CHAPTER 1

Diagnosis of Lower Extremity Infections

Definition of Infection

At the beginning of a book on infectious diseases, it is important to make sure that the most basic terms are defined to start all readers off on the proverbial "same page." Although clinicians may see infection on a daily basis, most have difficulty when asked to put a definition of the term into words. For this reason the following is offered:

Infection can be defined as the pathologic presence of bacteria in a site or wound. This pathogenesis is evidenced by the body's response through the presence of inflammation and white blood cells.

There are some important points to take away from this definition.

1. This definition and these subsequent points are applicable for any skin, skin structure or bone and joint infection that will be covered in this book. The same may not hold true for systemic infections, pulmonary infection, urinary tract infections, etc.
2. The word "pathologic" is really the key. Bacteria can be isolated from practically any body surface. This does not mean that the site is infected. The bacteria must be causing damage to the tissues and not be just a harmless commensal.
3. Although it is true that in some very rare cases there may be an altered local response to the infection, in the vast majority of cases there is some identifiable response by the body. This is even true in patients with diabetes, on systemic steroids, with vascular

insufficiency and those with Human Immunodeficiency Virus (HIV) infection.

4. Inflammation is a result of vasodilatation in the involved area, which allows greater blood flow. This causes the usual signs of redness, swelling, heat, etc., all of which will be discussed in more detail later. Likewise, the infection will cause a chemotactic cascade that will deliver more white blood cells to the area. The combination of increased blood flow and increased white blood cells leads to two of the classic clinical findings of infection, cellulitis and pus.

Point 4 above introduces the next section and a vitally important point that needs to be made at the outset of this chapter on diagnosis:

Infection is a CLINICAL condition and its diagnosis is made on CLINICAL grounds.

CLINICAL DIAGNOSIS

History

Obtaining a complete history of the patient's chief complaint, although considered a banality in today's world of high technology, high cost medicine, is the important first step in the clinical diagnosis of infection. By asking the proper questions, the diagnosis can frequently be made and the patient begun on accurate empiric therapy before laboratory results are received.

Etiology

The causative factor or factors precipitating the infection are known as its etiology. Different etiologies will lead to different types of infections with various organisms. It is important to obtain a detailed history to determine the diagnosis. For example, if the patient relates lacerating the foot while swimming, it must be determined whether the water was fresh, salt, or brackish. Each of these milieus contains distinctive microbiologic flora. If the foot is punctured, the history should include the site of the wound (both anatomically on the foot and the scene of the injury), the cause of the wound (be it a nail, glass, etc.), the suspected depth of the wound and whether or not shoes were being worn. This history in and of itself can lead to a presumptive diagnosis of osteomyelitis or soft tissue injury only.

Sample Etiologies and Potential Organisms

Below are some examples of common lower extremity infections and their typically associated bacterial pathogens that can be based on

just obtaining a basic history. Each will be covered in more detail in individual sections of the text.

1. Postoperative infection (no implants) – by far the most common organism is *Staphylococcus aureus*. The setting in which the surgery took place can also play a role. For example, if the surgery was performed in a hospital with a high incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection, then that particular organism could be suspect. Likewise, if the patient has a prior history of MRSA infection, this is the presumed organism until proven otherwise. The topic of MRSA is covered in detail elsewhere in this book.
2. Post operative infection (use of implants) – *Staphylococcus epidermidis* or other coagulase-negative *staphylococcus* are frequent causes of these infections. This is of particular importance since a large percentage of these organisms are methicillin resistant.
3. Puncture wound osteomyelitis – *Pseudomonas aeruginosa* has been found to cause upwards of 90 percent of cases of osteomyelitis following a puncture wound.
4. Cellulitis following a puncture wound – Although a common misconception is that *Pseudomonas aeruginosa* is also the culprit here, as in osteomyelitis, actually, *staphylococcus* and *streptococcus* are most common.
5. Infected ulceration in a patient with diabetes – The most common pathogens are *Staphylococcus aureus* and group B *streptococcus.*

