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124 Approach to the Patient with an Infectious Disease

Section 1 Basic Considerations in Infectious Diseases Neeraj K. Surana, Dennis L. Kasper

Approach to the Patient

with an Infectious Disease ■ ■HISTORIC PERSPECTIVE The origins of the field of infectious diseases are humble. The notion that communicable diseases were due to a miasma (“bad air”) can be traced back to at least the mid-sixteenth century. Not until the work of Louis Pasteur and Robert Koch in the late nineteenth century was there credible evidence supporting the germ theory of disease—i.e., that microorganisms are the direct cause of infections. In contrast to this relatively slow start, the twentieth century saw remarkable advances in the field of infectious diseases, and the etiologic agents of numerous infectious diseases were soon identified. Furthermore, the discovery of antibiotics and the advent of vaccines against some of the most deadly and debilitating infections greatly altered the landscape of human health. Indeed, the twentieth century saw the elimination of smallpox, one of the great scourges in the history of humanity. These remarkable successes prompted Sir Frank MacFarlane Burnet, a noted immunolo gist and Nobel laureate, to write in a 1962 publication entitled Natural History of Infectious Diseases: “In many ways one can think of the middle of the twentieth century as the end of one of the most impor tant social revolutions in history, the virtual elimination of infectious disease.” Professor Burnet was not alone in this view. Robert Peters dorf, a renowned infectious disease expert and former editor of this textbook, wrote in 1978 that “even with my great personal loyalties to infectious diseases, I cannot conceive a need for 309 more [graduating trainees in infectious diseases] unless they spend their time culturing each other.” Given the enormous growth of interest in the microbiome in the past 20 years, Dr. Petersdorf’s statement might have been ironi cally clairvoyant, although he could have had no idea what was in store for humanity, with an onslaught of new, emerging, and reemerging infectious diseases. Clearly, even with all the advances of the twentieth century, infectious diseases continue to represent a formidable challenge for patients and physicians alike. Furthermore, during the latter half of the century, several chronic diseases were demonstrated to

be directly or indirectly caused by infectious microbes; perhaps the most notable examples are the associations of Helicobacter pylori with peptic ulcer disease and gastric carcinoma, human papillomavirus with cervi cal cancer, and hepatitis B and C viruses with liver cancer. In fact, ~16% of all malignancies are now known to be associated with an infectious cause. In addition, numerous emerging and reemerging infectious diseases continue to have a dire impact on global health: HIV/AIDS, SARS-CoV-2, Ebola, and mpox are but a few examples. The fear of weaponizing pathogens for bioterrorism is ever present and poses a potentially enormous threat to public health. Moreover, escalating antimicrobial resistance in clinically relevant microbes (e.g., carbapenem-resistant Enterobacteriaceae and Acinetobacter spp., Candida auris, drug-resistant Mycobacterium tuberculosis, and vancomycin-resistant enterococci) signifies that the administration of antimicrobial agents—once thought to be a panacea—requires appropriate stewardship. For all these reasons, infectious diseases continue to exert grim effects on individual patients as well as on international public health. Even with all the successes of the past century, physicians must be as thoughtful about infectious diseases now as they were at the beginning of the twentieth century.

