53 - 170 Infections Due to Pseudomonas, Burkholderia, and Stenotrophomonas Species

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Infections Due to

Pseudomonas, Burkholderia,

and Stenotrophomonas Species The pseudomonads are a heterogeneous group of gram-negative bacteria that have in common an inability to ferment lactose. Formerly classified in the genus Pseudomonas, the members of this group have been assigned to three medically important genera—Pseudomonas, Burkhold eria, and Stenotrophomonas—whose biologic behaviors encompass both similarities and marked differences and whose genetic repertoires differ in many respects. The pathogenicity of most pseudomonads is based on opportunism; the exceptions are Burkholderia pseudomallei and Burkholderia mallei, which are primary pathogens. The genus Pseudomonas now contains >140 species. Pseudomonas aeruginosa, the major pathogen of the group, is a significant cause of infections in hospitalized patients and in patients with cystic fibrosis (CF; Chap. 302). Cytotoxic chemotherapy, mechanical ventilation, chronic lung diseases, and broad-spectrum antibiotic therapy set up conditions that predispose to colonization and infection of increasing numbers of hospitalized patients by this pathogen. Other significant members of the genus—Pseudomonas putida, Pseudomonas fluorescens, Pseudomonas oryzihabitans, and Pseudomonas stutzeri—infect humans infrequently and are generally opportunists that are always present in the environment. The genus Burkholderia comprises >20 species, of which Burk holderia

cepacia is most frequently encountered in Western countries. Similar to P. aeruginosa, B. cepacia (now referred to as the B. cepacia complex species) is both an opportunistic nosocomial pathogen and a cause of infection in CF. The other medically important members of this genus are B. pseudomallei and B. mallei, the etiologic agents of melioidosis and glanders, respectively. The genus Stenotrophomonas contains one species of medical sig nificance, Stenotrophomonas maltophilia. This organism is strictly an opportunist that “overgrows” in the setting of broad-spectrum antibi otic use. PSEUDOMONAS AERUGINOSA ■ ■EPIDEMIOLOGY P. aeruginosa is found in most moist environments. Soil, plants, veg etables, tap water, and countertops are all potential reservoirs for this microbe, as it has simple nutritional needs. Given the ubiquity of P. aeruginosa, it is clear that simple contact with the organism is not sufficient for colonization or infection. Clinical and experimental observations suggest that infection by P. aeruginosa occurs concomi tantly with compromised host defenses, mucosal trauma, physiologic derangement, and antibiotic-mediated suppression of normal flora. Thus, it comes as no surprise that the majority of P. aeruginosa infec tions occur in intensive care units (ICUs), where these factors fre quently converge. Although the organism is initially acquired from environmental sources, patient-to-patient spread occurs in CF clinics and may occur in closed hospital units. In the past, patients with burns appeared to be unusually suscep tible to P. aeruginosa. For example, in 1959–1963, Pseudomonas burnwound sepsis was the principal cause of death in 60% of patients with burns dying at the U.S. Army Institute of Surgical Research. For reasons that are unclear, P. aeruginosa infection in burns is no longer the major problem that it was during the 1950s and 1960s. Similarly, in the 1960s, P. aeruginosa appeared as a common pathogen in patients receiving cytotoxic chemotherapy at many institutions in the United States, but it has subsequently diminished in importance. Despite this subsidence,

P. aeruginosa remains one of the most feared pathogens in this population because of its high attributable mortality.

In some parts of Asia and Latin America, P. aeruginosa continues to be the most common cause of gram-negative bacteremia in neutrope nic patients.

In contrast to the trends for patients with burns or neutropenia in the United States, the incidence of P. aeruginosa infections among patients with CF has not changed. P. aeruginosa remains the most com mon contributing factor to respiratory failure in CF and is responsible for the majority of deaths among CF patients. ■ ■LABORATORY FEATURES P. aeruginosa is a nonfastidious, motile, gram-negative rod that grows on most common laboratory media, including blood and MacConkey agars. It is easily identified in the laboratory on primary-isolation agar plates by pigment production that confers a yellow to dark green or even bluish appearance. Colonies have a shiny “gun-metal” appearance and a characteristic fruity odor. Two of the identifying biochemical characteristics of P. aeruginosa are an inability to ferment lactose on MacConkey agar and a positive reaction in the oxidase test. Most strains are identified on the basis of these readily detectable labora tory features even before extensive biochemical testing is done. Some isolates from CF patients are easily identified by their mucoid appear ance, which is due to the production of large amounts of the mucoid exopolysaccharide or alginate. Recently, there has been increasing use of molecular testing with multiplex polymerase chain reaction (PCR) platforms, which rapidly identify P. aeruginosa in respiratory and blood samples much earlier than the classical methods. ■ ■PATHOGENESIS Unraveling the mechanisms that underlie disease caused by P. aeruginosa has

proved challenging. Of the common gram-negative bacteria, no other species produces such a large number of putative virulence fac tors (Table 170-1). Yet P. aeruginosa rarely initiates an infectious pro cess in the absence of host injury or compromise, and few of its putative virulence factors have been shown definitively to be involved in disease in humans. Despite its metabolic versatility and possession of multiple colonizing factors, P. aeruginosa exhibits no competitive advantage over enteric bacteria in the human gut; it is not a normal inhabitant of the healthy human gastrointestinal tract, despite the host's continuous environmental exposure to the organism. CHAPTER 170 Infections Due to Pseudomonas, Burkholderia, and Stenotrophomonas Species Virulence Attributes Involved in Acute P. aeruginosa Infec tions • MOTILITY AND COLONIZATION A general tenet of bac terial pathogenesis is that most bacteria must adhere to surfaces or colonize a host niche in order to initiate disease. Most gram-negative bacteria examined thus far possess adherence factors called adhesins. P. aeruginosa is no exception. Among its many adhesins are its pili, which demonstrate adhesive properties for a variety of cells and adhere best to injured cell surfaces. In the organism's flagellum, the flagel lin molecule binds to cells, and the flagellar cap attaches to mucins through the recognition of glycan chains. Other P. aeruginosa adhesins TABLE 170-1 Main Putative Virulence Factors of Pseudomonas aeruginosa SUBSTANCE/ ORGANELLE FUNCTION VIRULENCE IN ANIMAL DISEASE Pili Adhesion to cells ? Flagella Adhesion, motility, inflammation Yes Lipopolysaccharide Antiphagocytic activity, inflammation Yes Type III secretion system Toxic activity (ExoU, ExoS) Yes Type II secretion system Toxic activity Yes Proteases Proteolytic activity ? Phospholipases Cytotoxicity ? Exotoxin A Cytotoxicity ? Pyocyanin Cytotoxicity Yes