Clinical Signs and Symptoms

The type and severity of clinical presentation should be noted. Ask yourself these questions:

1. Has the patient been running a fever or feeling "feverish or flu-like"?
2. Has the patient experienced shaking or chills, including the uncontrollable chattering of teeth?
3. Has the patient awakened at night to find the bed sheets or bedclothes damp? These night sweats are a good indicator of the presence of fever.
4. Has the patient noticed the presence of lumps or stiffness behind the knees or in the groin? The patient may not relate the lumps or stiffness to the infection, and frequently it is easier to question the patient than to actually palpate the nodes. Care should be taken in evaluating the patient's answer however. More than one patient has

confused the stiffness of arthritis with the clinician's probing about lymph nodes.

5. Finally, has the patient noted the presence of red streaking originating at the site of infection and traveling up the leg? Patients frequently know this lymphangitis as "blood poisoning."

Duration of Signs and Symptoms

Generally, the more severe the infection the more rapidly it will spread. For example, a patient with a necrotizing, gas-forming infection of 24 hours' duration and signs of septicemia should be managed differently from a patient with a necrotizing infection that has been "brewing" for five days. This point may also help lead to a bacteriologic diagnosis. In the above situation, the first patient would be treated as having a myonecrosis caused by *Clostridium perfringens*. The second patient's infection would more likely be a synergistic process containing numerous organisms. Another example is the postoperative patient, in whom *Staphylococcus epidermidis* may sequester in a wound for protracted periods before becoming clinically evident. *Staphylococcus aureus*, on the other hand, tends to exhibit more rapid virulence.

Prior Therapy

A patient who presents with an infection may have already started a course of antibiotic therapy. This should be noted as it may affect the diagnosis and subsequent treatment. One commonly held belief is that an antibiotic may "mask" an infection, making diagnosis difficult. However, there really is no such thing as a "masked" infection. If an antibiotic has been given to the patient for a presumptive diagnosis of infection and the signs and symptoms disappear, this represents "successful therapy," not some nefarious failure. Furthermore, if there is a true infection present and the antibiotic does not appropriately cover the organism, then the condition will surely worsen.

1. Has the patient received any antibiotics from another source, whether from another physician or an illicit source, to treat the infection? The black market for oral antibiotics is so active that it must be assumed that most intravenous drug users have already taken an antibiotic at the time of presentation. This frequent usage may be responsible for the predominance of multi-resistant infections in this population.
2. Frequently patients have partially empty bottles from past prescriptions in their medicine cabinets. They may begin a course of therapy on their own accord.

3. Has the patient been receiving empiric therapy that has not been effective? If so, a change in that therapy, whether antibiotic or surgical, is probably indicated.
4. If the patient had been given a prior course of therapy that was seemingly not effective, make sure that the patient actually got the prescription filled in a timely manner and took the medication as ordered. If there is any doubt, a call to the pharmacy or a pill count may be in order.

Medical History

Numerous underlying medical conditions have important consequences in both the diagnosis and treatment of lower extremity infections.

1. The most evident pre-existing condition is diabetes mellitus. Diabetic infections have unique bacteriologic and treatment considerations, which are discussed in detail in Chapter 5.
2. HIV infection will generally NOT have a major impact on the presentation of lower extremity bacterial infections. Most of the immune alterations in this disease involve the T-cells and therefore response to fungal, viral and parasitic infections may be altered.
3. Hypertension, and the treatment thereof, may have profound effects on electrolyte balance and renal function, complicating antibiotic selection.
4. Peripheral vascular disease may affect antibiotic delivery to the site of infection although this may be a more theoretical consideration than a real problem.
5. Venous diseases such as deep vein thrombophlebitis (DVT) may mimic infection by presenting with an acutely inflamed, painful, erythematous lower extremity. Even chronic venous congestion may present with swelling, erythema and flaccid, draining bullae that may be misdiagnosed as infectious cellulitis.
6. Other renal and hepatic dysfunctions will affect the pharmacokinetics of antibiotics.
7. Metabolic disorders, such as glucose-6-phosphate dehydrogenase deficiency, will exclude the use of sulfonamides.
8. Current medication usage may alter antibiotic selection because of the potential for drug interactions.

