23
Other Bacterial Infections After Hematopoietic Stem Cell or Solid Organ Transplantation

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23.1 Introduction

This chapter describes the epidemiology, clinical presentation, diagnosis, and management of infections caused by a diverse group of bacterial pathogens. These include classic opportunistic infections and also infections that are common in immunocompetent patients, but particularly prevalent or morbid in transplant populations. Some uncommon bacterial pathogens that have a predilection for patients with impaired immunity are discussed. Finally, the chapter touches on some miscellaneous bacterial infections that are important because they may be unanticipated in transplant recipients or present diagnostic or therapeutic challenges.

23.2 Gram-Positive Organisms

23.2.1 Listeria Monocytogenes

Listeria are small gram-positive bacilli that produce weak beta hemolysis on blood agar and have characteristic tumbling motility when observed by light microscopy [1]. Isolation from mixed specimens such as stool requires special media or a process called "cold enrichment" that capitalizes on the ability of *Listeria* to grow well at refrigerator temperatures. In clinical specimens, the organisms may appear gram-variable or resemble diphtheroids. Indeed, isolation of a "diptheroid" from the blood or CSF should raise concern for laboratory misidentification of *Listeria*.

Of the seven species of *Listeria*, only one, *L. monocytogenes,* is responsible for almost all cases of listeriosis. This organism is widespread in nature and has been isolated from tap water, sewage, several animals, and multiple foodstuffs including dairy products, fruits, vegetables, fish, and meats [1]. Human exposure to *Listeria* appears to be universal. Gastrointestinal carriage has been documented in about 5% of healthy adults and asymptomatic kidney transplant recipients [1–3].

Excepting perinatal transmission and rare cases of person-to-person spread, *Listeria* infections are thought to be acquired by ingestion of contaminated food [4]. High profile outbreaks [4, 5] have highlighted the foodborne nature of this infection, but most sporadic cases have no identified food source. The incubation period for self-limited cases of febrile gastroenteritis is about 24 h, while the incubation period of invasive infection averages 35 days, with a range of 1–91 days [5, 6]. Invasive listeriosis occurs predominately in four risk groups: immunocompromised individuals, pregnant women, infants, and adults over 60 years of age. Three quarters of the 1651 of patients identified with listeriosis in the USA between 2009 and 2011 who did not have age or pregnancy as a risk factor were immunocompromised [7]. Recent surveillance data indicate that the incidence of both non-perinatal *Listeria* infection and *Listeria*-associated mortality are decreasing, trends that are likely due to improved control mechanisms in the food industry [8].

Experiments by Mackaness in the 1960s demonstrated the central role of cell-mediated immunity in protection against *Listeria* infection [9]. Multiple arms of the immune response are involved, but memory CD8 T cells seem to be most important to protection. *Listeria* infection has been reported after both solid organ transplantation (SOT) and hematopoietic cell transplantation (HCT). The risk for invasive listeriosis is highest early after transplantation or following augmentation of immune suppression [10, 11]. Some early posttransplant *Listeria* infections are postulated to arise by translocation from pretransplant gut carriage [12, 13]. *Listeria* infections also occur years after transplantation, when immunosuppression is generally less intensive [12]. Recent 7-year data from France showed an incidence of *Listeria* infection of 7.91 cases /100,000 persons/year in SOT recipients, which was 21 times higher than in the general population; the mortality rate in transplant patients was 6% [14].

In transplant recipients, listeriosis typically presents as a sepsis syndrome, often accompanied by central nervous system (CNS) involvement. The presentation can be acute or can follow a prodrome of milder symptoms. Almost all transplant recipients with listeriosis have bacteremia and between 40 and 60% have meningitis [11, 15]. Signs of CNS

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involvement may be subtle, and nuchal rigidity is present in only about one-half of patients [1]. Focal neurologic signs are less common than diffuse signs, such as personality changes or forgetfulness.

In the largest series of *Listeria* meningitis, the median cerebrospinal fluid (CSF) leukocyte count was 585 cells/mm^3 and nearly 70% of patients had <1000 leukocytes/mm^3 [16]. CSF smears typically showed a predominance of neutrophils. Elevated CSF protein and low CSF glucose levels were common, although these values were sometimes normal, particularly early in the illness. The organism is only occasionally visualized on Gram stains of CSF, but centrifugation of CSF may increase the yield. Cultures of CSF are relatively insensitive, identifying only 30–35% of cases [16, 17].

In addition to meningitis, *L. monocytogenes* can cause cerebritis, encephalitis, and brain abscess (see Figure 23-1). Rhombencephalitis is an unusual form of listerial encephalitis involving the brainstem. It presents with movement disorders, facial nerve palsies, cerebellar signs, and hemiparesis or hemisensory deficits. *Listeria* brain abscesses often involve subcortical areas, including the brain stem. Most patients with *Listeria* brain abscess are bacteremic, and 10–25% have meningitis [1, 11, 16, 17]. The mortality of isolated bacteremia with *L. monocytogenes* is only 3%, but is as high as 30% in patients with CNS involvement [11, 15–17]. Non-CNS *Listeria* also occasionally causes localized infection in transplant recipients, including peritonitis [18], hepatitis [19], arthritis [20], endophthalmitis [21], and endocarditis [22].

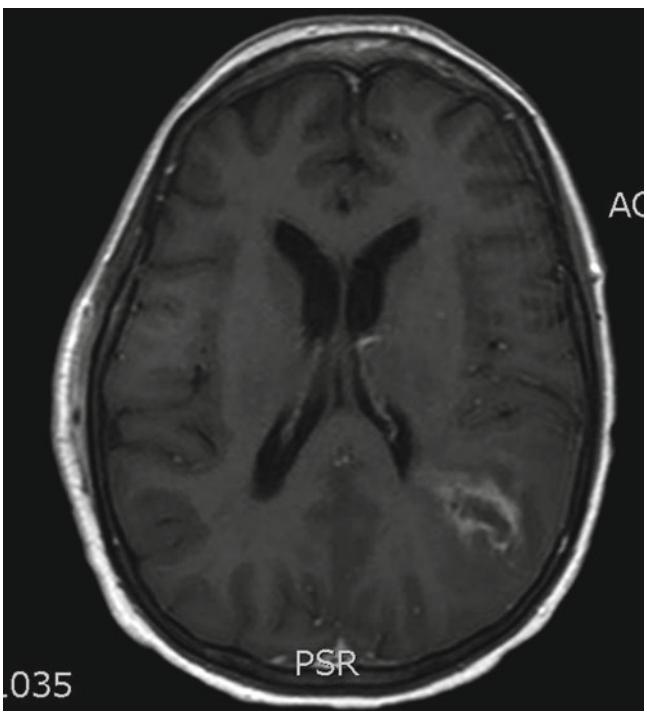

FIGURE 23-1. MRI demonstrating ill-defined enhancing focus with surrounding vasogenic-type edema in the juxtacortical left parietal lobe.