include the outer core of the lipopolysaccharide (LPS) molecule, which binds to the cystic fibrosis transmembrane conductance regulator (CFTR) and aids in internalization of the organism, and the alginate coat of mucoid strains, which enhances adhesion to cells and mucins. In addition, membrane proteins and lectins have been proposed as colonization factors. The deletion of any given adhesin by itself is not sufficient to abrogate the ability of P. aeruginosa to colonize surfaces probably because of the redundancy of adhesins. Motility is important in host invasion via mucosal surfaces or burned skin in animal models of infection; however, nonmotile strains are not uniformly avirulent. It has been well demonstrated that nonmotile strains of P. aeruginosa are poorly phagocytosed in vitro, possibly leading to enhancement of the virulence of this organism in vivo.

EVASION OF HOST DEFENSES The transition from bacterial coloniza tion to disease requires the evasion of host defenses followed by inva sion by the microorganism. P. aeruginosa appears to be well equipped for evasion. Attached bacteria inject four known toxins (ExoS or ExoU, ExoT, and ExoY) via a type III secretion system that allows the bacteria to evade phagocytic cells either by direct cytotoxicity or by inhibi tion of phagocytosis. Clinical studies suggest that the mortality rate is higher among patients infected by strains that secrete the ExoU toxin. Another secretion system—the type II system—secretes toxins that can kill animals, and some of its secreted toxins, such as exotoxin A, have the potential to kill phagocytic cells. Multiple proteases secreted by this system may degrade host effector molecules, such as cytokines and chemokines, that are released in response to infection and appear to play a role in corneal infections in mice. TISSUE INJURY Among gram-negative bacteria, P. aeruginosa prob ably produces the largest number of substances that are toxic to cells and thus have the potential to injure tissues. The toxins secreted by the organism's type III secretion system are capable of injuring tissue. However, their delivery requires the adherence of the organism to cells. Thus, the effects of these toxins are likely to be

local or to depend on the presence of large numbers of bacteria at the site of an infection or in the bloodstream. On the other hand, diffusible toxins, secreted by the organism’s type II secretion system, can act freely wherever they come into contact with cells. Possible effectors of this system include exotoxin A, at least four different proteases, and at least two phospholipases. In addition to these secreted toxins, rhamnolipids, pyocyanins—the pigments that confer the characteristic color and odor of P. aeruginosa colonies—and hydrocyanic acid, are produced by P. aeruginosa and are all capable of causing host tissue injury and even neutrophil death. PART 5 Infectious Diseases INFLAMMATORY COMPONENTS The inflammatory responses to the lipid A component of Pseudomonas LPS and to its flagellin, mediated through the Toll-like receptor (TLR) system (principally TLR4 and TLR5, respectively), are thought to represent important factors in dis ease causation. Although these inflammatory responses are required for successful defense against P. aeruginosa (i.e., in their absence, ani mals are defenseless against P. aeruginosa infection), florid responses are likely to result in severe disease. Thus, when the sepsis syndrome and septic shock develop in P. aeruginosa infection, they are probably the result of the host response to one or both of these substances, but injury to the lung by Pseudomonas toxins may also result in sepsis syndromes, possibly by causing cell death and the release of cellular components (e.g., heat-shock proteins) that may activate the TLR or another proinflammatory system. Thus, the virulence of this bacterium in acute infections is likely to be multifactorial with a great redundancy of effector molecules being produced. Chronic P. aeruginosa Infections Chronic infection due to P. aeruginosa occurs mainly in the lungs in the setting of structural pulmonary diseases. The classic example is CF; others include bron chiectasis and chronic relapsing panbronchiolitis, a disease seen in Japan and some Pacific Islands. A hallmark of these illnesses is severely defective mucociliary clearance leading to mucus stasis and mucus accumulation in the lungs. There is probably a common factor that selects for P. aeruginosa colonization in these lung diseases—perhaps

the adhesiveness of P. aeruginosa for mucus, a phenomenon that is not noted for most other common gram-negative bacteria, and/or the ability of P. aeruginosa to evade host defenses in mucus. Furthermore,

P. aeruginosa undergoes evolutionary adaptations and diversification in ways that allow its prolonged survival in the lung without an early fatal outcome for the host. The strains found in CF patients exhibit minimal production of virulence factors. Many strains lose the ability to pro duce pili and flagella, and most become complement-sensitive because of the loss of the O side chain of their LPS molecules. In addition, most strains found in CF patients overproduce a mucoid exopolysaccharide. These changes probably dampen the host response, allowing the organ ism to survive in CF mucus. P. aeruginosa is also believed to lose its ability to secrete many of its injectable toxins during growth in mucus. Although the alginate coat is thought to play a role in the organism’s survival, alginate is not essential as nonmucoid strains may predomi nate for long periods. In short, virulence in chronic infections may be mediated by the chronic but attenuated host inflammatory response, which injures the lungs over decades. ■ ■CLINICAL MANIFESTATIONS P. aeruginosa causes infections at almost all sites in the body but shows a rather marked predilection for the lungs. The infections encountered most commonly in hospitalized patients are described below. Bacteremia Crude mortality rates exceeding 50% have been reported among patients with P. aeruginosa bacteremia. Consequently, this clinical entity has been much feared, and its management has been attempted with the use of multiple antibiotics. Recent publica tions report attributable mortality rates of 28–44%, with the precise figure depending on the adequacy

