of these represent data collected during licensing trials. Data may be incomplete or not available (N/A) for some agents.

Keep in mind the following points...

- √ **B-lactams:** Among antibiotic classes, penicillins (especially amoxicillin and ampicillin) have some of the highest reaction rates. Cephalosporins generally have a lower reaction rate except with specific drugs such as cefaclor that have "side chains" similar to ampicillin.
- √ **Sulfonamides:** Sulfa drugs also have a fairly high reaction rate, especially in AIDS patients—although reaction rates among the general population are less than 5%, HIV patients have recorded rates of up to 15-20% when receiving trimethoprim-sulfamethoxazole.
- √ **Anti-tuberculosis agents:** Of the anti-tuberculous drugs, rifampin—and it's sister drug rifabutin—have the highest reaction rates (5-10%).
- √ **Other agents:** Aminoglycosides, macrolides and tetracyclines have relatively low rates of adverse skin reactions; however, almost any drug can be associated with adverse skin eruptions and certain drugs (e.g. doxycycline and photosensitivity) may be linked to specific types of drug eruptions.

Although many reaction patterns are possible, maculopapular (morbilliform) or urticarial reactions are the most common patterns seen with antibiotic-associated drug hypersensitivity reactions.

3. Reaction patterns and timing of the eruption? Carefully review the patient record and construct a timeline showing a medication "timeline" in comparison to the onset of the eruption—most skin eruptions occur within 7-10 days of starting a new drug; reactions may occur more quickly (within 24-48 hours) if in patients previously sensitized to an agent. On rare occasions, a patient may develop a reaction to a long-term drug, especially if there has been an alteration in drug metabolism due to addition of another agent or a change in the patient's health status. Try to identify the reaction pattern by careful physical exam and laboratory testing.[1,2]

When confronted by patient with a possible drug-induced skin rash, look at the following factors:

- **Primary lesion:** Are the primary lesions urticaria (hives), maculopapular lesions (exanthematous rxn), erythema (vascular rxn) or vesicles/bullae (SJ/TEN, FDE, AGEP, LABD)? Is there + Nikolsky sign (cutaneous separation with lateral pressure on skin—seen in SJS/TEN)?
- **Mucous membrane involvement**: Evidence of mucous membrane involvement (mouth, conjunctiva, rectum, vagina) is critical and suggests the possibility of Stevens-Johnson syndrome or early TEN.
- **Distribution and progression of the rash:** Is it generalized or localized (fixed drug, photosensitivity rxn)? Does it occur predominantly in sun-exposed areas (photosensitivity eruption)? Are the lesions progressing or has the rash "stabilized"?
- **Timing:** What is the timing of the eruption compared to initiation of the suspect drug(s)?
- **Associated findings:** Does the patient have signs of IgE mediated anaphylaxis (e.g. wheezing, airway obstruction, angioedema), serum sickness (e.g. lymphadenopathy, arthritis) or laboratory abnormalities suggesting systemic involvement (e.g. eosinophilia, renal/liver dysfunction)? Does the patient appear "toxic" with fever or hypotension?

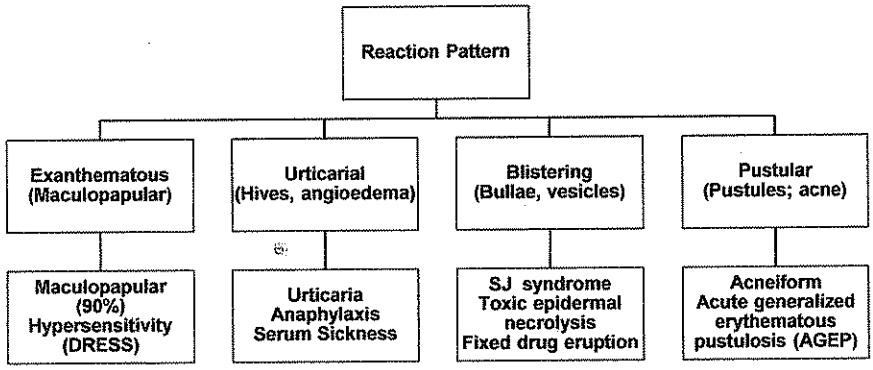
Use these features and Table 2 to help determine the nature of the drug eruption...