Lacking controlled studies, recommendations for treatment of listeriosis are based on in vitro testing, animal models, and clinical observation. The therapy of choice is high-dose ampicillin or penicillin [1, 17]. Laboratory evidence of synergy between ampicillin and aminoglycosides has led to the recommendation for combination therapy when infection is severe or occurs in immunocompromised hosts [23]. In transplant recipients, however, the potential benefit of aminoglycoside therapy must be weighed against the risk of nephrotoxicity. Trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice in penicillin-allergic patients [1]. Imipenem and meropenem have been successfully used to treat *Listeria* infections, but they are generally less active than ampicillin and may lower the seizure threshold [24, 25]. Linezolid can be considered for patients with multiple drug allergies based on its excellent CNS penetration and effectiveness in a few clinical cases [26]. Vancomycin has good in vitro activity against *Listeria* but suffers from poor penetration into the CNS; clinical failure for both CNS and non-CNS listeriosis has been reported with vancomycin [27, 28]. Cephalosporins are inactive against *Listeria*. Due to the high risk of recurrence, transplant recipients should receive 3 weeks of therapy for bacteremia or meningitis, and longer courses for brain abscess.

Guidelines for preventing *Listeria* infection from the Centers for Disease Control and Prevention (CDC) include standard approaches to food safety, such as thorough cooking of meat, washing of fresh fruits and vegetables, and physical separation of uncooked meat from other foods [29]. Persons at high risk of listeriosis are encouraged to avoid foods that may harbor *Listeria*, including unpasteurized milk, soft cheeses, hot dogs, and luncheon meats. Standard sulfonamide prophylaxis for *Pneumocystis* infection is thought to prevent *Listeria* infection but the low incidence of infection has made this difficult to prove [1, 17].

23.2.2 Nocardia

Nocardia are aerobic gram-positive rods that have characteristic filamentous, branching chains (see Figure 23-2a). They are present in soil and decaying organic material, and most human infections result from the inhalation of airborne bacilli. A small number of patients are infected by accidental inoculation into the skin. *Nocardia* infection was first described in transplant recipients in the 1960s [30]. *Nocardia* infections occur in between 0.1 and 3.5% of SOT patients, with lung and heart recipients at highest risk [31, 32]. The reported frequency of nocardiosis after HCT is low. An incidence of 0.3% was reported in 6759 HCT recipients at three large transplant centers [33]; cases occurred exclusively in allogeneic recipients. In a separate single-center study, nocardial infection occurred in 1.7% of 302 allogeneic HCT recipients but only 0.2% of 542 autologous recipients [34];

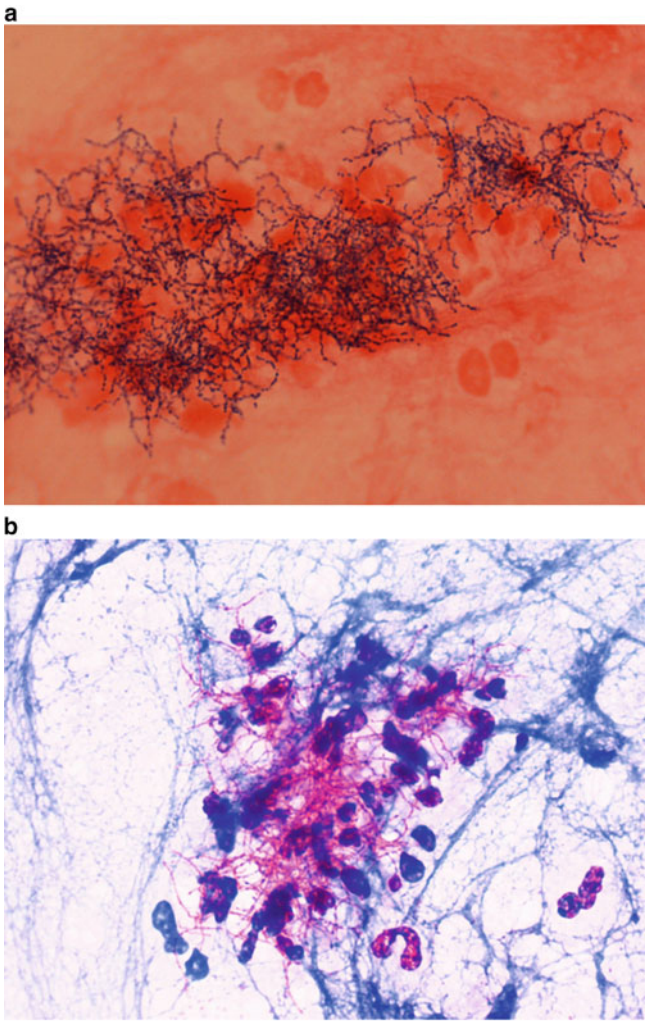

FIGURE 23-2. (**a**) Branching, beaded filamentous rods (hematoxylin and eosin stain). (**b**) Modified acid fast stain, demonstrating the weakly acid fast staining property of *Nocardia* species.

all patients with *Nocardia* infection had recently received immunosuppressive medications.

Nocardia infections are usually sporadic and acquired in the outpatient setting, but small nosocomial outbreaks have been reported [35]. Wilson and coauthors [30] noted few *Nocardia* infections in the first month after SOT; the frequency of cases peaked between 1 and 6 months after transplantation and then occurred sporadically at lower rates thereafter. Similarly, most cases of nocardiosis in HCT recipients occur after engraftment but within the first post-transplant year [33, 34]. Receipt of high-dose corticosteroids in the previous 6 months, high blood levels of calcineurin inhibitors and a history of cytomegalovirus disease have been shown to be independent risk factors for *Nocardia* infection in SOT recipients [32].

The clinical manifestations of nocardiosis are similar in SOT and HCT recipients [30–34]. Eighty percent to 90% of patients have a respiratory illness, ongoing for a week or more. Typical symptoms are fever, productive cough, pleuritic chest pain, dyspnea, weight loss, and hemoptysis. Lung nodules, which may be cavitary, are the classic radiographic finding, but alveolar consolidation and/or pleural effusion are also seen [36]. At presentation, up to one-half of patients have disseminated infection. Sites of dissemination include the CNS in roughly one-third of patients and the skin in up to 15%. Occasional patients have spread to the bone, joints or muscle [30–33]. Skin lesions of disseminated nocardiosis are palpable, mildly tender, deep abscesses that may or may not appear erythematous. Cerebral abscesses are the usual manifestation of CNS infection. They may manifest with focal neurologic defects, headache, and/or seizures [30]. Some brain abscesses are clinically silent. Given the relative frequency of CNS involvement, neuroimaging is advised in all patients with nocardiosis. Meningitis due to *Nocardia* also occurs but is considerably less common than brain abscess.

The gold standard for diagnosis of *Nocardia* infection is culture of the organism from a clinical specimen. Biopsy of lung, brain, or other involved tissue is often necessary. *Nocardia* colonies may appear on aerobic cultures as early as 3–5 days, but can take 2 weeks or longer to be detected. In a study of 11 lung transplant recipients with *Nocardia* infection, the mean time of culture diagnosis was 9 days [37]. The appearance of *Nocardia* on Gram stain (see Figure 23-2a) is distinctive enough to allow for a presumptive early diagnosis. Most strains of *Nocardia* are weakly acid fast (see Figure 23-2b), a feature that aids in identification and in differentiation from *Actinomyces* species.