Allergies

Patients who relate “allergic reactions” must be questioned carefully. Many patients may have had minor gastrointestinal irritation many years ago upon taking a particular antibiotic. These patients now

either assume for themselves or were instructed by their physicians that they are "allergic" to the drug. In fact, most of these reactions are due to impurities in early formulations. Other allergy considerations are covered in Chapter 7.

Social History

Knowing the patient's social history can assist in both leading to a proper diagnosis and therapy.

1. Some patients are still reluctant to come right out in their medical history and disclose that they have been diagnosed with HIV or Acquired Immunodeficiency Syndrome (AIDS). Although it is still uncomfortable for many clinicians, even after almost 25 years of AIDS awareness, to ask about risk factors for this disease, it should still be done. If a patient discloses that they have the disease, or it is suspected, but not admitted to, based on the social history, be very aware of any treatment decisions. According to the Americans with Disabilities Act (ADA) it is illegal to be discriminatory in treatment based on the presence of these conditions.
2. Intravenous drug users will present with infections of unusual bacterial etiology regardless of the presence of AIDS. Methicillin-resistant *S. aureus and P. aeruginosa* infections are so common that empiric therapy of any infection in this population should include coverage of these organisms.
3. Acute alcohol abuse can affect immune defenses. Primarily, ethanol can suppress bone marrow leukopoiesis and impair neutrophil adherence. Abuse leading to cirrhosis can further impair defenses by causing lymphocyte and neutrophil dysfunction. Also, alcohol use can interfere with therapy since some antibiotics exhibit a striking disulfiram-like (Antabuse®) reaction.
4. Smoking can lead to vascular disease with all of its attendant lower extremity problems.

Pets

1. Pet-borne zoonosis, although rare in the foot, must also be considered.
2. Bite wounds to the lower extremity are fairly common, and may lead to potentially severe infections.

Travel History

Indigenous organisms vary in different parts of the country and the world.

1. Travelers who have returned from rural areas and spent time camping or outdoors may present with Lyme disease, which is caused by a tick-borne *Borrelia.*
2. Vacationers returning from southern coastal areas of the United States may present with cutaneous larva migrans, which is unseen in the north.
3. Many veterans of past wars still suffer with "jungle rot," which is seemingly untreatable with any current antifungal agent. Likewise, travelers to Southeast Asia may present with unusually resistant fungal infections. Military personnel returning from the conflict in Iraq have been presenting with an increased incidence of infection caused by *Acinetobacter.*
4. *Mycetomas* and *Mycobacterium leprae* infections, both of which directly or indirectly involve the lower extremity, still plague people from some parts of the world.

Physical Examination

Performing a thorough physical examination is the second step in the clinical diagnosis of a lower extremity infection.

Overall Appearance of the Patient

Patients with a severe infection will appear "sick." They may be lethargic and slow to respond to questions. They may be diaphoretic. A man may appear unshaven and disheveled. A woman may not have applied makeup. This appearance must then be correlated with the severity of the foot infection. If the foot infection appears relatively mild yet the patient appears ill, there may be distant foci of infection. Systemic diseases that can cause this reaction in patients include subacute bacterial endocarditis (SBE) and urosepsis. SBE should be ruled out in most intravenous drug users presenting with infection.