Table 2: Reaction patterns associated with Drug Eruption

Reaction pattern	Comments	Drugs (Antibiotics
Exanthematous	Most common drug reaction—a generalized erythematous, maculopapular or morbilliform (measles-like) rash with or without pruritus	Almost any drug but most common with B-lactam agents (penicillins, cephalosporins) and sulfa drugs
Urticarial/angioedema	IgE-mediated reaction associated with anaphylaxis and presence of hives/urticaria. Look for concomitant angioedema (tongue swelling) and respiratory difficulty (+ wheezing, stridor)	B-lactam agents predominantly but can be seen with any class of antibiotic
Stevens Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN)	A severe, life threatening reaction with a continuum from SJ syndrome (< 30% skin surface) to TEN (extensive bullous skin lesions with + Nikolsky sign). Pts almost always have fever and significant mucous membrane involvement.	Sulfa drugs Ampicillin and B-lactams
Hypersensivity syndrome (HS/DRESS)	Intense, widespread erythroderma with varying degrees of scaling. Fever, chills, lymphadenopathy (50%), hepatitis and nephritis are common with accompanying pain, malaise and chills. Usually spares mucous membranes. DRESS syndrome: Drug related rash, eosinophilia and system symptoms—Often associated with anti-seizure meds	Aromatic anticonvulsants Penicillin/cephalosporins Sulfonamides Nevirapine Rare: Isoniazid, Rifampin, Miinocycline, Aminoglycosides, Vancomycin
Acute generalized erythematous pustulosis (AGEP)	Generalized skin reaction characterized by disseminated erythematous pustules—culture of lesions are negative and skin biopsy shows subcorneal pustulosis.	Aminopenicillins Macrolides
Fixed drug eruption (FDE)	Pruritic, erythematous nodules and plaque that recur in same place following reexposure to drug; may blister and typically resolves with hyperpigmentation; common in perioral area and genital region.	Tetracyclines
Linear IgA bullous dermatosis (LABD)[3]	Annular plaques with "sausaged-shaped" bullous lesions on periphery; most common in extremities but may be generalized and mimic TEN [4]. Dx: Skin bx with IgA linear dermatosis on immunoflouresence staining.	Vancomycin Rare: B-lactam; sulfa agents
Serum-sickness like reaction[5]	Fever, arthritis and rash (often urticarial) May have generalized lymphadenopathy, serpiginous rash on side of hand and proteinuria	Cefaclor Penicillins (high dose—prolonged Rx) Minocycline, sulfonamides
Photosensitivity[6]	Reaction in sun-exposed surfaces such as face (usually spares area under chin), dorsal surface of arms/hands and anterior chest (V –shaped area below neck).	Tetracyclines Quinolones Sulfonamides
Generalized erythema	"Anaphylactoid" reaction with macular, blanching erythema associated with histamine release.	Vancomycin (red man or red neck syndrome)[7]

What to do if the patient has a suspected drug rash...

- ❑ **Is the patient on a drug likely to cause rash?** Review the list of drugs above and see if any of the patient's treatments are likely to cause rash—in infectious disease, B-lactam agents (penicillins; cephalosporins) and sulfa agents (trimethoprim/sulfamethoxazole) are particularly associated with drug eruptions. Pay especial attention of the onset of the rash in comparison to any new agents added to the regimen.
- ❑ **What is the reaction pattern?** Try to identify the nature of the rash based on timing, presence of primary lesions, distribution and progression of the eruption and presence (or absence) of mucous membrane lesions. See if there are any associated findings such as liver/renal failure or eosinophlilia.