Sulfonamides are the agents of choice for nocardiosis because of their reliable activity and the high drug concentrations achieved in affected tissues. Trimethoprim-sulfamethoxazole is the preferred sulfonamide, but excellent results also have been achieved with other sulfonamides [30, 34, 38, 39]. Adjustment of sulfonamide dosing for creatinine clearance is often necessary in transplant patients. Ideal serum levels are between 100 and 150 mcg/mL. Clinical failure of sulfonamide therapy is uncommon. A high rate of in vitro resistance of *Nocardia* isolates to sulfonamides was reported in one recent study [40]. However, a subsequent study from six reference laboratories showed resistance to TMP-SMX in only 2 of 552 *Nocardia* isolates [41]. Other antimicrobials that have good activity against most species are minocycline, amikacin, imipenem, meropenem, cefotaxime, and ceftriaxone [31]. A recent in vitro study demonstrated that tigecycline and moxifloxacin were active against the majority of 51 clinical isolates of *Nocardia* [42]. Selected strains are susceptible to ampicillin, ampicillin-clavulanate, ciprofloxacin, erythromycin, and other macrolides, but use of these antibiotics is only advised if supported by susceptibility testing. Ertapenem is 16-fold less active than imipenem and should not be viewed as a useful agent [42]. Linezolid has excellent in vitro activity against *Nocardia* species and has demonstrated therapeutic potential in case reports [43, 44]. Unfortunately, the long-term use of linezolid may

be limited by adverse effects such as myelosuppression and peripheral neuropathy.

Susceptibility testing of *Nocardia* species has not been rigorously correlated with clinical outcomes, but offers comparative data and may be helpful with more resistant strains, such as *N. farcinica* or *N. transvalensis*, or if therapy must be changed from a first-line agent because of toxicity or inadequate response [42, 45].

Animal models have demonstrated that certain antimicrobial combinations, such as imipenem with amikacin or moxifloxacin, may achieve more rapid reduction in bacterial colony counts than sulfonamides [46–48]. These regimens may be an excellent alternative to sulfonamides or serve as initial therapy until clinical stability is achieved and susceptibility data is available. Ultimately, most patients respond to initial therapy and can be transitioned to a simple oral regimen to complete treatment. The optimal duration of therapy is unknown, but treatment courses of 4–6 months are typical for pulmonary and soft tissue infections. Treatment is usually extended to 12 months or longer in patients who have disseminated or CNS disease.

Although TMP-SMX is generally an active agent for treatment of nocardiosis, low-dose TMP-SMX prophylaxis for *Pneumocystis* is not consistently protective against *Nocardia* infection [32–34, 37]. Interestingly, isolates from patients who develop nocardiosis while on low-dose TMP-SMX are usually susceptible to TMP-SMX [32].

23.2.3 Lactobacilli

Lactobacilli are strict or facultatively anaerobic, gram-positive rods that are ubiquitous inhabitants of the human oral cavity, vagina, and gastrointestinal tract. Previously, they have often been considered nonpathogenic. However, serious infections due to lactobacilli have been reported in both immunosuppressed and immunocompetent patient populations [49–55].

A review of 200 *Lactobacillus* infections found that 9% of the infections occurred in transplant recipients [54]. Patel et al. described *Lactobacillus* bloodstream infections in 8 patients within the first 6 months after liver transplantation [51]. All of the infections but one were polymicrobial, and in most cases the organisms were also isolated from abscess fluid or bile. The presence of a Roux-en-Y choledochojejunostomy was a strong risk factor for infection. Other reports of serious infection include endocarditis and mediastinitis in a heart recipient [49], splenic abscess in a kidney recipient with concomitant HIV infection [53] and relapsing bacteremia and meningitis in a cord blood transplant recipient [56]. A case of *Lactobacillus* pneumonia and empyema occurring early after lung transplantation was thought to be transmitted by the transplanted lung [52].

The current use of probiotics containing "non-pathogenic" microorganisms for various gastrointestinal conditions has raised concerns that this may be an unsafe practice in transplant patients. Indeed, serious *Lactobacillus* infections have been described in transplant recipients receiving probiotics that contained *Lactobacillus species* [57, 58]. In one case, an isolate from an empyema collection was found to be identical by molecular typing to the organism in the patient's probiotic preparation [58].

The standard treatment for *Lactobacillus* infection is high-dose penicillin or ampicillin, with or without an aminoglycoside for synergy [54, 55]. Other active antibiotics include erythromycin and other macrolides, carbapenems, linezolid, and quinupristin-dalfopristin [54, 55, 59]. Trimethoprim-sulfamethoxazole, metronidazole, and vancomycin have unreliable activity [51, 54, 55, 59]. Whenever possible, in vitro susceptibility tests should be obtained to direct therapy.

23.2.4 *Rhodococcus equi*

R. equi is a gram-positive coccobacillus of the order Actinomycetales. It is a veterinary pathogen that causes chronic suppurative pneumonia in foals and submaxillary lymphadenitis in swine [60]. Herbivores, such as horses and cattle, are colonized in the gut, and the organism inhabits soil contaminated by their manure. Approximately one-third of individuals with *Rhodococcus* infection report contact with farms or livestock [60]. *R. equi* infections occur primarily in patients who have defects in cell-mediated immunity. Approximately 10% of human *R. equi* infections occur in SOT and HCT recipients [61–64].

The lung is most common site of *Rhodococcus* infection. Patients present with a subacute course, characterized by fever, dyspnea, and nonproductive cough [60, 64, 65]. Other common symptoms include fatigue, weight loss, pleuritic chest pain and hemoptysis. Chest imaging demonstrates infiltrates or nodules, which frequently cavitate. Pleural effusions are common and often infected. Infection frequently disseminates to extrapulmonary sites such as the skin, bones, and brain. Disseminated infection is seen in roughly one-half of transplant recipients [61, 63].

The diagnosis of *Rhodococcus* requires laboratory isolation of the organism from a patient with a compatible clinical presentation. Early growth of *R. equi* may occur within 24–48 h, but the characteristic, mucoid, salmon-colored appearance of the colonies is not evident until a few days later [60]. The organism is easily missed in respiratory cultures and can be mistaken for "diptheroids" [66]; therefore, the laboratory should be alerted whenever *R. equi* infection is being considered. Blood cultures are positive in more than one-half of immunocompromised hosts [61, 65].

Many antibiotics are active against *Rhodococcus*. The most potent agents are vancomycin, imipenem, rifampin, quinolones, macrolides, and linezolid [61, 67, 68]. Clinical experience with linezolid is limited, but Munoz et al.

reported successful treatment of multidrug-resistant, relapsing *Rhodococcus* pulmonary infection in a heart transplant recipient [70]. Treatment with penicillins and cephalosporins has been unreliable and these antibiotics should be avoided. Treatment for immunocompromised hosts should consist of combination therapy with 2 or 3 active antibiotics. Intravenous therapy is commonly used initially, especially in patients with bacteremia or pulmonary abscesses. After the patient stabilizes and susceptibility results are available, therapy can be switched to an oral regimen. A treatment course of several months is typically required and it may be extended to 6 months or longer in disseminated infection [61]. Even with prolonged treatment, relapses may occur [71]. Adjunctive surgical therapy may be useful in selected patients [72].

23.2.5 *Clostridium difficile*

C. difficile is a spore-forming, gram-positive, anaerobic bacillus that elaborates toxins that cause colitis. Infection is usually associated with current or recent antibiotic use. *C. difficile* is part of the intestinal flora in approximately 3% of healthy adults, and as many as 30% of hospitalized patients [73]. Transmission in the health care setting is well documented.