Cellulitis

Cellulitis is frequently defined as an inflammatory process of the skin and connective tissues. Traditionally used to refer to infections with Gram-positive organisms, in particular streptococci, the term is now applied to any inflammation having an infectious etiology. Almost any clinically important bacteria can cause this symptom. Cellulitis is usually diagnosed by the presence of the five cardinal signs of inflammation noted by Celsus:

1. redness (*rubor)*
2. swelling *(tumor)*
3. pain *(dolor)*

4. heat *(calor)*
5. loss of function *(functio laesa)*

In response to the presence of foreign bacteria, capillaries in the invaded region dilate, allowing increased blood flow to the part (*rubor* and *calor)*. This dilatation causes spaces to form in the capillary wall, allowing extravasation of phagocytes and fluid into the perivascular space (*tumor*). The migration of phagocytes to the site of infection (chemotaxis) is mediated by chemicals released by the organism known as chemotactic factors. The resulting edema causes stretching of cutaneous nerve fibers and pain (*dolor*). Because of this pain, the patient is unable to move easily (*functio laesa*).

The presence or absence of any or all of these signs is neither diagnostic nor exclusionary for infection. However, in the majority of cases, most if not all of these signs will be present. This is not a quantitative issue of how many signs equal infection. Just because the patient has three out of the five or four out of five does not mean that there is an infection present. A number of non-infectious inflammatory conditions can mimic infectious cellulitis. For example:

1. Gout
2. Deep vein thrombosis (DVT)
3. Chronic indurated cellulitis (venous disease)
4. Acute Charcot joint
5. Acute trauma
6. Early stages of wound healing
7. Post-surgical changes

As an example, take a patient one-week post bunion surgery. The patient presents with edema of the region, pain that may limit their function, and some peri-incisional erythema. This patient now has four out of five signs of cellulitis; surely they must be infected! Of course, there is no infection. These are all normal changes seen post-operatively. This is an example of where the clinician's diagnostic acumen overrides any definitions written in books and papers: A prime example of the axiom that infection is a clinical diagnosis.

The extent of the cellulitis (or, as importantly, the lack thereof) should be documented. This will establish a baseline against which the resolution of the process may be compared. Some clinicians find it useful to mark the leading edge of the cellulitis in indelible ink for this purpose.

Lymphadenitis

The lymph nodes act to filter out infectious agents along the lymph channel draining the acute site. In the presence of these organisms, the nodes can become enlarged and inflamed, causing palpable masses and pain. Infections of the foot and leg will drain proximally into the popliteal fossa and the inguinal region; however, the absence of palpable nodes in the popliteal fossa does not rule out inguinal involvement. Also, popliteal nodes are significantly more challenging to find than inguinal.

Lymphangitis

Lymphangitis is an acute inflammation of the lymphatic channels draining a site of infection. It presents as red linear streaks following the course of the superficial vessels.

Fever

Fever and thermoregulation are complex topics that have warranted entire chapters in textbooks, not to mention hundreds of scientific papers. A simplistic definition of fever would be *an elevation in the core temperature as part of a defensive strategy against invasion by a pathogen*. "Normal" temperature, contrary to popular belief, is not necessarily 98.6 F (37 C). This value varies based on the time of day, the site from which the temperature is taken and the individual. Normal may be as high as 100.4 F (38 C) or higher.

Pyrogens

Fever is the body's response to the presence of pyrogens. There are two types of pyrogens:

1. An **exogenous pyrogen** is produced by some bacteria, especially the Gram-negative rods. It is not, however, responsible for all fevers, as many common organisms are incapable of producing them.
2. An **endogenous pyrogen** is produced by the leukocytes, in particular the monocytes, in the presence of infection.

Exogenous pyrogens have also been shown to directly induce the cells to produce their own pyrogen. The temperature control center of the brain is located in the anterior hypothalamus. Both endogenous and exogenous pyrogens appear to have a limited direct effect on this site. They mediate their activity through the production of prostaglandins, which are more readily capable of exerting their action on the brain. This prostaglandin production helps explain

the antipyretic mechanism of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), which have an inhibitory effect on prostaglandin synthesis.

These various factors cause the hypothalamus to increase the body's temperature set point. Once the set point is elevated, various physiologic responses must occur in order for the body to reach that new level. The most common of these is shivering and shaking chills which cause excessive muscular activity thus warming the core to the new set point.