- ❑ **Is the rash a consequence of a non-antibiotic agent?** Other drugs such as anti-seizure medications, NSAIDs, allopurinol and thiazide diuretics are commonly associated with adverse skin reactions.
- ❑ **? Rash due to underlying disease:** Don't automatically blame the antibiotic—keep in mind the possibility that the rash is due to the patient's underlying disease or non-antibiotic medical therapy. Other causes of rash include the following..;
  - **Rickettsial disease:** Patients with rickettsial disease (e.g. murine typhus, Rocky Mountain Spotted Fever) may develop a rash 2-3 days into hospitalization and are sometimes falsely labeled with a "drug allergy".
  - **Acute viral infection:** Patients with primary acute viral infection (HIV, EBV, CMV, HHV-6) have an especially increased risk of skin reactions (MP reaction) to ampicillin and related drugs.
  - **Vasculitis syndromes:** Conditions such as systemic lupus erythematosus (SLE) are frequently associated with "vascular" type skin eruptions—if the cause of the rash is unclear, consider obtaining an ANA, RF and ANCA.
- ❑ **Obtain a dermatologist...consider a skin biopsy.** Don't be afraid to request expert consultation in a puzzling case. A dermatologist might suggest an alternative diagnosis or have more up-to-date information about a suspect drug. Although skin biopsies are usually non-specific in common skin eruptions (MP rxn; urticaria), they may be helpful in confirming certain diagnoses (SJS/TEN, LABD, FDE) or ruling out other cutaneous conditions.
- ❑ **Stop the suspected drug and/or switch to alternative agent.** Whenever possible, stop the suspect drug, especially in patients with extensive or life-threatening reactions. Although you might be able to "treat through" a mild reaction, this could prove quite dangerous in patients with IgE-mediated reactions (e.g. hives, urticaria) or suspected SJS/TEN. In most cases, the patient will begin to improve within 24-48 hours of discontinuing the causative agent.

[1] Roujeau J-C, Clinical heterogeneity of drug hypersensitivity. Toxicology 2005;209:123-9.
[2] Bachot N, Roujeau J-C, Differential Diagnosis of Severe Cutaneous Drug Eruptions. Am J Clin Dermatol 2003;4:561-72.
[3] Kuechle MK, Stegemeir E, Maynard B et al. Drug-induced linear IgA bullous dermatosis: Report of six cases and review of the literature. J Am Acad Dermatol 1994;30:187-92.
[4] Waldman MA, Black DR, Callen JP. Vancomycin-induced linear IgA bullous disease presenting as toxic epidermal necrolysis. Clin and Exp Derm 2004;29:633-6.
[5] Yerushalmi, J, Zvulunov A, Halevy S. Serum Sickness-like Reactions. Cutis 2002;69:395-7.
[6] Vassileva SG, Mateev G, Parish LC. Antimicrobial Photosensitive Reactions. Arch Int Med 1998;158:1993-2000.
[7] Red Men Should Go: Vancomycin and Histamine Release. Lancet 1990;335:1006-7.

Hospital management of the infected intravenous drug abuser

For the houseofficer, the intravenous drug user often represents one of the most unwelcome hospital admissions. Their stay on the ward is frequently marked by difficulties with IV access, disagreements about pain management ("I want more pain meds or I'm leaving!) and conflicts with staff. Difficult as these patients may be, they often have legitimate medical problems that require genuine thought and care. What follows is a list of "tips" that will minimize manipulative behavior and maximize the possibility of a satisfactory outcome...

- **Recognize the risk of serious infection in intravenous drug users** and don't underestimate the severity of the patient's condition. While malingering and drug seeking certainly occurs, most hospitalized drug users have serious medical problems and merit quality care despite their behavioral problems. Don't overlook the possibility of serious, life-threatening infections (gas gangrene, endocarditis, epidural abscess) because the patient appears to be "drug-seeking".

- **Provide adequate pain control.** Recognize the medical sophistication of these patients and avoid placebos. Remember that they often require higher doses of pain medications because of underlying opiate tolerance. In patients with potentially serious infection, be liberal in the use of methadone—a properly medicated patient is much easier for physician and nursing staff to manage (Once the patient is stabilized, you can gradually taper the methadone).

- **Avoid the medical malpractice trap.** Because of their difficult behavior—and haphazard interactions with the health care system—drug addicts may not always get the best care and sometimes have legitimate malpractice cases. Make sure you fully explain the treatment to the patient and carefully document your plan in the medical record. If a patient is abusive or clearly non-compliant, don't be afraid to document this behavior in the chart; however, avoid statements that might appear "judgmental" or discriminatory since these could backfire in a subsequent legal proceeding.

- **Use a team approach and form a unified front.** These patients are masters of "divide and conquer" and tend to play one staff member off against another. Try to use a team approach with one individual designated as the "primary" who is responsible for managing the medical care including pain medications. Involve consultation-liason psychiatry early in the hospitalization—especially in patients with underlying psychiatric conditions or previous suicide attempts.