The frequency of *C. difficile* infection is substantially higher in transplant populations than in other hospitalized patients. A meta-analysis, drawing on data from 21,683 SOT recipients, reported a pooled prevalence of *C. difficile* infection from transplantation to the first discharge of 7.4% [74]. The prevalence varied from 3.2% in pancreas transplant recipients to 10.8% in lung recipients. The *C. difficile* recurrence rate across the population was estimated to be 19.7%. In a large retrospective single center study spanning 6 years, the 1-year incidence of *C. difficile* infection among HCT recipients was 9.2%, with a breakdown of 6.5% among autologous and 12.5% among allogeneic recipients [75]. Relapsing *C. difficile* infection was observed in 21.7% of the patients at a median of 69 days after initial infection. Risk factor analysis showed the presence of gastrointestinal graft-versus-host disease (GVHD) to be highly associated with both overall and recurring *C. difficile* infection. *C. difficile* infection also correlated with the subsequent development of gastrointestinal GVHD. It was postulated that *C. difficile* infection triggered gastrointestinal GVHD by disruption of the mucosal barrier and release of proinflammatory cytokines. This association between *C. difficile* infection and gastrointestinal GVHD has been found in some but not all studies [76–78].

The symptoms of *C. difficile* infection in transplant recipients resemble those in other patients—watery diarrhea, lower abdominal pain and, at times, fever—and may be similar to symptoms of GVHD. The severity of *C. difficile* infection in transplant populations has been variably reported to be greater or less than in control populations [75–77, 79]. Authors who have found less severe disease in transplant recipients have speculated that immunosuppression attenuated the colonic inflammatory response and led to a less severe clinical course. It is also possible that less severe manifestations in transplant recipients were simply due to earlier diagnosis and treatment.

The cytotoxicity cell assay is the gold standard for diagnosis of *C. difficile* infection, but it is labor intensive and not widely used. Until recently the diagnosis was usually made by enzyme linked immunoassay (ELISA) for *C. difficile* toxin. Detection of *C. difficile* DNA by polymerase chain reaction (PCR) testing is more sensitive than ELISA and it is increasingly the primary test used for diagnosis. PCR testing has the drawback that it also detects asymptomatic carriage. Another accepted option for diagnosis is to employ a two-step algorithm, with an initial stool screen for a cell wall protein (glutamate dehydrogenase) common to both toxigenic and nontoxigenic strains, with subsequent testing by ELISA and/or PCR [80, 81].

The first consideration in treating *C. difficile* infection is cessation of the inciting antimicrobial agent(s) or transition to a narrower spectrum regimen, whenever possible. Management protocols for *C. difficile* infection generally recommend a stratified approach: oral metronidazole (500 mg every 8 h) is given for initial episodes of mild-to-moderate infection; oral vancomycin (125 mg every 6 h) is used for severe infection; and high-dose vancomycin (500 mg every 6 h) is administered orally or per rectum with or without intravenous metronidazole for severe, complicated infections [82]. Mild first recurrences can be retreated with oral metronidazole, but additional or severe recurrences should be managed with oral vancomycin using a tapered or pulse regimen. Fidaxomicin is an effective but costly alternative treatment which may be associated with a lower recurrence rate [83, 84]. For severely ill patients, especially those with toxic megacolon, colectomy may be a life-saving intervention.

No controlled studies are available to inform the treatment of *C. difficile* infection in transplant patients. Initial therapy is typically administered for 10–14 days, or longer if other antimicrobial therapy cannot be discontinued. If a prolonged duration of *C. difficile* treatment is planned, oral vancomycin is often the preferred agent to avoid the neurologic and hematologic toxicities associated with the extended use of metronidazole. Recently, fecal microbiota transplant (FMT) has emerged as an effective treatment for recurrent *C. difficile* infection [85]. Initial data on use of FMT in transplant recipients is limited but encouraging [86, 87]. There is a lack of conclusive data to support the use of probiotics to prevent *C. difficile* infection, particularly in transplant recipients where there is risk for bloodstream infection [57, 58, 82]. Prevention of *C. difficile* infection in populations at risk requires a multifaceted program, including aggressive infection control measures and an effective antibiotic stewardship program.

23.3 Gram-Negative Organisms

23.3.1 Legionella

Legionella are fastidious, aerobic, gram-negative rods that have been found in soil and freshwater lakes and streams. Over 50 species and 70 serogroups of *Legionella* have been described, and 20 species have been linked to human infection. The predominant species, *Legionella pneumophila* causes 95% or more of human illness in Europe and the USA [88]. Serogroup 1 makes up 80–90% of infectious isolates of *L. pneumophila*. Other *Legionella* species known to cause clinical infection in transplant patients include *Legionella micdadei, Legionella longbeachae*, and *Legionella dumoffii* [89–91].

Defects in cell-mediated immunity make transplant recipients particularly susceptible to legionellosis. Infection has been frequently reported in recipients of kidney [89, 90, 92], heart [93], liver [94], and hematopoietic cell [95, 96] transplants. *Legionella* infections can occur at any time after transplantation, but the frequency is greatest early after transplantation or following anti-rejection treatment.

Legionella infection is acquired by inhalation of infectious aerosols or by aspiration of infected water. Person-to-person transmission does not occur. Infections may be sporadic or part of health care-associated or community-associated outbreaks. Several outbreaks of *Legionella* infection in transplant recipients have been described [97–99]. *Legionellae* have a major, clinically relevant reservoir in institutional plumbing systems. They enter these systems via cold water intakes and subsequently colonize hot water heaters, from which they are dispersed to spigots and showerheads on patient wards [100, 101]. Outbreaks of *Legionella* pneumonia have been epidemiologically linked to several sources, including potable tap water, cooling towers, evaporative condensers, humidifiers, whirlpools, and decorative water fountains [88, 100, 102–107].

Pneumonia is the usual clinical presentation of *Legionella* infection. Some clinical features may suggest the diagnosis of legionellosis. Patients often experience a flu-like prodrome of high fever, chills, myalgias, and malaise, but antecedent upper respiratory symptoms are usually absent. Progressive infection results in dyspnea and a mildly productive cough, which is often associated with pleuritic chest pain. Approximately one-half of patients develop watery diarrhea. Mild CNS symptoms, such as headache and confusion, are often present. Some investigators have noted the presence of a pulse–temperature disassociation with a relative bradycardia [92]. The most common radiographic appearance of *Legionella* pneumonia is alveolar consolidation, which is frequently multilobar [108]. Pleural effusions, cavitation may be seen and focal nodular densities, mimicking invasive fungal infection, have been described [109] (see Figure 23-3).

Extrapulmonary *Legionella* infection is a rare occurrence, usually seen in immunocompromised hosts, with or without primary pneumonia. Some reported types of extrapulmonary involvement are cutaneous infection [110], aortitis [111], prosthetic valve endocarditis and sternal wound infection [112]. The morbidity of legionellosis in transplant recipients is substantial; the reported mortality ranges from 14 to 30% [96, 113], but can be as high as 80% for untreated health care-associated infection [92].