and timing of treatment and the seriousness of the underlying disease. In the past, the patient with P. aeruginosa bacteremia classically was neutropenic or had a burn injury. Today, however, a minority of such patients have bacteremic P. aeruginosa infections. Rather, P. aeruginosa bacteremia is seen most often in patients in ICUs, with the lungs, the urinary tract, central venous lines, or wounds being the most important portals for systemic invasion. The clinical presentation of P. aeruginosa bacteremia rarely differs from that of sepsis in general (Chap. 315). Patients are usually febrile, but those who are most severely ill may be in shock or even hypother mic. The only point differentiating this entity from gram-negative sep sis due to other bacteria may be the distinctive skin lesions (ecthyma gangrenosum) of Pseudomonas infection, which occur almost exclu sively in markedly neutropenic patients and patients with AIDS. These small or large, painful, reddish, maculopapular lesions have a geographic margin; they are initially pink, then darken to purple, and finally become black and necrotic (Fig. 170-1). Histopathologic studies indicate that the lesions are due to vascular invasion and are teeming with bacteria. Although similar lesions may occur in aspergillosis, mucormycosis, and occasionally Staphylococcus aureus bacteremia, their presence in a neutropenic patient generally suggests P. aeruginosa bacteremia as the most likely cause. TREATMENT P. aeruginosa Bacteremia (Table 170-2) Antimicrobial treatment of P. aeruginosa bacte remia has been controversial. Combination therapy with an FIGURE 170-1 Ecthyma gangrenosum in a neutropenic patient 3 days after onset.

TABLE 170-2 Antibiotic Treatment of Infections Due to Pseudomonas aeruginosa and Related Species INFECTION ANTIBIOTICS AND DOSAGES OTHER CONSIDERATIONS Bacteremia Nonneutropenic host Ceftazidime (2 g q8h IV) or cefepime (2 g q8h IV) or piperacillin/tazobactam (4.5 g q6h IV) or imipenem (500 mg q6h IV) or meropenem (1–2 g q8h IV) or doripenem (500 mg q8h IV) Optional: Amikacin (7.5 mg/kg q12h or 15 mg/kg q24h IV) Neutropenic host Cefepime (2 g q8h IV) or any of the other agents above (except doripenem) in the above dosages Endocarditis Antibiotic regimens as for bacteremia for 6–8 weeks Resistance during therapy is common. Surgery is required for relapse. Pneumonia Drugs and dosages as for bacteremia, except that the available carbapenems should not be the sole primary drugs because of high rates of resistance during therapy. Bone infection, malignant otitis externa Cefepime or ceftazidime at the same dosages as for bacteremia; aminoglycosides not a necessary component of therapy; ciprofloxacin (500–750 mg q12h PO) may be used Central nervous system infection Ceftazidime or cefepime (2 g q8h IV) or meropenem

(2 g q8h IV) Eye infection Keratitis/ulcer Topical therapy with tobramycin/ciprofloxacin/levofloxacin eyedrops Endophthalmitis Ceftazidime or cefepime as for central nervous system infection plus Topical therapy Urinary tract infection (UTI) Ciprofloxacin (500 mg q12h PO) or levofloxacin (750 mg q24h) or any aminoglycoside (total daily dose given once daily). Cefepime or ceftazidime (1g q8h) or piperacillin/tazobactam (3.375 g q6h) Multidrug- and extreme drugresistant P. aeruginosa infection Ceftazidime/avibactam (2.5 g q8h, infused over 2 h) or ceftolozane/tazobactam (1.5–3 g q8h) or imipenem/ relebactam (500 mg q6h) or cefiderocol (2 g q8h) or colistin (100 mg q12h IV for the shortest possible period to obtain a clinical response) Burkholderia cepacia complex infection Meropenem (2 g q8h IV) or TMP-SMX (1600/320 mg q12h IV) for 14 days Melioidosis (B. pseudomallei), glanders (B. mallei) Ceftazidime (2 g q6h) or meropenem (1 g q8h) or imipenem (500 mg q6h) for 2 weeks followed by TMP-SMX (1600/320 mg q12h PO) for 3 months Stenotrophomonas maltophilia infection TMP-SMX (1600/320 mg q12h IV) plus either levofloxacin (750 mg q24h) or minocycline (100-200 mg q12h) or ticarcillin/clavulanate (3.1 g q4h IV) for 7 to

14 days Abbreviations: MIC, minimum inhibitory concentration; TMP-SMX, trimethoprim-sulfamethoxazole. antipseudomonal β-lactam and an aminoglycoside became the standard of care because of the dismal outcome of single-drug ther apy, mainly with aminoglycosides and polymixins, prior to 1971— first for P. aeruginosa bacteremia in febrile neutropenic patients and then extrapolated to all P. aeruginosa bacteremic infections in both neutropenic and nonneutropenic patients. Following the introduction of new antipseudomonal drugs, a number of studies have revisited the choice between combina tion treatment and monotherapy for Pseudomonas bacteremia. Although some clinicians still favor combination therapy, most recent observational studies indicate that a single modern antip seudomonal β-lactam agent to which the isolate is sensitive is as efficacious as a combination. Even in patients at greatest risk of early death from P. aeruginosa bacteremia (i.e., those with fever and neutropenia), empirical antipseudomonal monotherapy is deemed to be as efficacious as empirical combination therapy by the practice guidelines of the Infectious Diseases Society of America (IDSA).