Infectious Diseases PART 5 ■ ■GLOBAL CONSIDERATIONS Infectious diseases remain the second leading cause of death world wide. Although the rate of infectious disease–related deaths has decreased dramatically over the past 25 years, there were still 9.6 mil lion such deaths in 2019 (Fig. 124-1A). These deaths disproportion ately affect children <1 year of age, adults older than 70 years, and persons living in low- and middle-income countries (Fig. 124-1B and 124-1C; Chap. 487); in 2019, ~17% of all deaths worldwide were related to infectious diseases, with a rate as high as ~69% in sub-Saharan Africa. Given that infectious diseases are still a major cause of global mortal ity, understanding the local epidemiology of disease is critically impor tant in evaluating patients. Diseases such as HIV/AIDS have decimated southern Africa, with HIV-infected adults representing 16–20% of the total population in countries like South Africa, Botswana, and Lesotho, and more than 25% in Eswatini. Moreover, drug-resistant tuberculosis is rampant throughout the former Soviet-bloc countries, India, China, and South Africa. The ready availability of this type of information allows physicians to develop appropriate differential diagnoses and treatment plans for individual patients. Programs such as the Global Burden of Disease seek to quantify human losses (e.g., deaths, disability-adjusted life-years) due to diseases by age, sex, and country over time; these data not only help inform local, national, and international health policy but can also help guide local medical decision-making. Even though some diseases (e.g., pandemic influenza, mpox) are seemingly geographically restricted, the increasing ease of rapid worldwide travel has raised concern about their swift spread around the globe. Indeed, human migration has historically been the source of epidemics: Yersinia pestis spread along trade routes in the fourteenth century, Native American populations were devastated by diseases such as smallpox and Salmonella that were imported by European explorers in the fifteenth and sixteenth centuries, military maneu vers helped facilitate the spread of the 1918 influenza pandemic, and religious pilgrimages (e.g., the Hajj) provide the means for worldwide dissemination of diseases. The continued effects of global travel on the spread of infectious diseases are perhaps best highlighted by the SARS-CoV-2 pandemic (Chap. 204). Although this virus was first identified in Wuhan, China, it quickly spread across the globe and brought an abrupt end to virtually all travel and commerce throughout the world, plunging economies into a deep recession, resulting at one point in more than half the world’s population living under stay-athome orders, and causing the death of ~7 million people worldwide. Not only can travelers carry person-to-person transmitted infections (e.g., SARS-CoV-2,

HIV) anywhere in the world, but they can also introduce vector-borne infections to new geographic areas (e.g., chi kungunya and Zika viruses) and contribute to the worldwide spread of multidrug-resistant organisms. The world's increasing interconnected ness has profound implications not only for the global economy but also for medicine and the spread of infectious diseases. ■ ■UNDERSTANDING THE MICROBIOTA Normal, healthy humans are colonized with ~40 trillion bacteria as well as countless viruses, fungi, and archaea; taken together, these microor ganisms outnumber human cells by ~10 times in the human body (Chap. 484). The major reservoir of these microbes is the gastrointesti nal tract, but substantial numbers of microbes live in the female genital tract, the oral cavity, and the nasopharynx. There is increasing interest in the skin and lungs as sites where microbial colonization might be highly relevant to the biology and disease susceptibility of the host. These com mensal organisms provide the host with myriad benefits, from aiding in metabolism to shaping the immune system. With regard to infectious diseases, the vast majority of infections are caused by organisms that are part of the normal microbiota (e.g., Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa), with relatively few infections due to organisms that are strictly pathogens (e.g., Neisseria gonorrhoeae, rabies virus). Perhaps it is not surprising that a general understanding

Number of deaths (in millions)

A

PART 5 Infectious Diseases 0.1 C 0.2 0.3 0.4 0.5 0.6 FIGURE 124-1 Magnitude of infectious disease–related deaths globally. A. The absolute number (blue line; left axis) and rate (red line; right axis) of infectious disease– related deaths throughout the world since 1990. B. Age-specific rates of infectious disease–related deaths in 2019. In both A and B, the charts depict the mean estimate and 95% uncertainty intervals. C. A map depicting country-specific data for the percent of total deaths that were attributable to communicable, maternal, neonatal, and nutritional disorders in 2019. (Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.) of the microbiota is essential in the evaluation of infectious diseases. Individuals' microbiotas have a major impact on their susceptibility to infectious diseases and even their responses to vaccines. Site-specific knowledge of the indigenous microbiota may facilitate appropriate interpretation of culture results, aid in selection of empirical antimicro bial therapy based on the likely causative agents, and provide additional impetus for rational antibiotic use to minimize the untoward effects of these drugs on the "beneficial" microbes that inhabit the body. ■ ■WHEN TO CONSIDER AN INFECTIOUS ETIOLOGY The title of this chapter may appear to presuppose that the physician knows when a patient has an infectious disease. In reality, this chapter can serve only as a guide to the evaluation of a patient in whom an infectious disease is a possibility. Once a specific diagnosis is made, the reader should consult the subsequent chapters that deal with specific microorganisms in detail. The challenge for the physician is to recog nize which patients may have an infectious disease as opposed to some other underlying disorder. This task is greatly complicated by the fact that infections have an infinite range of presentations, from acute lifethreatening conditions (e.g., meningococcemia) to chronic diseases of varying severity (e.g., H. pylori–associated peptic ulcer disease) to