- **Be professional and don't overreact.** These patients often act out and like to "push the buttons" of hospital health care staff. Manage the patient in a calm, deliberate manner and avoid statements that suggest you are "punishing" them for their drug use. Nevertheless, set limits on abusive or potentially violent behavior—make sure they understand that this is unacceptable and don't be afraid to call hospital security in potentially dangerous situations

- **Provide practical solutions** without seriously compromising care. It is rare that drug user that completes a full 4-week course of intravenous antibiotics in the hospital—be prepared for patients to suddenly leave or sign out against medical advice. When this happens, consider offering the patient an alternative therapy (oral antibiotics) but make sure you document your discussion with the patient and the possibility of a less satisfactory outcome.

- **Be skeptical but avoid cynicism.** Recognize the relapsing and remitting nature of substance abuse problems and always hold out the possibility for a positive change in the future. Many patients have been through treatment programs and some have been "clean" for substantial periods of time—this can happen again if they have done it before. While the relapse rate is admittedly high, keep in mind that even the most hardcore abuser will sometimes surprise everyone and turn his or her life around.

Ten practical tips to prevent infections

1. **Wash your hands:** You've probably heard this a million times but it's true—hand-washing is the single most effective measure for preventing spread of infection between patients in the hospital. Many hospital outbreaks appear to be linked to transmission by hospital staff, with poor hand-washing practices being at the top of the list of infractions.

   Tip: Your behavior is likely to influence those around you. Studies show that housestaff and students are more likely to wash their hands when they observe their attending performing the rite.

2. **Observe infection control procedures:** Again, the rules are there for a reason and should be observed. Its been observed many times—control of hospital outbreaks usually requires identification of infected patients with strict observation of infection control procedures such as hand-washing and barrier control techniques.

   Tip: In following hospital infection control procedures, make sure your own equipment is not a risk—keep your stethoscope clean with frequent alcohol wipes and make sure other devices (thermometers, ultrasound probes, respiratory therapy equipment) are also properly sterilized.

3. **Pull out the catheter:** Countless unnecessary hospital days result from catheter-associated infections—whenever possible, "pull out" unnecessary catheters (e.g. intravenous lines, Foley catheter, NG tubes), the prime source of hospital-acquired infection.

   Tip: Even in they appear "normal" on examination, remember that intravenous catheters are almost always infected after 72 hours in place. On your daily rounds, develop the habit of checking catheters for evidence of phlebitis or infection (e.g. erythema, purulence, tenderness)—if the catheter has been in place longer than 72 hours, make sure it is pulled out and replaced, no matter how it looks!

4. **Place ventilator patients in a semi-recumbent position:** Studies demonstrate that this act will decrease the incidence of nosocomial pneumonia, probably by decreasing the incidence of aspiration.

   Tip: During ICU rounds, make a point of checking lines (for infection or phlebitis), rolling the patient over (check for decubitus ulcers) and observing patients for proper position in bed (semi-recumbent position)

5. **Obtain cultures (Make a diagnosis!)** Part of effective antimicrobial therapy depends upon targeting the infection and treating with the most effective, narrow-spectrum antibiotic. Whenever possible, obtain cultures and try to make a microbiological diagnosis.

   Tip: Whenever you make a decision to begin antibiotics, think about the appropriate cultures necessary to confirm your diagnosis and try to obtain them prior to starting antibiotic therapy. This is especially important in sicker patients requiring hospitalization—make a specific diagnosis will permit accurate targeting of the bacterial pathogen with the most effective and targeted antibiotic regimen.

6. **Know the local data:** Take the time to review your hospital's antimicrobial susceptibility data—you'll make smarter antibiotic choices and avoid use of inappropriate agents.

   Tip: Several key organisms will give you an overview of resistance patterns in your community (hospital). On a yearly basis, review resistance data on the following "bugs":

   - ***Streptococcus pneumoniae:*** *Still the most common organism isolated in CAP, this bug is a harbinger of local trends in respiratory infection.*

- ***Staphylococcus aureus:*** *In many communities, MRSA is now isolated in over 50% of community-acquired staphylococcal infection. Know your local resistance pattern.*
- ***Escherichia coli :*** *The most common gram negative bacillus, knowledge of local resistance patterns will help guide therapy of urinary tract and intraabdominal infection.*
- ***Pseudomonas aeruginosa :*** *Look upon Pseudomonas aeruginosa as a marker for in-hospital Gram-negative antibiotic resistance.*

7. **Don't treat colonization:** If a patient is clinically stable, don't treat simple colonization or a "positive" culture that is likely to be a contaminant. *Staphylococcus epidermidis* is a common blood culture contaminant—avoid prolonged antibiotic therapy if the blood culture is likely to be a "false positive" contaminant (e.g. no clear source for *S. epidermidis,* only one set positive.)