Add an aminoglycoside empirically for patients in shock and in regions or hospitals where rates of resistance to the primary β-lactam agents are high. Tobramycin may be used instead of amikacin (susceptibility permitting). A duration of 6–10 days of therapy can be used for uncomplicated bacteremia. Febrile neutropenic patients should be treated until no longer neutropenic. Add aminoglycoside or ciprofloxacin, as for bacteremia, until sensitivities available. The duration of therapy is 7 days. Duration of therapy varies with the drug used and type of infection (e.g., 6 weeks for a β-lactam agent; except in puncture-wound osteomyelitis, for which the duration should be 2–4 weeks; oral therapy can be used). Abscesses or other closed-space infections may require drainage. The duration of therapy is ≥2 weeks. Use maximal strengths available or compounded by pharmacy. Therapy should be administered for 2 weeks or until the resolution of eye lesions, whichever is shorter. CHAPTER 170 Uncomplicated cystitis may be treated for 3 days with oral agents. Relapse may occur if an obstruction or a foreign body is present. The duration of therapy for complicated cystitis and uncomplicated pyelonephritis is 5–7 days. Infections Due to Pseudomonas, Burkholderia, and Stenotrophomonas Species Use 3-g dose of ceftolozane/tazobactam for pneumonia. Meropenem-vaborbactam offers minimal benefit in carbapenem resistant strains. Alternatives to colistin are preferred, if available. Colistin dosing requires renal adjustment and expertise in its use. Inhaled colistin may be added for pneumonia (100 mg q12h). Resistance to both agents is increasing. Do not use them in combination because of possible antagonism. Broad-spectrum antibiotic therapy leads to respiratory tract colonization and often warrants no treatment. Ceftazidimeavibactam plus aztreonam, cefiderocol, or tigecycline are alternatives for XDR strains. Combination therapy should be used for bacteremia, especially in immunosuppressed patients. One firm conclusion is that monotherapy with an aminoglycoside is not optimal. There are, of course, institutions and countries where rates of susceptibility of P. aeruginosa to first-line antibiotics are <80%. Thus, when a septic patient with a high probability of P. aeruginosa infection is encountered in such settings, empirical combination therapy should be administered until the pathogen is identified and susceptibility data become available. Thereafter, whether one or two agents should be continued remains a matter of individual preference. Recent studies suggest that extended or continuous infusions of β-lactams such as cefepime, piperacillin-tazobactam, or meropenem may result in better outcomes of Pseudomonas bac teremia and possibly of Pseudomonas pneumonia. The duration of antibiotic therapy has now become an important consideration due to the increasing isolation of multiple drug-resistant (MDR) and extensively drug-resistant (XDR) P. aeruginosa strains. Recently published studies now strongly

support the use of shorter courses of

therapy (7 days) rather than the longer duration (10−14 days) that is commonly recommended for many cases of Pseudomonas bacte remia. As in S. aureus bacteremia, catheter removal is important.

Acute Pneumonia Respiratory infections are the most common of all infections caused by P. aeruginosa. P. aeruginosa is common in both hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). This organism appears first or second among the causes of VAP. However, much debate centers on the actual role of

P. aeruginosa in VAP. Many of the relevant data are based on cultures of sputum or endotracheal tube aspirates and may represent nonpatho genic colonization of the tracheobronchial tree, biofilms on the endo tracheal tube, or simple tracheobronchitis. The increasing use of PCR testing on endotracheal samples has further compounded this issue. PCR coupled with the widespread use of computed tomography with poor specificity for pneumonia, and overlap in appearance with fluid overload in patients with low to intermediate clinical suspicion, may contribute to the overdiagnosis of HAP and VAP. This scenario empha sizes the importance of clinical judgment in adjudicating P. aeruginosa colonization versus infection. Older reports of P. aeruginosa pneumonia described patients with an acute clinical syndrome of fever, chills, cough, and necrotizing pneu monia indistinguishable from other gram-negative bacterial pneumo nias. The traditional accounts described a fulminant infection. Chest radiographs demonstrated bilateral pneumonia, often with nodular densities with or without cavities. This picture is now remarkably rare. Today, the typical patient is on a ventilator, has a slowly progressive infiltrate, and has been colonized with P. aeruginosa for days. While some cases may progress rapidly over 48–72 h, they are the exceptions. Nodular densities are not commonly seen. However, infiltrates may go on to necrosis. Necrotizing pneumonia has also been seen in the community (e.g., after inhalation of hot-tub water contaminated with P. aeruginosa). The typical patient has fever, leukocytosis, tachypnea, hypoxemia, and purulent sputum, and the chest radiograph shows a new infiltrate or the expansion of a preexisting infiltrate. A sputum Gram’s stain showing mainly polymorphonuclear leukocytes (PMNs) in conjunction with a culture positive for P. aeruginosa in this setting suggests a diagnosis of acute P. aeruginosa pneumonia. PART 5 Infectious Diseases There have been increasing reports of the occurrence of communityacquired P. aeruginosa pneumonia among patients with underlying lung diseases. While this undoubtedly occurs, it is difficult to make this diagnosis with a great degree of certainty with the use of sputum cultures in a population prone to airway colonization by multiple strains of bacteria. The patient population in whom the possibility of a community-acquired P. aeruginosa pneumonia should be considered is the neutropenic patient, given the pivotal role that neutrophils play in defense against this bacterium. Such a patient, whether hospitalized or admitted from the community with a pneumonia, should be treated empirically for P. aeruginosa. TREATMENT Acute Pneumonia (Table 170-2) Therapy for P. aeruginosa pneumonia remains unsat isfactory. Reports suggest mortality rates of 40–80%, but how many of these deaths are attributable to underlying disease remains unknown. The drugs of choice for P. aeruginosa pneumonia are similar to those given for bacteremia. A potent antipseudomonal β-lactam drug is the mainstay of therapy. Failure rates were high when aminoglycosides were used as single agents, possibly because of their poor penetration into the airways and their binding to airway secretions. Nonetheless, for the treatment of patients at high risk of death, some experts suggest

the combination of a β-lactam agent and an antipseudomonal fluoroquinolone or aminoglycoside. As for the duration of therapy, recent IDSA/American Thoracic Society (ATS) guidelines recommend 7 days of treatment for HAP or VAP, even when P. aeruginosa is the offending organism. However, the outcome in neutropenic patients is poor, especially