Fever Curves

There are a number of different fever patterns that have been described. They were once though useful for the diagnosis of a specific type of malaria but are now mostly of historical interest. The two most common that are seen in lower extremity infections are:

1. Continuous fever, in which the temperature is elevated throughout a 24 hour period with only small variation. This is seen in diseases characterized by continuous seeding of bacteria into the blood (e.g., subacute bacterial endocarditis).
2. Intermittent fever, in which there are significant swings over 24 hours with an occasional return to baseline. It is seen in the case of abscesses, which intermittently seed the blood, and is most common in lower extremity infections.

When evaluating fever curves, it should be remembered that most people have a normal diurnal variation, with temperature spikes occurring daily. High temperature usually occurs between 4 to 6 p.m. and possibly as late as 8 p.m. The low point for fever usually occurs around 8 a.m.

Antipyretic Therapy

Fever seems to have a physiologic purpose. More and more studies are showing that fever helps the body to fight off the infection and if suppressed, can actually worsen the condition. The exception to this is in patients in whom fever takes too high of a metabolic toll, mostly those with underlying cardiac or pulmonary disease and the frail elderly. The other population in which fever should be suppressed is the very young, in order to prevent febrile seizures.

A fever curve is also useful in assessing the progress of a treatment regimen. With adequate therapy the curve should show a definite downward trend over a few days. The usefulness of this parameter can be masked by the use of antipyretic agents.

Therefore, as a general rule, unless there is imminent danger of seizures or metabolic derangement in the case of extremely high fever, antipyretics should be used sparingly and carefully. Standing antipyretic orders should be avoided. Even in cases where the antipyretic is being used for the purpose of patient comfort, there is a risk-benefit ratio to consider. Even though the patient may be temporarily more comfortable, the drug may increase the severity and duration of the condition.

Nosocomial Fever

Frequently, hospitalized patients will develop fever in the face of an apparently improved wound infection or no obvious infection at all. This is referred to as *nosocomial fever*. There can be many causes of this condition and many different mnemonics have been tried to make them easy to remember.

1. A few of the commonly involved sites that should be examined include:
   a) Lungs: Examine for atelectasis, pneumonia, and pulmonary emboli.
   b) Genitourinary tract: Order urinalysis for urinary tract infection, which is common in women but very unusual in men without an underlying predisposing factor such as catheterization, blockage, or malignancy.
   c) Indwelling catheters: This includes all intravenous and feeding tubes. Check for signs of drainage or cellulitis around the ingress (line sepsis). If found, the lines should be removed and replaced.
   d) Veins: Examine for thrombophlebitis.
   e) Blood: Blood cultures, repeated two or three times, should be performed to rule out bacteremia from any of the above or from SBE.
2. Any number of drugs can cause fever. This so-called "drug fever" is thought to be an allergic reaction. Common drugs capable of causing fever include NSAIDs, phenytoin, phenobarbital, penicillin, aspirin, and antihistamines.
3. For some patients, most commonly those with malignancies, there will be no explanation for their fever. The cause is believed to be secondary to alterations in the thermoregulatory center of the brain. This is referred to as "central fever."

Fever of Unknown Origin

To determine the etiology of a fever when no obvious wound infection is present, a systematic approach, such as the one listed below, is used to examine the above-mentioned possibilities.

1. Stop all antibiotics.
2. Stop all other drugs (if possible).
3. Observe patient for two to three days.
4. Fully reculture the wound, urine, sputum, and blood.
5. Consider the use of imaging techniques such as CT scanning or nuclear scans. If the cause of the fever cannot be determined after two to three weeks of clinical and laboratory workup, the patient is classified as having a fever of unknown origin (FUO).

Sepsis

Sepsis is the clinical and physiologic response of the body to microorganisms or their by-products in the bloodstream. It should be differentiated from bacteremia, which is simply the presence of these organisms in the blood, or septicemia, which is generally considered to be the same as bacteremia yet more severe. Sepsis causes the peripheral circulation to collapse, leading to inadequate perfusion of tissues. This is known as septic shock.