   Tip: Urinary tract colonization (with GNRs or Candida) is common in patients with `chronic indwelling foley catheters—avoid routine treatment of these patients unless they have signs or symptoms of urinary tract infection (e.g. fever, lower pelvic pain, shaking chills, leukocytosis). In the asymptomatic patient, watchful waiting is generally safe; in these patients, excessive antimicrobial use will lead to increasing, more difficult-to-treat bacterial resistance.

8. **Avoid excessive antibiotic use:** Much of today's resistance is due to excessive use of broad spectrum antibiotics. Although such therapy may be appropriate for initial empiric coverage, prolonged treatment with such agents is likely to lead to colonization with more resistant, "hospital-acquired" pathogens (e.g. *C. difficile,* VRE, MDR-GNR). When culture results are available, if possible, "narrow" therapy to agents active against the specific pathogen.

   Tip: When you have started antibiotics on a patient, review the case at 72 hours—if cultures are negative and real infection unlikely, stop therapy and look for another cause for fever. Likewise, in a patient with documented infection, administer the standard, recommended course of therapy and avoid over treatment—prolonged, unnecessary treatment leads to colonization with more resistant organisms.

9. **Immunize!** Vaccination with some of the common, recommended vaccines is a way to cut down on future infections, thus minimizing the need for antimicrobial therapy. Although targeted towards a viral infection, aggressive immunization against influenza is likely to decrease inappropriate antibiotic use.

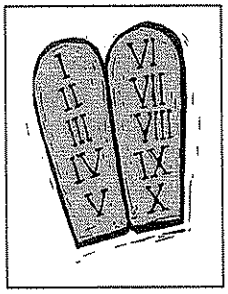
   Tip: At the beginning of flu season, depending upon current recommendations, make sure your patients have received vaccination against influenza and are up-to-date on pneumococcal vaccination.

10. ***Educate patients:*** Some of inappropriate antibiotic therapy is driven by patient expectations for an "antibiotic" whenever they have a fever or are "sick", even if it is an apparently trivial URI or viral infection. Educate patients about the proper use of antibiotic therapy and the potential dangers of antibiotic overuse.

    Tip: In an office based setting, many patients with trivial infection will demand therapy. If you strongly suspect viral infection (and really would prefer to observe the patient for 24-48 hours), consider giving the patient a script and the following admonition: "I really don't think you have a bacterial infection; however, if you don't start improving within 24-48 hours, consider filling this script and starting the antibiotic". Knowing they have the option available, patients will often feel more comfortable and be more willing to give a strategy of "watchful waiting" a trial.

Appendix

Other Topics Related to ID



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:

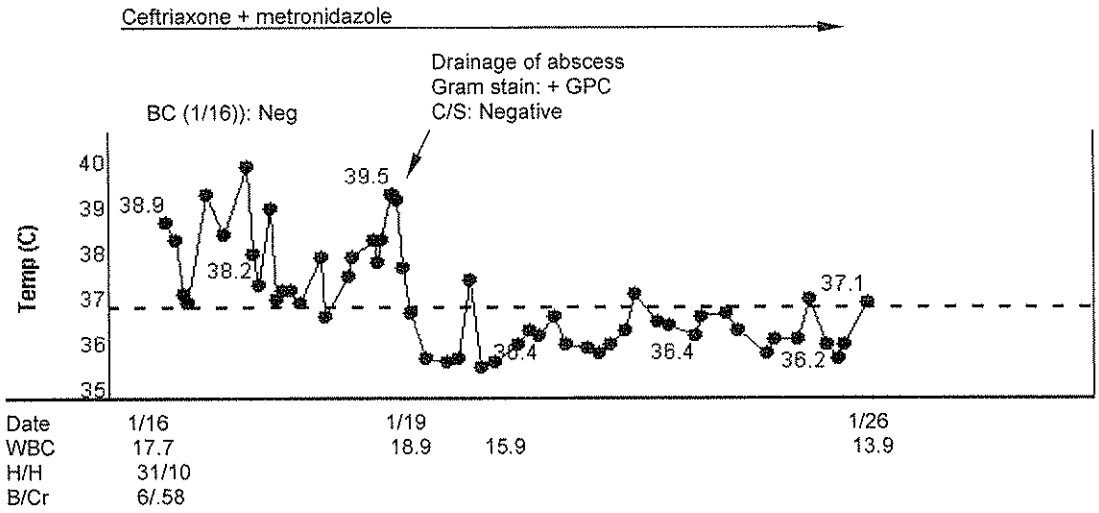
   √ **Date the "true" onset of the fever/disease:** While a patient may have come to medical attention recently, try to date the real onset of the disease. If it was six months ago, try to focus your exposure questions (travel, animals, food) around this period of time.