if accompanied by bacteremia; thus, therapy needs to be extended until neutropenia resolves. In addition, therapy longer than 7 days should be used in patients with P. aeruginosa necrotizing pneumo nia as, functionally, this entity is similar to a lung abscess. Chronic Respiratory Tract Infections P. aeruginosa is respon sible for chronic infections of the airways associated with a number of underlying or predisposing conditions—most commonly CF (Chap. 302). A state of chronic colonization beginning early in child hood is seen in some Asian populations with chronic or diffuse pan bronchiolitis, a disease of unknown etiology. P. aeruginosa is one of the organisms that colonizes damaged bronchi in bronchiectasis, a disease secondary to multiple causes in which profound structural abnormali ties of the airways result in mucus stasis. TREATMENT Chronic Respiratory Tract Infections Optimal management of chronic P. aeruginosa lung infection has not been determined. Patients respond clinically to antipseudomonal therapy, but the organism is rarely eradicated. Because eradication is unlikely, the aim of treatment for chronic infection is to quell exac erbations of inflammation. The regimens used are similar to those used for pneumonia, but an aminoglycoside is almost always added because resistance is common in chronic disease. However, it may be more appropriate to use an inhaled aminoglycoside preparation in order to maximize airway drug levels. MDR strains are now com monly found in such patients given their increased life span and the repeated courses of antibiotics they receive. Endovascular Infections Infective endocarditis of native valves due to P. aeruginosa is most commonly seen in those who use IV drugs. This organism has also been reported to cause prosthetic-valve endocarditis. Sites of prior native-valve injury due to the injection of foreign material such as talc or fibers probably serve as niduses for bacterial attachment to the heart valve. The manifestations of P. aeru ginosa endocarditis resemble those of other forms of endocarditis in those who use IV drugs except that the disease is more indolent than

S. aureus endocarditis. While most disease involves the right side of the heart, left-sided involvement is not rare, and multivalvular disease is common. Fever is a common manifestation, as is pulmonary involve ment (due to septic emboli to the lungs). Thus, patients may also experience chest pain and hemoptysis. Involvement of the left side of the heart may lead to signs of cardiac failure, systemic emboli, and local cardiac involvement with sinus of Valsalva abscesses and conduction defects. Skin manifestations other than injection site infections are rare in this disease, and ecthyma gangrenosum is not common. Vertebral osteomyelitis and sternoclavicular joint septic arthritis are uncommon but pathognomic complications of this disease. The diagnosis is based on positive blood cultures along with clinical signs of endocarditis. TREATMENT Endovascular Infections (Table 170-2) It has been customary to use synergistic antibiotic combinations in treating P. aeruginosa endocarditis because of the development of resistance during therapy with a single antipseudo monal β-lactam agent. Which combination therapy is preferable is unclear, as all combinations have failed. Treatment is likely to more often be successful in cases of right-sided endocarditis. Cases of P. aeruginosa endocarditis that relapse during or fail to respond to therapy are often caused by resistant organisms and may require surgical therapy. Other considerations for valve replacement are similar to those in other forms of endocarditis (Chap. 133). Bone and Joint Infections P. aeruginosa is an infrequent cause of bone and joint infections. However, Pseudomonas

bacteremia or

infective endocarditis caused by the injection of contaminated illicit drugs has been documented to result in vertebral osteomyelitis and sternoclavicular joint arthritis. The clinical presentation of vertebral

P. aeruginosa osteomyelitis is more indolent than that of staphylococcal osteomyelitis. The duration of symptoms in IV drug users with verte bral osteomyelitis due to P. aeruginosa varies from weeks to months. Fever is not uniformly present; when present, it tends to be low grade. There may be mild tenderness at the site of involvement. Blood cul tures are usually negative unless there is concomitant endocarditis. The erythrocyte sedimentation rate (ESR) is generally elevated. Vertebral osteomyelitis due to P. aeruginosa has also been reported in the elderly, in whom it originates from urinary tract infections (UTIs). The infec tion generally involves the lumbosacral area because of a shared venous drainage (Batson's plexus) between the lumbosacral spine and the pel vis. Sternoclavicular septic arthritis due to P. aeruginosa is seen almost exclusively in persons who use IV drugs. This disease may occur with or without endocarditis, and a primary site of infection often is not found. Plain radiographs show joint or bone involvement. Treatment of these forms of disease is generally successful. Pseudomonas osteomyelitis of the foot most often follows punc ture wounds through sneakers and mostly affects children. The main manifestation is pain in the foot, sometimes with superficial cellulitis around the puncture wound and tenderness on deep palpation of the wound. Multiple joints or bones of the foot may be involved. Systemic symptoms are generally absent, and blood cultures are usually negative. Radiographs may or may not be abnormal, but the bone scan is usu ally positive, as are magnetic resonance imaging (MRI) studies. Needle aspiration usually yields a diagnosis. Prompt surgery, with exploration of the nail puncture tract and debridement of the involved bones and cartilage, is generally recommended in addition to antibiotic therapy. Osteomyelitis due to P. aeruginosa is also seen following trauma and with decubitus ulcers. In these settings, the cause of osteomyelitis is often polymicrobial, and the role of P. aeruginosa can be questioned. It is therefore critical that deep bone biopsies be requested to ascertain its significance prior to starting treatment that targets P. aeruginosa. TREATMENT Bone and Joint Infections The treatment of bone and joint infections due to P. aeruginosa is often governed by the primary Pseudomonas infection. Since endocarditis is often the primary infection, the agents used for endocarditis will dic tate treatment. In other situations, a 6-week course of therapy with an antipseudomonal β-lactam is recommended, and in case of puncturewound osteomyelitis, oral ciprofloxacin may be used. Central Nervous System (CNS) Infections CNS infections due to P. aeruginosa are relatively rare. Involvement of the CNS is almost always secondary to a surgical procedure, head trauma, implanted devices, temporary external ventricular drains, and rarely bacteremia. The entity seen most often is postoperative or posttraumatic meningi tis. Subdural or epidural infection occasionally results from contamina tion of these areas. Embolic disease arising from endocarditis in users of IV drugs and leading to brain abscesses has also been described. The cerebrospinal fluid (CSF) profile of P. aeruginosa meningitis is no dif ferent from that of pyogenic meningitis of any other etiology. TREATMENT Central Nervous System Infections (Table 170-2) Treatment of Pseudomonas meningitis is difficult; little information has been published. However, the general prin ciples involved in the treatment of meningitis apply, including the need for high doses of bactericidal antibiotics to attain high drug levels in the CSF. The agent with which there is the most published experience in P. aeruginosa meningitis is ceftazidime, but other antipseudomonal β-lactam drugs

that attain reasonable CSF concentrations, such as cefepime, piperacillin/tazobactam, and

meropenem, have also been used successfully. Other forms of

P. aeruginosa CNS infection, such as brain abscesses and epidural and subdural empyema, generally require surgical drainage and removal of devices, in addition to antibiotic therapy.