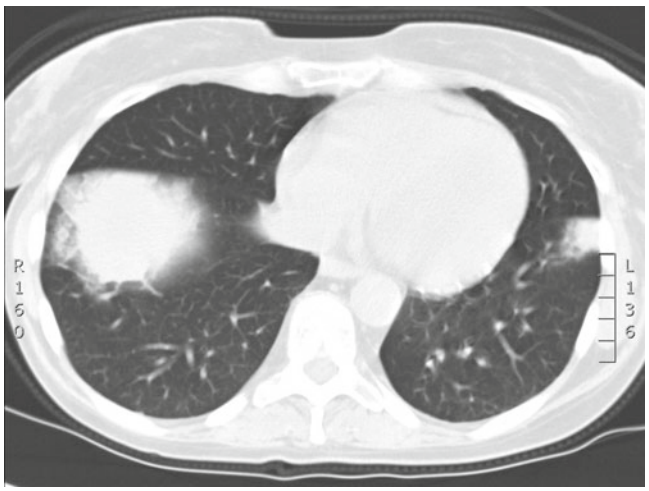

FIGURE 23-3. CT chest demonstrating multifocal nodular consolidations in a stem cell transplant recipient on high-dose immune suppression, demonstrated to have *Legionella* infection.

The laboratory diagnosis of legionellosis is often difficult and depends on the available level of expertise. Although *Legionella* are gram-negative bacilli, they are usually not visualized on Gram stain because of their small size and poor stain avidity. The definitive method of diagnosis is by culture. *Legionella* are fastidious and their isolation requires the use of enriched media (buffered charcoal yeast extract agar) in a CO2-rich environment (see Figure 23-4). Colonies appear after 3–5 days on agar plates but may be masked by overgrowth of other less fastidious organisms. Cultured organisms are more readily visualized by Gram stain than those in clinical specimens. It is notable that on tissue biopsy specimens *L. micdadei* can demonstrate weak acid-fast staining, highlighting the importance of *Legionella* culture when this diagnosis is suspected [114].

Several indirect methods for *Legionella* diagnosis are available. Direct fluorescent antibody (DFA) staining of sputum or tissue specimens is a rapid technique, but it has a low sensitivity (50%), and reagents are lacking for some species and serogroups [115]. *Legionella* serology has been useful for epidemiological studies but has limited value for diagnosis. The detection of urinary antigen is a well-established, rapid-turnaround assay with a sensitivity of greater than 85% for infections caused by *L. pneumophila* serogroup 1, but has little utility for the diagnosis of infection by other *Legionella* species. In the current era, most diagnoses of legionellosis are made by urinary antigen testing [88, 116]. Methods employing detection of *Legionella*

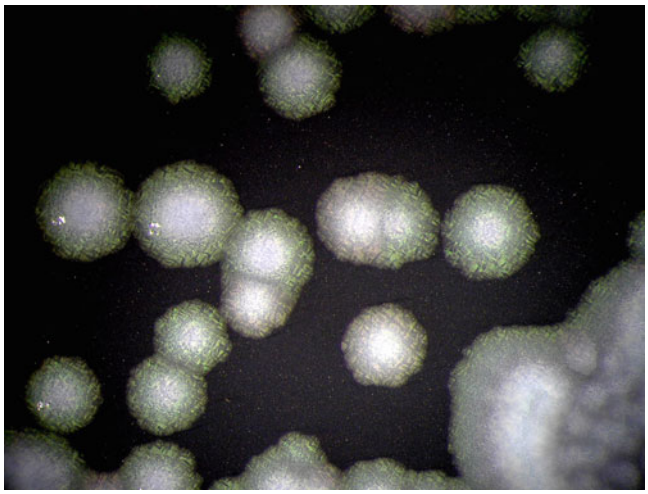

FIGURE 23-4. Colonies of *Legionella pneumophila* on buffered charcoal yeast extract (BCYE) agar. (Photo provided courtesy of A. William Pasculle Sc. D, Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA).

DNA by PCR have been developed and have potential for clinical application [88].

The most active antibiotics for *Legionella* treatment are the newer macrolides, such as azithromycin, and fluoroquinolones, especially levofloxacin and moxifloxacin. Erythromycin, rifampin, the tetracyclines, and TMP-SMX also have activity. All beta-lactam antibiotics, the aminoglycosides, vancomycin, and clindamycin are ineffective [92, 117–119]. Data regarding the benefit of combination therapy with rifampin are inconclusive [120], and drug-drug interactions pose a major drawback to the use of rifamycins in transplant populations.

Isolation for hospitalized patients with *Legionella* infection is unnecessary. If a hospital outbreak of legionellosis is detected, surveillance should include culturing of hospital water sources. Routine environmental sampling for *Legionella* in hospitals has been adopted in several states and by the US Veterans Affairs Healthcare System. It has also been recommended by the CDC for institutions with HCT programs. Community outbreaks of legionellosis have been linked to recreational or occupational exposure to aerosolized water, such as occurs in whirlpool spas or commercial water displays. It is therefore prudent to warn transplant recipients about the potential hazards of prolonged exposure to such aerosols.

23.3.2 Bartonella

Bartonella henselae is a fastidious, gram-negative bacillus that has a natural reservoir in domestic cats. Immunocompetent patients with *B. henselae* infection typically develop painful regional adenopathy and fever after a cat bite or scratch ("cat scratch disease"). Bacillary peliosis, bacillary angiomatosis, and persistent bacteremia with fever are typical manifestations of disseminated infection seen in patients with AIDS and other immunosuppressed hosts. Patients with bacillary peliosis have studding of the liver and spleen with numerous small inflammatory nodules that appear as hypodense lesions on computed tomography scanning. Bacillary angiomatosis is a vasculoproliferative form of disseminated *B. henselae* infection associated with lytic bone lesions and characteristic violaceous, friable skin nodules [121–123].

B. henselae infection has been reported in kidney, liver, heart, lung, and HCT recipients [121, 124]. Transplant recipients may present with localized cat scratch disease or with one or more of the syndromes associated with disseminated disease. Of 29 cases of *B. henselae* infection in SOT recipients reported by Psarros and coauthors, two-thirds were classified as disseminated [121]. An unusual form of bacillary angiomatosis with vegetating papillomatous lesions in the oral cavity has been described following HCT [124]. *Bartonella* endocarditis has been described in transplant recipients [121]. Unusual manifestations of *Bartonella* infection reported in kidney recipients include hemophagocytic syndrome [125] and vasculitis with allograft glomerulonephritis [126].

Donor-transmitted bartonellosis has been suspected in some cases, one of which had good documentation [121, 127]. In this case, a pediatric liver recipient was found to have a nodule of the liver and enlarged abdominal lymph nodes 2 months after transplantation [127]. Biopsies of the liver and lymph nodes showed granulomatous changes. *Bartonella* infection was confirmed by PCR of the liver. The recipient had no cat exposure and the donor was found to be seropositive for *B. henselae.*

Unlike *B. henselae*, humans are the only known reservoir of *Bartonella quintana. B. quintana* is transmitted by the human body louse, *Pediculus humanus*, and is the etiologic agent of trench fever. There is a single report of *B. quintana* infection after SOT presenting as bacillary angiomatosis in a kidney recipient from the Czech Republic [128].

Bartonella organisms are not routinely isolated from blood. Culture of tissue specimens on blood or chocolate agar may require an incubation period of 30 days and is not sensitive. For this reason, performing PCR on tissue specimens or blood is increasingly relied upon for diagnosis [129, 130]. Serology can be used as supportive evidence of infection in the appropriate clinical setting [121]. The diagnosis is strongly suggested when typical pathological changes are found in tissue sections, especially if Warthin–Starry stains of the tissue show organisms.