   √ **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.



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.

How to perform a lumbar puncture

What are the indications—and contraindications—for performing a LP?

Indications:

- Suspected meningeal infection or carcinomatous meningitis
- Documentation of subarachnoid hemorrhage (SAH)
- Therapeutic tap to relieve elevated CSF pressure (e.g. cryptococcal meningitis)

Contraindications:

- Intracranial mass lesion with "brain shift"—suspected cerebral herniation
- Local infection at lumbar puncture site (folliculitis, decubitus ulcer, cellulitis)
- Possible spinal cord compression
- Coagulopathy (Platelet count < 50 K; INR ≥ 1.5)

Pitfalls:

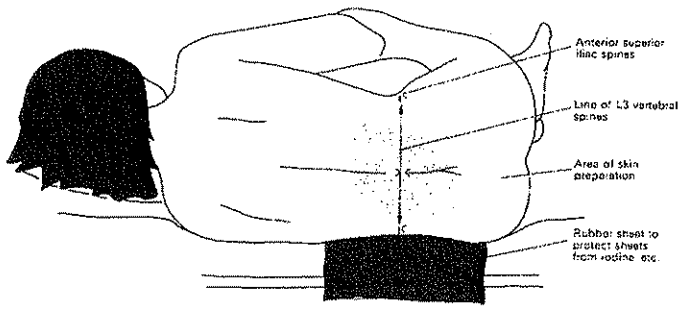
- Failure to due lumbar puncture in patient with suspected CSF infection
- Failure to recognize early signs of cerebral herniation
- Failure to prepare the patient properly
- Overly zealous attempts to obtain tap

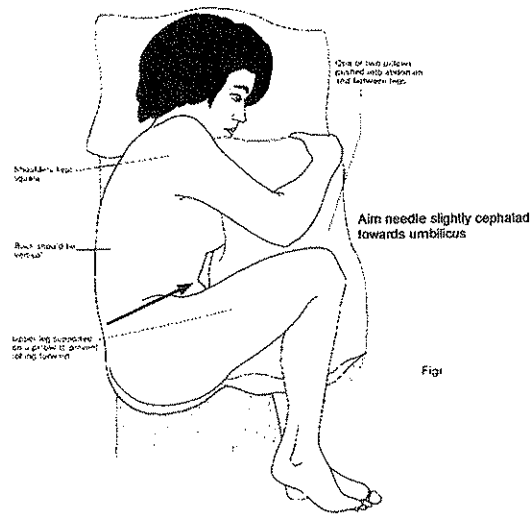
Follow the correct procedure... When performing a lumbar puncture, remember the following steps...

- ❑ **Make sure the patient has no contraindications**
  - In most cases, perform CT prior to elective lumbar puncture
  - Examine patient's fundus for signs of papilledema (check for central venous pulsation)
  - Papilledema, confusion, focal neurological/clinical findings? → Obtain CT prior to LP
  - Check coagulation studies if available

- ❑ **Obtain informed consent**
  - Possible complications: Bleeding, leg/back pain, paralysis, infection, death

- ❑ **Position the patient properly and identify the puncture site**
  - Place the patient on a firm surface with a pillow under the head and between legs
  - Make sure the back is perpendicular to the bed/ table
  - Identify ant illiac crest and drop a perpendicular line to estimate the L3/L4 space
  - Identify the intravertebral space and mark it with the tip of a ballpoint pen





- **Open the LP kit and familiarize yourself with the contents**

- **Prep the site and administer local anesthesia**
  Prep the site with providone iodine and allow it to dry
  Drape the site to prevent bacterial contamination—clean the LP site with alcohol
  Inject small amount of lidocaine (enough to raise bleb) at marked LP site
  Inject 0.5 cc lidocaine directly into deeper tissues (No need to give 5-10 cc !)