Eye Infections Eye infections due to P. aeruginosa occur mainly as a result of direct inoculation into the tissue during trauma or sur face injury by contact lenses. Keratitis and corneal ulcers are the most common types of eye disease and are often associated with contact lenses (especially the extended-wear variety). Keratitis can be slowly or rapidly progressive, but the classic description is disease progress ing over 48 h to involve the entire cornea, with opacification and sometimes perforation. P. aeruginosa keratitis should be considered a medical emergency because of the rapidity with which it can progress to loss of sight. P. aeruginosa endophthalmitis secondary to bacteremia is the most devastating of P. aeruginosa eye infections. The disease is fulminant, with severe pain, chemosis, decreased visual acuity, anterior uveitis, vitreous involvement, and panophthalmitis. It is also a rare complication of cataract removal with lens insertion. In the United States, a recent outbreak associated with artificial tears with carbape nem-resistant P. aeruginosa led to serious eye infections and, in some cases, vision loss, enucleation, or death. TREATMENT Eye Infections (Table 170-2) The usual therapy for keratitis is the administration of topical antibiotics. Therapy for endophthalmitis includes the use of high-dose local and systemic antibiotics (to achieve higher drug concentrations in the eye) and vitrectomy. CHAPTER 170 Ear Infections P. aeruginosa infections of the ears vary from mild swimmer’s ear to serious life-threatening infections with neurologic sequelae. Swimmer’s ear is common among children and results from infection of moist macerated skin of the external ear canal. Most cases resolve with treatment, but some patients develop chronic drainage. Swimmer’s ear is managed with topical antibiotic agents (otic solu tions). The use of hearing aids may also predispose to this type of infec tion. The most serious form of Pseudomonas infection involving the ear has been given various names: two of these designations, malignant otitis externa and necrotizing otitis externa, are now used for the same entity. This disease was originally described in elderly patients with diabetes, in whom the majority of cases still occur. However, it has also been described in patients with AIDS and in elderly patients without underlying diabetes or immunocompromise. The usual presenting symptoms are decreased hearing and ear pain, which may be severe and lancinating. The pinna is usually painful, and the external canal may be tender. The ear canal almost always shows signs of inflamma tion, with granulation tissue and exudate. Tenderness anterior to the tragus may extend as far as the temporomandibular joint and mastoid process. A small minority of patients have systemic symptoms. Patients in whom the diagnosis is made late may present with cranial nerve palsies, most commonly cranial nerve VII, or even with cavernous venous sinus thrombosis. The ESR is invariably elevated (≥100 mm/h). The diagnosis is made on clinical grounds in severe cases; however, the “gold standard” is a positive technetium-99 bone scan in a patient with otitis externa due to P. aeruginosa. In diabetic patients, a positive bone scan constitutes presumptive evidence for this diagnosis and should prompt biopsy or empirical therapy. However, it should be kept in mind that S. aureus and Aspergillus spp. can also cause this entity. Infections Due to Pseudomonas, Burkholderia, and Stenotrophomonas Species TREATMENT Ear Infections (Table 170-2) Given the infection of the ear cartilage, sometimes with mastoid or petrous ridge involvement, patients with malignant (necrotizing) otitis externa are treated as for osteomyelitis.

Urinary Tract Infections UTIs due to P. aeruginosa generally occur as a complication of a catheter in the urinary tract, an obstruc tion or stone in the genitourinary system, urinary tract instrumenta tion, or surgery. A P. aeruginosa UTI occurring in the community often signals the presence of an abnormality in the urinary tract. It has been reported that the urinary tract is the second most important site of infection leading to Pseudomonas bacteremia.

TREATMENT Urinary Tract Infections (Table 170-2) Most P. aeruginosa UTIs are considered complicated infections that must be treated longer than uncomplicated cystitis. In general, a 7- to 10-day course of treatment suffices. Urinary cath eters, stents, or stones should be removed to prevent relapse, which is common and may not be due to antibiotic resistance but rather to factors such as a foreign body that has been left in place or an ongo ing obstruction. Removal of a urinary catheter will allow shorter courses of antibiotic therapy if that is the only predisposing factor. Skin and Soft Tissue Infections Besides pyoderma (ecthyma) gangrenosum in neutropenic patients, folliculitis and other papular or vesicular lesions due to P. aeruginosa have been extensively described and are collectively referred to as dermatitis. Multiple outbreaks have been linked to whirlpools, spas, and swimming pools. To prevent such outbreaks, the growth of P. aeruginosa in the home and in recreational environments must be controlled by proper chlorination of water. Most cases of hot-tub folliculitis are self-limited, requiring only the avoid ance of exposure to the contaminated source of water. Approximately one-third of reported outbreaks are associated with hotel facilities. Patients may also have ear pain, skin rashes, and eye irritation. PART 5 Infectious Diseases Toe-web infections occur especially often in the tropics, and the “green-nail syndrome” is caused by P. aeruginosa paronychia, which results from frequent submersion of the hands in water. In the latter entity, the green discoloration results from diffusion of pyocyanin into the nail bed. P. aeruginosa remains a prominent cause of burn wound infections in some parts of the world. The management of these infec tions is best left to specialists in burn wound care. Infections in Febrile Neutropenic Patients In febrile neutro penia, P. aeruginosa has historically been the organism against which empirical coverage is always essential. Although in Western countries these infections are now less common, their importance has not diminished because of persistently high mortality rates. In other parts of the world, P. aeruginosa continues to be a significant problem in febrile neutropenia, causing a larger proportion of infections in febrile neutropenic patients than any other single organism. For example,