Clinical signs and symptoms of sepsis include fever, tachycardia, tachypnea, changes in mental status, and hematologic abnormalities, including eosinopenia, hyperglycemia, and leukocytosis. In more severe cases, paradoxical hypothermia and leukopenia can result. Other manifestations of severe sepsis include adult respiratory distress syndrome and disseminated intravascular coagulopathy.

In 1992 the American College of Chest Physicians and the Society of Critical Care Medicine developed criteria for the diagnosis of sepsis. These criteria were reviewed by a consensus panel in 2003 and, although some other specific organ system changes were added, the original criteria were still found to be valid. In order to have a diagnosis of sepsis there must be clinical evidence of infection plus evidence of a systemic response to infection. This systemic response is manifested by two or more of the following:

1. Temperature >38 C or <36 C
2. Heart Rate > 90 beats/min
3. Respiratory Rate >20 breaths/min
4. White Blood Count >12,000 cells/mm^3, <4000 cells/mm^3, or >10% immature (band) forms

This brief discussion of sepsis appears in this chapter instead of as a separate clinical entity because recognition of sepsis is paramount in its treatment. Along with antimicrobial therapy directed at the specific causative organism, medical management of the above manifestations is the proper approach to therapy.

LABORATORY DIAGNOSIS

It bears repeating that the diagnosis of a lower extremity infection is first and foremost a clinical judgment. Once a history is obtained and the physical examination completed, if it is suspected that an infection exists, then the laboratory may be an adjunct in the confirmation of that infection and assist in determining the causative organisms and proper therapy. Laboratory testing not only can be helpful in the confirmation of a diagnosis of an infection but can also be used to follow the course of therapy.

Complete Blood Count with Differential

Probably the single most useful test for both diagnosing and following the course of therapy in an infection is the complete blood count (CBC) with differential.

White Blood Cell Count

In an acute infectious process, the body responds by increasing the production of polymorphonuclear leukocytes (PMNs) (or "polys" or "segs"). Therefore, the first index of importance is the white blood cell count (WBC). An absolute leukocytosis is highly suggestive of infection. That being said, however, in localized infections of the foot the WBC count may be totally within normal limits. Also, the WBC can be elevated for a host of reasons other than infection. Therefore, WBC testing in and of itself will not confirm or rule out the diagnosis of infection.

In an acute process, the PMN: lymphocyte ratio will favor the PMNs. This may reverse in more chronic disease. Patients with infections caused by parasitic organisms may present with an increase in the eosinophil count. Eosinophilia can also be useful in detecting the presence of allergic reaction to an antibiotic.

Left Shift

When bone marrow production of PMNs becomes overwhelmed, immature forms, or band forms, will be released into the peripheral bloodstream. The presence of these band forms constitutes the second index of importance in evaluating the CBC, the "left shift." Unfortunately, as mentioned above, because of the localized nature of many foot infections, the left shift may not be present or remain equivocal. Interestingly, the left shift got its name because standard pictorial drawings of the morphologic development of white blood cells always began with the most immature cells on the left of the page with the progressively more mature cell drawings being added

on from left to right until the fully mature cell is on the right side of the chart. Therefore, the more immature cells there are, the more types represented by drawings on the left side of the page.

Once appropriate therapy is begun, both the leukocytosis and the left shift will return to normal fairly rapidly. If there is no trend toward normalization following two to three days of treatment, the therapy should be reconsidered.

Absolute Neutrophil Count

In patients who are leukopenic as a result of underlying disease, chemotherapy, or antibiotic side effect, the absolute neutrophil count (ANC) can be employed to determine the level of the patient's host defenses. The ANC is calculated by adding the percentage of PMNs and the percentage of band forms and multiplying the total by the WBC. For example, a WBC of 10,000 cells/mm^3 with 65 percent PMNs and five percent band forms yields an ANC of 7,000 cells/mm^3. If the ANC falls below 1,000 cells/mm^3, reverse isolation precautions may become necessary to prevent exposure of the patient to exogenous infection with patients being below 500 cells/mm^3 being at the greatest risk.