- **Insert the needle**
  Insert the needle into the space with the bevel parallel to the longitudinal fibers of the spinous ligament
  Aim the needle slightly cephalad (toward the umbilicus) and push till you feel a "pop"
  Withdraw the stylet and wait for a CSF return
  When CSF return is obtained, measure the CSF pressure

- **Potential problems: Here is what to do in the following situations...**

If there is no fluid return...

Insert the stylet and twist the needle 90°--the hole may be up against a nerve root
Insert the stylet and advance the needle 2 millimeters and check again
Insert the stylet, withdraw the needle (almost to the skin) and reinsert at different angle
If unable to obtain tap in lateral decubitus position, consider an LP with pt sitting up.

What to do with a "bloody tap"...

See if it clears by the second or third tube—if so, is likely a traumatic tap
Is a clot present? Indicates a traumatic tap (Blood does not clot with SAH)
Immediately centrifuge fluid to see if there is a clear supernatant
(Subarachnoid hemorrhage has xanthochromic supernatant)
Collect 1st and 4th tubes for cell count (↓RBC count in tube #4 suggests traumatic tap)

What to do with high opening pressure (> 230 mm H2O)...

Make sure patient is relaxed
Collect only enough CSF (5 cc) for diagnostic purposes
(Generally safe to collect more in pt with negative CT scan)
Terminate LP and consider measures to reduce intracranial pressure...
Place pt on back at 30° angle
Consider IV mannitol (Potential danger of rebound increase in ICP)
Corticosteroids
Consider intubation and hyperventilation

What to do with a low opening pressure (< 80 mm H2O)...

Consider possibility of spinal block with impending herniation
Terminate LP after small amount of CSF for diagnostic purposes

- **Collect the cerebrospinal fluid**

Tube #1: 1 cc Glucose (Normal 50-80 mg/dL) and total protein (Normal 15-45 mg/dL)
Draw simultaneous serum glucose *before* the lumbar puncture
(Normally about 2/3 of serum glucose—less than 50% is of concern)
Tube #2: ~ 5 cc Culture and sensitivity/Gram stain
(Collect 7-10 cc if TB or fungal meningitis suspected)
Tube #3: 2 cc Cell count (Do immediately—normal cell count is < 5 cells, 0 polys)
(In the case of a bloody tap, perform cell count on tube #1 and #3)

Tube #4: 1-5 cc Special studies (VDRL, cytology, cryptococcal antigen, PCR tests)

- ❑ **Measure the closing pressure and withdraw the needle—write a procedure note**

- ❑ **Proper post-procedure care**
  Have the patient lie down after the procedure
  Increase fluid and caffeinated beverage consumption at home
  Likelihood of headache depends upon size of dural tear…small needle (#22)—low headache incidence
  Persistent headache…Consider epidural patch

- ❑ **Watch patient for complications of the procedure**

  Post LP headache (40% of patients)
  Cerebral herniation (Increasing obtundation, signs of brainstem involvement—pupil dilation)
  Spinal epidural hematoma (Increasing back pain with leg weakness and loss of sensation in saddle distribution)
  CNS infection (fever and signs of meningitis)

Sources: Patten J. Neurological Differential Diagnosis 1983. Springer-Verlag; New York.
Roos K. "Lumbar Puncture" in Seminars of Neurology 2003;23:105-15.

"How to write a case report"—A brief guide

In our day-to-day work, we all see interesting cases that might be of value to our fellow physicians. The following checklist gives some guidelines to organizing and writing a case report that will increase the likelihood that it will be accepted:

❑ Is your case worth reporting?

Does the case have something unique about that is worth reporting? Many case reports break down into a number of potential "angles"—see if your case fits one of the following categories:

- A truly unique observation including a new disease or unusual presentation for a previously described condition.
- A rare disease or condition not likely to be seen by the average practitioner.
- A new form of treatment for a specific condition.
- A warning about an unexpected clinical presentation or therapeutic complication.
- Utilizing advanced diagnostics (e.g. radiology, laboratory, molecular biology) to diagnose or manage a previously described condition.