P. aeruginosa was responsible for 28% of documented infections in 499 febrile neutropenic patients in one study from the Indian subcontinent and for 31% of such infections in another. In a large study of infections in leukemia patients from Japan, P. aeruginosa was the most frequently documented cause of bacterial infection. In studies performed in North America, northern Europe, and Australia, the incidence of

P. aeruginosa bacteremia in febrile neutropenia was quite variable. In a review of 97 reports published between 1987 and 1994, the incidence was reported to be 1–2.5% among febrile neutropenic patients given empirical therapy and 5–12% among patients with microbiologi cally documented infections. The most common clinical syndromes encountered were bacteremia, pneumonia, and soft tissue infections manifesting mainly as ecthyma gangrenosum. TREATMENT Infections in Febrile Neutropenic Patients (Table 170-2) Compared with rates three decades ago, improved rates of response to antibiotic therapy have been reported in many studies. A study of 127 patients demonstrated a reduction in the mortality rate from 71 to 25% with the introduction

of ceftazidime

and imipenem. Because neutrophils—the normal host defenses against this organism—are absent in febrile neutropenic patients, maximal doses of antipseudomonal β-lactam antibiotics should be used for the management of P. aeruginosa bacteremia in this setting. Infections in Patients with AIDS P. aeruginosa infections were well documented in patients with AIDS before the advent of antiret roviral therapy. Since the introduction of protease inhibitors, P. aeru ginosa infections in patients with AIDS have been seen less frequently but still occur, particularly in the form of sinusitis. While this entity is now uncommon in developed nations, there are still large numbers of patients with untreated HIV infection or poorly controlled disease in developing nations who are likely to suffer from P. aeruginosa infec tions. The clinical presentation of Pseudomonas infection (especially pneumonia and bacteremia) in patients with AIDS is remarkable in that, although the illness may appear not to be severe, the infection may nonetheless be fatal. Patients with bacteremia may have only a lowgrade fever and may present with ecthyma gangrenosum. Pneumonia, with or without bacteremia, is perhaps the most common type of

P. aeruginosa infection. Patients with P. aeruginosa pneumonia exhibit the classic clinical signs and symptoms of pneumonia, such as fever, productive cough, and chest pain. The infection may be lobar or mul tilobar and shows no predisposition for any particular location. The most striking feature is the high frequency of cavitary disease. TREATMENT Infections in Patients with AIDS Therapy for any of these conditions in AIDS patients is no different from that in other patients. However, relapse is the rule unless the patient’s CD4+ T-cell count rises to >50/μL or suppressive antibiotic therapy is given. In attempts to achieve cures and prevent relapses, therapy tends to be more prolonged. Gastrointestinal Infections A poorly understood syndrome caused by P. aeruginosa has been described in the Far East and has been called Shanghai fever and Pseudomonas enterocolitis. This syndrome occurs in young children; its occurrence in adults appears to be rare. Shanghai fever manifests as severe enteric disease, sepsis with inva sive disease, and complications, whereas Pseudomonas enterocolitis is characterized by prolonged fever with bloody or mucoid diarrhea mimicking bacterial enterocolitis. The mortality rate ranges between 23 and 89%, with ecthyma gangrenosum occurring in >50% of cases. Early recognition and treatment have led to a reduction in the mortal ity rate. There is an above-average occurrence of the exoU gene among Pseudomonas isolates from patients with this syndrome. Multidrug-Resistant Infections (Table 170-2) P. aeruginosa has a notorious propensity to develop antibiotic resistance. Over three decades, the impact of resistance was minimized by the rapid develop ment of several potent antipseudomonal β-lactams and fluoroquino lones. However, rates of resistance to these agents that revolutionized the treatment of P. aeruginosa have risen to the point where some are almost unusable empirically because of the worldwide emergence of strains carrying determinants that mediate resistance. Extremely high rates of MDR strains have been reported from eastern and southern Europe, Latin America, India, and China, especially in ICUs. Physi cians have had to resort to drugs such as colistin and polymyxin B, which were discarded decades ago. This surge in resistance is mediated by multiple mechanisms sometimes converging in individual strains. Chief among these are chromosomal or plasmid-borne penicillinases, extended-spectrum β-lactamases, cephalosporinases, and carbapen emases. Any of these may be combined with permeability mutations and efflux pump overexpression. The greatest nemesis in this regard is the worldwide presence of carbapenemases in P. aeruginosa leading to resistance to most β-lactams except some of the newest agents recently developed. These new agents are generally combinations of a

cephalo sporin or a carbapenem most often with a novel β-lactamase inhibitor. Several have been approved for clinical use, and all are active against

MDR P. aeruginosa to varying degrees. Currently approved agents include ceftolozane-tazobactam, ceftazidime-avibactam, meropenemvaborbactam, and imipenem-relebactam. A novel cephalosporin, cefiderocol, which uses the iron uptake pathway of P. aeruginosa, also demonstrates activity against MDR strains. Since MDR and XDR