Cat scratch disease generally resolves without therapy in immunocompetent hosts. One small randomized trial showed a greater decrease in volume of affected lymph nodes in patients treated with azithromycin as compared with placebo [131]. No studies specifically address the treatment of bartonellosis in transplant recipients. Given the theoretical risk for dissemination, it seems prudent to recommend antimicrobial therapy for all transplant recipients with *Bartonella* infection.

Based on 2004 recommendations [132], a 5-day course of azithromycin is recommended as first-line treatment for cat scratch disease. Treatment for disseminated bartonellosis has not been studied, but observational data suggest that both macrolides and doxycycline should be effective agents; a treatment duration of 3–4 months is recommended [132]. Rifampin and gentamicin appear to be active agents and might be considered for adjunctive treatment of difficult or refractory cases [132]. Prevention of bartonellosis in transplant populations entails counseling individuals to avoid contact with cats, particularly younger cats, as they are associated with the highest risk for transmission [133].

23.3.3 *Bordetella bronchiseptica*

Bordetella bronchiseptica is a small, pleomorphic, aerobic, gram-negative coccobacillus. It is a cause of infection in household and farm animals and is known among pet owners as the etiologic agent of "kennel cough." Most human infections with *B. bronchiseptica* occur in immunocompromised hosts. There are numerous reports of *B. bronchiseptica* infection after SOT and HCT [134–140]. Most patients present with fever and cough. Findings on chest imaging are variable and include infiltrates, nodular densities, or cavities [136]. Some patients develop respiratory failure or bacteremia. The organism can be cultured from respiratory secretions or blood using standard laboratory techniques.

Infected patients frequently report contact with animals and sometimes there is a documented or suspected infection in a household pet [135, 137, 138]. In one instance, a kidney–pancreas transplant recipient with pneumonia appeared to have acquired the organism from a pet dog that had been immunized with live-attenuated, intranasal *B. bronchiseptica* vaccine [134]. In another report, two allogeneic HCT recipients at the same center developed severe *B. bronchiseptica* infection within 3 days of each other [139]. Pulsed-field gel electrophoresis analysis indicated that the two patients' isolates were identical. Neither patient reported contact with animals after transplantation, but both were being treated in the same transplant ward and clinic, suggesting the possibility that *B. bronchiseptica* was transmitted in the health care setting.

There are no definitive guidelines on treatment of *B. bronchiseptica* infection. The organism is often susceptible to erythromycin and azithromycin, antipseudomonal penicillins, third-generation cephalosporins, TMP-SMX, aminoglycosides, tetracyclines, and fluoroquinolones [135, 136, 139]; it is usually resistant to penicillin, ampicillin, and clindamycin [135–137]. Treatment is complicated by the fact that antibiotic susceptibilities do not always predict the clinical response. Patients may suffer microbiological or clinical relapses, possibly due to the capacity of *B. bronchiseptica* to invade and persist in respiratory epithelium and alveolar macrophages. Emergence of resistance after antibiotic treatment has also been documented [134, 137, 140]. Infection with *B. bronchiseptica* might be prevented by advising transplant recipients to avoid close contact with animals that are sick or have recently received live *B. bronchiseptica* vaccine.

23.3.4 *Helicobacter pylori*

H. pylori is a curved, gram-negative bacillus that infects 25–50% of adults in developed countries and causes chronic gastritis [141]. Infection with *H. pylori* has been definitively linked to the occurrence of peptic ulcer disease, and it is a major risk factor for the development of gastric cancer. Infected persons develop antibodies to *H. pylori*, and seropositivity is a reliable indicator of chronic infection in the stomach.

Several studies have investigated *H. pylori* infection in transplant recipients. An investigation found that 29% of 202 kidney transplant recipients were seropositive for *H. pylori* antibodies, a rate similar to patients on hemodialysis [142]. Seropositivity was associated with dyspeptic symptoms. In another study, 48% of 33 kidney recipients undergoing upper endoscopy between 2 and 4 months after transplantation had *H. pylori* identified by histology or urease testing [143]. The *Helicobacter*-infected patients were more likely to have gastritis, peptic ulcers, or dyspeptic symptoms. Somewhat disparate results were seen in a longitudinal study of 100 heart transplant recipients, 35% of whom were seropositive before transplantation [144]. Only 1 of the 65 seronegative patients seroconverted over a follow-up of 3.5 years. Seropositive patients did not have more episodes of ulcer disease, gastritis, or gastrointestinal bleeding than seronegative patients, but 40% of *Helicobacter*-seropositive patients became seronegative in follow-up. This finding correlated with a more intensive use of antibiotics, which appeared to have inadvertently cured the patients of their *Helicobacter* infections. Similar reversions to seronegative status have been reported from liver transplant recipients in Germany [145] and kidney transplant recipients in Finland [146].

Information on *Helicobacter* infection in patients undergoing HCT is limited. A study of 276 HCT recipients undergoing endoscopy, either before or after transplantation, disclosed only one case of *H. pylori* infection [147]. Castagnola et al. diagnosed *H. pylori* infection using a stool antigen assay in 13 (3%) of 478 children with hematologic malignancy, including 3 children who had undergone HCT [148]. Patients presented with dyspepsia or gastrointestinal bleeding and all improved with treatment of the *Helicobacter* infection; however, there was no direct evidence that *Helicobacter* infection had caused the patients' symptoms.

Despite limitations, these studies suggest that SOT and HCT recipients are not more likely, and they may be less likely, to be chronically infected with *H. pylori* than the general population. The available data does not answer the question whether transplant recipients with *Helicobacter* infection are more or less likely than immunocompetent hosts to develop ulcer disease.

An intriguing manifestation of *H. pylori* infection in transplant recipients is the occurrence of mucosa-associated lymphoid tissue (MALT) B-cell lymphomas. MALT lymphomas in the stomach are associated with *H. pylori* infection. They have been reported to respond to and even be cured by treatment of *Helicobacter* infection, thus obviating the need for cancer chemotherapy. Four cases of gastric MALT lymphoma were described in 1850 liver transplant recipients, a rate of 0.2%, which is 10–100 times more common than in the general population [149]. MALT lymphomas have also been described in heart and kidney recipients [150]. The mortality of MALT lymphomas appears low compared to other transplant tumors, as only two deaths from malignancy were seen among 16 cases in a transplant tumor registry [150].

The most commonly used regimen for *H. pylori* infection is 3-drug therapy, consisting of a proton pump inhibitor, clarithromycin, and amoxicillin [141]. Metronidazole is substituted for amoxicillin in penicillin-allergic patients. In areas where clarithromycin resistance is high, a 4-drug regimen is preferred. The most common 4-drug regimen employs a proton pump inhibitor, bismuth subsalicylate, metronidazole, and a tetracycline compound. Confirmation of cure is recommended when patients have persistent symptoms, underlying ulcer disease or a *Helicobacter*-associated cancer. Testing can be done with a urea breath test, a stool antigen assay, or repeat endoscopy and should be delayed until at least 4 weeks after the end of therapy [141].