Even if your case is not particularly groundbreaking, many smaller ("throwaway") journals provide an opportunity to report a case and review the literature—this will give you valuable writing experience and begin the process of "growing" your bibliography.

❑ Choose a likely journal.

Make a decision as to what journal will be the likely recipient of your submission. Find several potential journals and read through their case reports. Does it seem like your article would be appropriate or of interest for their readership? Would it be more appropriate for a "letter to the editor", brief report or comprehensive review article? Having a general idea of your audience will help guide the writing of your report and increase the likelihood that it will be accepted. Be realistic and create a "tier" of several journals so that you have other options if your "first choice" sends you a rejection letter (Unfortunately, the New England Journal of Medicine turns down far more articles than it accepts!).

❑ Perform a computer search

Perform a computer search to begin building a series of references and to see if your subject is truly unique. You may find that your observation was already published in Journal X last month (Hint: Journal X is not likely to accept a similar work unless it builds on the previous article or has an additional insight). You will learn a great deal by reading the previous literature and seeing where your case fits in. This literature will also provide the core citations for your own paper's reference list.

❑ Make an outline and choose a focus.

Construct a brief outline that includes different components of the article structure (e.g. Introduction, Case report, Discussion, References) as well as a summary of the key points you want to make. Strive to create a focus for the article so that the reader will be left with a few key points to remember.

❑ Write the report.

After you have assembled all the necessary materials, write the report with an eye towards keeping it in the style of the journal you are shooting for. While whole books have been written about style and grammar, here are some recommendations that seem to be guidelines for many editors:

- Use "active" rather than "passive" voice: Nowadays, most editors look upon the "passive" voice as boring and encourage the use of the "active" voice in medical writing.

Ex: (Passive) The patient was seen by the physician and admitted to the hospital.
(Active) The physician saw the patient and admitted him to the hospital.

- Avoid tense changes throughout the article.
- Avoid "trite" language or clichés.
- Make sure spelling, abbreviations and references are correct: Most journals publish a yearly "Instructions for Authors" that gives critical information about article "style", approved abbreviations and the correct format for references. Following these rules increases the chance that your article will be favorably received.
- Don't plagiarize: Most medical writing relies heavily on the work of previous authors. Be careful to cite previous works and avoid direct copying. Even if you have "changed around the wording", it is wise to provide a footnote with the citation of the source.

❑ Give credit where credit is due.

If a colleague has made a significant contribution to the care of a patient, make sure they are aware of your efforts and give them the opportunity to participate in the paper. Even if they don't want to take on responsibility for writing or reviewing the paper, it may be appropriate to cite them in the "acknowledgements" section at the end of the manuscript. Another's desire or pledge to "write up an interesting case" often doesn't come to fruition—that shouldn't stop you from reporting the case but make sure that it is done in an honorable fashion with credit to those who played a key role in diagnosing or managing the case. In the end, another citation on your resume is not worth the bitterness arising from a colleague who believes that he or she was "robbed" of a case.

❑ Be a ruthless editor.

In modern medical publishing, space is at a premium—more words mean lengthier articles and higher printing costs. Edit your article with a goal towards providing a "concise" description of the case and reducing the amount of excess verbiage. In the "Discussion" section, avoid long, exhaustive reviews of a particular disease that includes information easily be found in a textbook. Concentrate on the unique aspects of your case and the lessons this provides for the reader or fellow clinician.

❑ Follow through and submit the article.

Unfortunately, far more projects are started than completed. Set aside time to work on the project and give yourself a deadline to get a rough draft together. Nowadays, many journals encourage electronic submissions—this practice permits a faster turnaround time and more rapid consideration of your work.

❑ Don't despair from rejection!

In some cases, your article will be tentatively accepted provided that you make some changes requested by the reviewer or editor. If it is rejected outright—don't despair! History is replete with key scientific papers and discoveries that were initially rejected. Nevertheless, take the reviewers comments seriously and, if possible, revise the paper with these ideas in mind for the next submission. As mentioned earlier, have a game plan to submit to another journal if your first choice rejects the paper. Although these additional journals may be less "prestigious", your submission may still make it into the literature and honor your name with a PUBMED citation.