P. aeruginosa are unpredictable in regard to the underlying mecha nisms of resistance, laboratory testing is absolutely required before the use of any of these agents. Most academic institutions restrict the use of these agents as there are increasing reports of resistance even to these agents, as well the cost implications of misuse. BURKHOLDERIA SPECIES ■ ■BURKHOLDERIA CEPACIA COMPLEX The B. cepacia complex (BCC) gained notoriety as the cause of a rap idly fatal syndrome of respiratory distress and septicemia (the “cepacia syndrome”) in CF patients. Of the more than 20 species of this com plex, the three most frequently seen in CF patients are B. cenocepacia, B. multivorans, and B. stabilis. In addition to their occurrence in CF, members of this complex were not uncommonly encountered in ICU patients (previously designated Pseudomonas cepacia) and patients with chronic granulomatous disease, in whom they caused lung dis ease. BCC organisms are environmental organisms that inhabit moist environments and are found in the rhizosphere. They possess multiple virulence factors that may play roles in disease as well as colonizing factors that are capable of binding to lung mucus—an ability that may explain the predilection of B. cepacia for the lungs in CF. B. cenocepacia is motile, secretes elastase, and possesses components of an injectable toxin-secretion system like that of P. aeruginosa; its LPS is among the most potent of all LPSs in stimulating an inflammatory response in the lungs. Inflammation may be the major cause of the lung disease seen in the “cepacia” syndrome. Besides infecting the lungs in CF, the BCC organisms appear as airway colonizers during broad-spectrum antibiotic therapy and are causes of VAP, catheter-associated infections, and wound infections. B. cenocepacia has emerged as a barrier to lung transplantation in CF, with relatively high mortality rates after a year compared to infection with other members of this complex. TREATMENT B. cepacia Complex Infections BCC organisms are intrinsically resistant to many antibiotics, ren dering empiric treatment difficult. Therefore, treatment must be tailored according to sensitivities. Trimethoprim-sulfamethoxazole (TMP-SMX), meropenem, and minocycline are the most active agents in vitro and may be started as first-line agents (Table 170-2). However, recent reports indicate that there has been increasing resistance to these agents especially in CF patients. Some strains are susceptible to third-generation ureidopenicillins, advanced cepha losporins, and fluoroquinolones, and these agents may be used against isolates known to be susceptible. Newer antibiotics such as ceftolozane-tazobactam and ceftazidime-avibactam show good activity against MDR strains in vitro. However, there is very limited clinical experience with these agents. ■ ■BURKHOLDERIA PSEUDOMALLEI B. pseudomallei is the causative agent of melioidosis, a disease of humans and animals that is geographically restricted to Southeast Asia and northern Australia, with occasional cases in countries such as India and China. This organism may be isolated from individuals returning directly from these endemic regions and from military per sonnel who have served in endemic regions. Symptoms of this illness may develop only at a later date because of the organism’s ability to cause latent infections, which has been attributed to its ability to sur vive within cells. B. pseudomallei is found in soil and water. Humans and animals are infected by inoculation, inhalation, or ingestion; only rarely is the organism transmitted from person to person. Humans are

not colonized without being infected. Among the pseudomonads,

B. pseudomallei is perhaps the most virulent species. Host compromise is not an essential prerequisite for disease, although many patients have common underlying medical diseases (e.g., diabetes, renal failure, or alcohol abuse). B. pseudomallei is a facultative intracellular organism whose replication in PMNs and macrophages may be aided by the possession of a polysaccharide capsule. The organism also possesses elements of a type III secretion system that plays a role in its intracel lular survival. During infection, there is a florid inflammatory response whose role in disease is unclear.

B. pseudomallei causes a wide spectrum of conditions, ranging from asymptomatic infection to abscesses, pneumonia, and disseminated disease. It is a significant cause of fatal community-acquired pneu monia and septicemia in endemic areas, with mortality rates as high as 44% reported in Thailand. Acute pulmonary infection is the most commonly diagnosed form of melioidosis. Pneumonia may be asymp tomatic (with routine chest radiographs showing mainly upper-lobe infiltrates) or may present as severe necrotizing disease. B. pseudom allei also causes chronic pulmonary infections with systemic mani festations that mimic those of tuberculosis, including chronic cough, fever, hemoptysis, night sweats, and cavitary lung disease. Besides pneumonia, the other principal form of B. pseudomallei disease is skin ulceration with associated lymphangitis and regional lymphadenopa thy. Spread from the lungs or skin, which is most often documented in debilitated individuals, gives rise to septicemic forms of melioidosis that carry a high mortality rate. TREATMENT B. pseudomallei Infections CHAPTER 170 B. pseudomallei is susceptible to advanced penicillins, cephalosporins, and carbapenems (Table 170-2). Treatment is divided into two stages: an intensive 2-week phase of therapy with ceftazidime or a carbape nem followed by at least 12 weeks of oral TMP-SMX to eradicate the organism and prevent relapse. Australian guidelines for treating this condition recommend longer periods of intensive therapy—4−8 weeks for severe infections, osteomyelitis, and CNS infections. The recogni tion of this bacterium as a potential agent of biologic warfare has stimulated interest in the development of a vaccine. Infections Due to Pseudomonas, Burkholderia, and Stenotrophomonas Species ■ ■BURKHOLDERIA MALLEI B. mallei causes the equine disease glanders in Africa, Asia, and South America. The organism was eradicated from Europe and North America decades ago. The last case seen in the United States occurred in 2001 in a laboratory worker; before that, B. mallei had last been seen in this coun try in 1949. In contrast to the other organisms discussed in this chapter, B. mallei is not an environmental organism and does not persist outside its equine hosts. Consequently, B. mallei infection is an occupational risk for handlers of horses, equine butchers, and veterinarians in areas of the world where it still exists. Diabetics are thought to be especially susceptible to infection by this organism. The polysaccharide capsule is a critical virulence determinant. The organism is transmitted from animals to humans by inoculation into the skin, where it causes local infection with nodules and lymphadenitis. Regional lymphadenopathy is common. Respiratory secretions from infected horses are extremely infectious. Inhalation results in clinical signs of typical pneumonia but may also cause an acute febrile illness with ulceration of the trachea. The organism may disseminate from the skin or lungs to cause septicemia with signs of sepsis. The septicemic form is frequently associated with shock and a high mortality rate. The infection may also enter a chronic phase and present as disseminated abscesses. B. mallei infection may present as early as 1–2 days after inhalation or (in cutaneous disease) may not become evident for months. TREATMENT B. mallei Infections The antibiotic susceptibility pattern of B. mallei is similar to that of B. pseudomallei; in addition, the organism is susceptible to the

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