23.4 Mycoplasma

23.4.1 *Mycoplasma* and *Ureaplasma*

The mycoplasmas and ureaplasmas differ from most bacteria in their small size (150–250 nm) and lack of a cell wall. The principal species causing transplant infections are *Mycoplasma pneumoniae*, which is a respiratory pathogen, and *M. hominis* and *Ureaplasma urealyticum*, which have a role in minor genitourinary infections, but occasionally cause severe extragenital disease [151, 152]. Because these organisms cannot be detected on Gram stain and their culture requires specialized techniques, only a minority of clinical infections receive an etiologic diagnosis.

M. pneumoniae is a common cause of bronchitis and pneumonia [151], but it is also is associated with a number of interesting extrapulmonary conditions, including cold agglutinin-positive hemolysis and Stevens–Johnson syndrome. Occasional patients with *M. pneumoniae* infection develop secondary carditis or CNS diseases such as aseptic meningitis or encephalitis [153, 154]. An unusual case of disseminated *M. pneumoniae* infection was diagnosed in a kidney recipient by PCR testing from multiple infected sites, including an axillo-femoral bypass graft, the knee joint, and a psoas abscess [155]. *M. pneumoniae* with Stevens–Johnson syndrome has been described in HCT and liver transplant recipients [156, 157]. Chronic *M. pneumoniae* pulmonary infection was reported in a pediatric kidney transplant recipient with hypogammaglobulinemia, The patient had fever and respiratory symptoms for 6 months and the diagnosis was finally established by PCR testing of BAL fluid [158].

M. hominis and *Ureaplasma species* have been isolated from the genitourinary flora of many sexually experienced men and women. They are often commensals, but seem to play a role in some common infections, such as nongonococcal urethritis (*U. urealyticum*) and bacterial vaginosis (*M. hominis*) [152]. *M. hominis* infections outside the genitourinary tract are well described, particularly in patients who are postpartum or have compromised immune systems [159]. Two-thirds of 17 patients in a case series of invasive extragenital *M. hominis* infections were immunosuppressed [159]. *M. hominis* infection has been reported in all types of SOT recipients [159–163]. Mixed infection with *M. hominis* and *U. urealyticum* has been reported in kidney, liver, and lung recipients [164–166].

Superficial or deep *M. hominis* sternal wound infections in heart and heart–lung recipients usually occur within a few weeks of transplantation. These patients have fever with sternal inflammation and drainage but Gram stains and cultures of the drainage are negative [167, 168]. Some reports of early posttransplant *M. hominis* pneumonia in lung recipients are suspicious for donor transmission, including a case of *M. hominis* and *U. urealyticum* coinfection [160, 166]. Cases of *M. hominis* deep wound infection reported following kidney transplantation seem likely to be due to spread of *Mycoplasma* colonizing either the donor or recipient urinary tract [169]. Other well-documented types of *M. hominis* infection are septic arthritis, peritonitis, meningitis and bacteremia [159]. *M. hominis* infection is rare after HCT. In the only reported case, *M. hominis* was cultured from BAL fluid, pharyngeal secretions and urine of a patient with diffuse alveolar hemorrhage [170]. It was unclear if the organism had any causal role in the clinical illness.

Diagnosis of *Mycoplasma* infection requires a high index of suspicion, as routine stains of purulent material are negative. Translucent colonies may be seen after 4–5 days of culture on blood agar plates but are often mistaken for water droplets. The organism grows best on *Mycoplasma*-specific media, producing colonies with a "fried egg" appearance. Because of these diagnostic challenges, clinicians should alert the microbiologist if *Mycoplasma* infection is suspected. Increasingly, diagnosis is made by PCR [155, 162].

Macrolides, tetracyclines and fluoroquinolones are active against *M. pneumoniae*, but resistance to macrolides has recently emerged in Asia and will undoubtedly spread to other countries [151, 171]. Most *M. hominis* isolates are sensitive to clindamycin, rifampin, fluoroquinolones, and tetracycline [159]. The organism is resistant to other macrolides, aminoglycosides, sulfonamides, and cell wall-active agents

including beta-lactam antibiotics. The treatment duration should be at least 2 weeks or longer when severe, deep-seated infection is present. There is a paucity of laboratory data to guide treatment of *Ureaplasma* infection, but resistance to macrolides and tetracycline appears to be increasing. Fluoroquinolones, particularly moxifloxacin, should be considered for management of complicated or refractory cases [172, 173].

23.5 Spirochetes

23.5.1 *Treponema pallidum*

T. pallidum, the causative organism of syphilis, is a non-cultivatable spirochete. The primary modes of acquisition are sexual contact, transplacental passage to the fetus or, rarely, accidental direct inoculation. Infection can also be transmitted by blood transfusion, but the risk is low because blood donors are screened and the organism cannot survive for longer than 24–48 h in stored blood units [174].

The potential for transmission of syphilis by donated organs is a concern and organ donors are routinely screened for syphilis. Transplantation of organs from donors with positive syphilis serology has been reported in kidney, liver, and lung transplantation [175, 176]. In these cases, the donors had no symptoms of active syphilis and were thought to have latent or convalesced infection. Transient seroconversion of both treponemal and non-treponemal serology occurred in some recipients, but without evidence of acute clinical disease or sequelae [175–177]. All recipients received penicillin therapy posttransplantation. Serological conversion may have represented an immune response to asymptomatic infection; however, it was also proposed that serological conversion in the recipients may have derived from antibodies elaborated by donor-derived B cells. This was likely the case in one Japanese patient who seroconverted their syphilis serology after allogeneic HCT [178]. The sibling donor had positive syphilis serology but had been appropriately treated with penicillin before harvest of stem cells. The available data are limited but suggest that screening of SOT and HCT donors should continue. Administering high-dose penicillin to recipients posttransplantation or to living donors pretransplantation should be adequate to prevent significant disease.

There are reports of active secondary syphilis in SOT recipients [179–181]. The clinical findings were typical and included fever, diffuse skin rash (see Figure 23-5), hepatitis and various neurological symptoms such as headache, dysesthesias and visual changes. Neurosyphilis was documented in over one-half of the patients. All patients responded well to antibiotic treatment.

The diagnosis of syphilis is based on serologic testing for non-treponemal antibodies (VDRL test or rapid plasma reagin) accompanied by a specific treponemal antibody test such as *T. pallidum* particle agglutination [TP-PA]. The diagnosis can also be suggested when typical pathological changes are found on tissue biopsy of affected organs [179, 181]. The treatment of choice is parenteral penicillin. Doxycycline or erythromycin are second-line agents for patients with penicillin allergy.

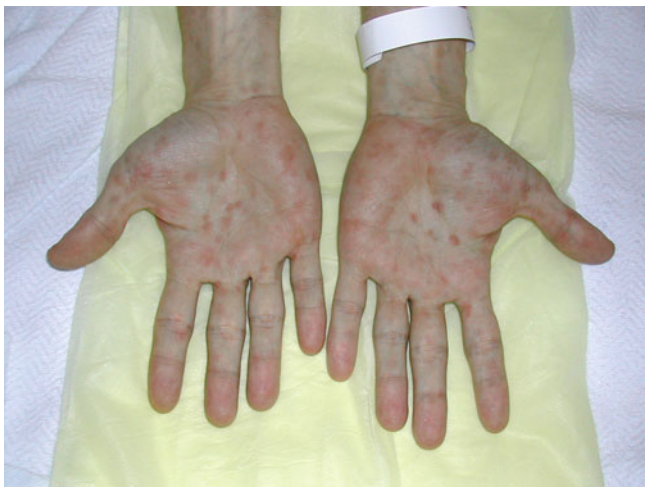

FIGURE 23-5. Classic skin findings of secondary syphilis. (Photo provided courtesy of Kent Sepkowitz, M.D., Division of Infectious Diseases, Memorial Sloan Kettering Cancer Center, New York, NY).