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate (ESR) is determined by measuring the distance in millimeters that a column of erythrocytes falls in one hour. The cells fall when formed into rouleaux, which only occurs when red cells' natural tendency to repel one another is overcome by the presence of acute phase reactants. These reactants are present when a patient has an underlying infection, malignancy, or inflammation. Because the ESR may be elevated in any of the above conditions, elevation may be too nonspecific to be diagnostic for infection. However, if the ESR is found to be elevated and it is believed that the elevation is because of infection, it can be useful as a baseline value to monitor the effectiveness of therapy.

C-Reactive Protein

One of the acute phase reactants discussed above is C-reactive protein (CRP). Although not as widely employed as the ESR, in the presence of infection the CRP is found to be positive almost immediately and is generally a more sensitive indicator of infection or inflammation. The difficulty with this test is, as with the ESR, it is relatively nonspecific.

Antistreptolysin O Titer

Used almost exclusively in the diagnosis of acute rheumatic fever, the usefulness of antistreptolysin O (ASO) titer in the diagnosis of skin and skin structure infections has not been well documented. Theoretically at least, in the presence of a streptococcal organism in an infection, the ASO titer should be positive. The only potential indication for its use is in cases in which standard culture techniques cannot be employed (e.g., cellulitis with no specimen to culture) or for suspected streptococcal skin infections, but it is rarely used.

Teichoic Acid Antibodies

Teichoic acid is a polymer present on the cell walls of Gram-positive organisms. Because it acts as a potent antigen, antibodies will be formed to it that can be assayed through immunologic tests such as the enzyme linked immunosorbent assay (ELISA). The usefulness of this assay in the diagnosis of staphylococcal skin and skin structure infections has not been demonstrated. There has been some work in the area of osteomyelitis but most of the studies are retrospective and success rates vary widely from 30 percent to 70 percent.

Blood Chemistry

Most laboratories run computerized panels consisting of six to 24 different chemistries. The following includes only those with direct relevance to the diagnosis and treatment of lower extremity infections.

Serum Creatinine

The serum creatinine level is the single most important chemistry. The test should be run on *every* patient receiving parenteral antibiotics. With only a few exceptions, all antibiotics are excreted to some extent by the kidneys. The serum creatinine level is the best hematologic index of renal function and therefore of antibiotic excretion. Dosage and dose interval of many agents may be calculated based on the renal function. Although dosing nomograms may be calculated from the results of the creatinine clearance test, the test is time consuming, requiring a 24 hour urine collection. Creatinine clearance can be calculated from the serum creatinine level by using the equation of Cockcroft and Gault. Although ideally committed to memory, “plug and play” calculators using the equation are easily found online by running a Web search or available for free download using any number of commonly used handheld devices:

$$C_{cr}\ (ml/min) = \frac{(140 - age)\ x\ weight\ in\ kg}{Cr\ x\ 72}\ (x\ 0.85\ for\ females)$$

Blood Urea Nitrogen

Less specific for renal function than the creatinine level, the blood urea nitrogen (BUN) level is affected more readily by the hydration state of the patient. It is used more as a secondary test to support renal function data garnered by serum creatinine testing.

Electrolytes

Sodium and potassium levels are particularly useful in determining antibiotic therapy. A number of antibiotics contain fairly high sodium loads at therapeutic dosage. Their use may cause hypernatremia, with resultant hypokalemia. The electrolytes are also useful adjuncts in determining renal function. Hypertension with concomitant diuretic use will have a major affect on the test.

Glucose

The stress of an infection will cause serum glucose levels to rise. Patients with diabetes will often present with elevated glucose levels between 400 and 1,200 mg/dl. Even patients with mild glucose intolerance may present with hyperglycemia. Furthermore, heretofore-undiagnosed diabetics will present with severity of infection out of line with the etiology. Hyperglycemia in these patients may be the only clue to their occult diabetes mellitus.

Liver Function Tests

Some antibiotics, most notably clindamycin and erythromycin, are metabolized in the liver. If these agents are to be used, then the liver function tests (LFTs) should be examined. The most common tests determine levels of bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). LFTs have also become of major importance with the availability of the newer generation oral antifungal medications used for onychomycosis. Therefore, an in depth discussion on LFTs can be found in the section on antifungal therapy.

BACTERIOLOGIC DIAGNOSIS

Gram Stain

The Gram stain is an easy, inexpensive, and rapid in-office procedure that yields a wealth of information concerning the etiology of infection. All that is required to perform this test is a set of commercially available reagents and a microscope with a 100X oil immersion objective. Exact timing of application for each reagent is unnecessary. The time needed to put down one bottle and reach for the next is usually sufficient to allow adequate staining. Despite this, essentially no clinicians are performing this test in their office and instead, depend on the same commercial laboratory to which they send their cultures. For this reason, often the gram stain result is not seen until the final culture report is received and therefore the results are passed over or downright ignored. Despite this delay, the information can still be useful.

Gram Stain Technique

1. Make a thin smear of drainage on a glass slide. Do not take the specimen with a cotton-tipped applicator as this may absorb some of the material. Use the wooden end of the applicator or a metal probe.
2. "Heat fixing" by running the slide under a flame is not necessary. Allowing the slide to air dry for five minutes is sufficient.
3. While holding the slide (there is no need to put the slide on a rack, just keep it tilted away from the fingers to avoid inadvertent staining), apply the Gram crystal violet and let it sit for five to 10 seconds.
4. Rinse the slide with tap water. This step applies between each of the following applications. Some believe that even this is unnecessary and that immediate application of the next reagent is sufficient "rinsing."
5. Apply Gram iodine. The residual blue stain will turn black almost immediately.
6. Holding the slide at a steep angle to allow immediate drainage, apply the decolorizer until the runoff is almost clear and most visible signs of stain are removed from the slide. Rinse immediately to halt the process. This is the most critical step to successful staining. Too long an application will cause all the organisms appear Gram-negative. Insufficient time causes everything to appear Gram-positive.
7. Apply the Safranin counterstain. Because this is a fairly light color, leave the stain on the slide for at least 10 seconds.

8. Rinse. Blot dry.
9. Examine microscopically using the 100X oil immersion objective. The organisms are too small to visualize at any lower power.

Evaluation of the Slide

The slide is properly Gram stained if the PMNs have light pink cytoplasm with darker pink-mauve nuclei. Organisms can also be used to evaluate the stain technique. If cocci appear Gram-negative the stain was probably overdecolorized. Most pathogenic cocci in the lower extremity are expected to be Gram-positive, except in the rare case in which gonococci are suspected (e.g., in septic arthritis).

Information Obtainable from the Gram Stain:

Organism Morphology

Most organisms have distinctive morphology upon examination that allows immediate identification and empiric therapy. *Staphylococci* appear as Gram-positive cocci in "grape-like" clusters. *Streptococci* appear as Gram-positive cocci in chains. Table 1-1 lists Gram stain morphologies for various organisms.

TABLE 1-1

Gram-Stain Appearance of Common Organisms[a]

Organism	Morphology
Gram-positive (Blue)	
Staphylococcus	Cocci in "grape-like" clusters
Streptococcus	Cocci in chains
Corynebacterium	Rods in "Chinese characters"
Clostridium	Rods with a "racquet shape" caused byspore
Gram-negative (Red)[b]	Gonococcus Diplococcus within the WBC
Klebsiella	Diplococcoid bacillus may show a heavy capsule
Pseudomonas	Slightly curved rod

[a] Slide check: The cytoplasm of the WBC is light pink; the nucleus of the WBC is dark pink-mauve; cocci are dark blue-purple, unless gonococci are suspected.

[b] It is difficult to identify most other Gram-negative rods on the basis of stain only.