23.5.2 Borrelia

Lyme disease is an infection transmitted by *Ixodes* ticks and caused by various *Borrelia* species (*B. burgdorferi* and *B. pacificus* in the USA, and primarily *B. afzelii* and *B. garinii* in Europe and Asia). The animal reservoirs in the USA are small rodents, but large animals, such as deer and cattle, support the life cycle of the *Ixodes* ticks. Lyme disease has been reported in SOT recipients [182–184] and in a HCT recipient [185], with manifestations ranging from localized erythema migrans to disseminated disease with carditis or neurologic involvement. Given the paucity of data on Lyme disease in transplant recipients, it is not clear if the severity of disease is greater than in immunocompetent patients.

Because serologic diagnosis of infection has potential limitations in immunocompromised patients, a high index of suspicion is warranted in any transplant patient who has exposure in an endemic area and has signs or symptoms suggestive of Lyme disease [184, 185]. Treatment is universally indicated in patients with active Lyme disease. Oral doxycycline is commonly prescribed for most patients with erythema migrans, those with isolated facial nerve palsy or with arthritis without neurologic involvement. Parenteral therapy (e.g., ceftriaxone) is usually reserved for patients who have disseminated disease with neurologic or cardiac involvement [186].

23.6 Rickettsiosis

23.6.1 *Coxiella burnetii*

C. burnetii, the etiologic agent of Q fever, is a pleomorphic gram-negative coccobacillus. Infection usually arises from exposure to infected livestock or unpasteurized milk. The most common clinical manifestation is an acute febrile illness associated with pneumonia or hepatitis. Many patients who are untreated recover, but a small proportion may develop a chronic febrile illness, often accompanied by endocarditis.

C. burnetii infection has been reported in patients with a variety of immunocompromising conditions, [187], and there are a few reports of acute or chronic Q fever after SOT and HCT that have demonstrated response to doxycycline-containing regimens [188–191]. Although the literature on Q fever in the transplant population is sparse, treating a patient who has a positive serologic response seems prudent to prevent chronic infection, even when symptoms are mild or resolving.

23.6.2 Other Rickettsial Organisms

Rickettsia, *Ehrlichia*, and *Anaplasma* species are members of the order *Rickettsiales*. They are fastidious, obligate intracellular bacteria with gram-negative cell walls, but are poorly visualized by Gram stain. A number of these organisms are important human pathogens that are transmitted by arthropod vectors.

A single case report describes a heart transplant recipient with Rocky Mountain spotted fever, a tick-borne illness caused by *Rickettsia rickettsi* [192]. The patient had a mild febrile illness with rash and responded to 3 weeks of treatment with doxycycline. The diagnosis was initially made by immunofluorescence staining of a skin biopsy and later confirmed by seroconversion. There are two case reports of SOT recipients with Mediterranean spotted fever, a tick-borne illness caused by *Rickettsia conorii.* One kidney recipient presented with rash and spontaneous splenic rupture after recent travel to southern France; the patient improved on empiric doxycycline and the diagnosis was ultimately made by PCR amplification of spleen and skin tissue [193]. The second patient was a liver recipient in Spain who developed high fever, myalgias and rash; the diagnosis of *R. conorii* infection was made serologically and the patient responded promptly to doxycycline treatment [194]. Murine typhus is caused by *Rickettsia typhi* and transmitted by fleas. A single case of murine typhus was reported in a liver transplant recipient from Thailand who had fever, hepatitis, and interstitial pneumonia; the diagnosis was made by serology and treatment with doxycycline resulted in clinical cure [195]. Murine typhus may be encountered around the world and some recent cases have been described in Texas and Southern California [196].

Human ehrlichiosis and anaplasmosis have similar clinical manifestations but differ in their geographic distributions, the tick vector and the specific blood cells—either monocytes or granulocytes—that support infection. Human monocytic ehrlichiosis is caused by *Ehrlichia chaffeensis* and transmitted by the lone star tick (*Amblyomma americanum*). It was first reported in a liver transplant recipient from Kentucky in 1995 [197]. This patient developed fever, pancytopenia, elevated transaminases, and shortness of breath 2 weeks after a tick bite. He made a full recovery on empiric doxycycline therapy, with the diagnosis subsequently established by serology. Human granulocytic anaplasmosis is caused by *Anaplasma phagocytophilum* and transmitted by *Ixodes scapularis*. It was first reported in a kidney transplant recipient from Minnesota who developed fever, myalgia, diarrhea, and pancytopenia a week after tick exposure [198]. *Ehrlichia ewingii* is the agent of canine granulocytic ehrlichiosis, It was first reported to cause human infection in 1999 [199]. Infection with *E. ewingii* generally produces a milder illness than *E. chaffeensis*. Most reported cases have been in immunocompromised hosts, including transplant recipients [199, 200].

Cellular immunity is an important host defense against rickettsial infection and poor outcomes have been reported in HIV-seropositive individuals [201, 202]. It is not clear if transplant recipients have more severe disease or worse outcomes. Thomas et al. compared clinical characteristics of ehrlichiosis (both *E. chaffeensis* and *E. ewingii*) in 15 SOT patients and 43 immunocompetent patients [200]. Transplant recipients had less rash and less hepatic enzyme elevation but more leukopenia and renal dysfunction than the immunocompetent patients. All transplant patients responded rapidly to doxycycline therapy and their mean hospital stay was only 4 days. In a review of 23 immunocompromised patients with *Ehrlichia* infection, severe disease occurred in some of the 7 SOT recipients, but they all survived; the six deaths reported in the series occurred in patients with HIV or splenectomy [202].

A case of probable donor-derived *Ehrlichia* infection has been reported in two kidney recipients of a common donor [203]. Both recipients developed high grade fever in the early posttransplant period. The diagnosis was made by detection of *E. chaffeensis* DNA by PCR from serum in one recipient and by serology in the other; unfortunately, no serum or tissue was available from the donor for confirmatory testing.

Monocytic ehrlichiosis and anaplasmosis can sometimes be diagnosed by finding "morulae," or characteristic intracytoplasmic inclusions, in a buffy coat smear. Morulae are found in monocytes in monocytic ehrlichiosis but are uncommon (<10%); they are found in granulocytes in anaplasmosis and are relatively frequent (20–80%). Serology for *E. chaffeensis* and *A. phagocytophilum* is useful for retrospective diagnosis and epidemiologic studies, but not rapid enough for clinical purposes. Specific serology is not available for *E. ewingii*, although patients with *E. ewingii* infection

often develop cross-reactive antibodies to *E. chaffeensis* [199]. Culture is not commercially available. PCR testing is now the preferred way to make a rapid, species-specific diagnosis [199, 200, 204]. Empirical treatment should be initiated in patients with suspected ehrlichiosis or anaplasmosis, pending results of diagnostic testing. The agent of choice is doxycycline. In regions endemic for anaplasmosis doxycycline will treat for the possibility of coinfection with *B. burgdorferi*, which is also transmitted by *Ixodes* ticks.

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