Rate of death (per 100,000)

Rate of death (per 100,000)

0–27 days 28–364 days 1–4 years 5–9 years 10–19 years 20–29 years 30–39 years 40–49 years 50–59 years 60–69 years 70–79 years 80–89 years 90+ years Age B no symptoms at all (e.g., latent M. tuberculosis infection). While it is impossible to generalize about a presentation that encompasses all infections, common findings in the history, physical examination, and basic laboratory testing often suggest that the patient either has an infectious disease or should be more closely evaluated for one. This chapter focuses on these common findings and how they may direct the ongoing evaluation of the patient. APPROACH TO THE PATIENT Infectious Disease See also Chap. 127. HISTORY As in all of medicine, a complete and thorough history is paramount in the evaluation of a patient with a possible infectious disease. The history is critical for developing a focused differential diagnosis and for guiding the physical exam and initial diagnostic testing. Although a detailing of all the elements of a history is beyond the scope of this chapter, specific components relevant to infectious diseases require

particular attention. In general, these aspects focus on two areas: (1) an exposure history that may identify microorganisms with which the patient may have come into contact and (2) host-specific factors that may predispose to the development of an infection. Exposure History • History of infections or exposure to drug-resistant microbes Information about a patient's previous infections, with the associated microbial susceptibility profiles, is very helpful in determining possible etiologic agents. Specifically, know ing whether a patient has a history of infection with drug-resistant organisms (e.g., methicillin-resistant S. aureus, vancomycin-resistant Enterococcus species, enteric organisms that produce an extendedspectrum β-lactamase or carbapenemase) or may have been exposed to drug-resistant microbes (e.g., during a recent stay in a hospital, nursing home, or long-term acute-care facility) may alter the choice of empirical antibiotics. For example, a patient presenting with sepsis who is known to have a history of invasive infection with a multi drug-resistant isolate of P. aeruginosa should be treated empirically with an antimicrobial regimen that will cover this strain. Social history Although the social history taken by physicians is often limited to inquiries about a patient's alcohol and tobacco use, a complete social history can offer a number of clues to the underlying diagnosis. Knowing whether the patient has any highrisk behaviors (e.g., unsafe sexual behaviors, intravenous [IV] drug use), potential hobby-associated exposures (e.g., avid gardening, with possible Sporothrix schenckii exposure), or occupational expo sures (e.g., increased risk for M. tuberculosis exposure in funeral service workers) can facilitate diagnosis. The importance of the social history is exemplified by a case in 2009 in which a laboratory researcher died of a Y. pestis infection acquired during his work; although this patient had visited both an outpatient clinic and an emergency department, his records at both sites failed to include his occupation—information that potentially could have led quickly to appropriate treatment and infection control measures. Dietary habits Because certain pathogens are associated with specific dietary habits, inquiring about a patient's diet can provide insight into possible exposures. For example, Shiga toxin–producing strains of Escherichia coli, and Toxoplasma gondii are associated with the consumption of raw or undercooked meat; Salmonella typhimurium, Listeria monocytogenes, and Mycobacterium bovis with unpasteurized milk; Leptospira species, parasites, and enteric bacteria with unpurified water; and Vibrio species, norovirus, hel minths, and protozoa with raw seafood. Animal exposures Because animals are often important vectors of infectious diseases, patients should be asked about exposures to any animals, including contact with their own pets, visits to petting zoos, or random encounters (e.g., home rodent infestation). For

example, dogs can carry ticks that serve as agents for the transmis sion of several infectious diseases, including Lyme disease, Rocky Mountain spotted fever, and ehrlichiosis. Cats are associated with Bartonella henselae infection, reptiles with Salmonella infection, rodents with leptospirosis, and rabbits with tularemia (Chap. 146). Travel history Attention should be paid to both international and domestic travel. Fever in a patient who has recently returned from abroad significantly broadens the differential diagnosis (Chap. 130) and, as exemplified by the COVID-19 pandemic, can help identify the beginnings of international outbreaks. Even a remote history of international travel may reflect patients' exposure to infections with pathogens such as M. tuberculosis or Strongyloides stercoralis. Similarly, domestic travel may have exposed patients to pathogens that are not normally found in their local environment and therefore may not routinely be considered in the differential diagnosis. For example, a patient who has recently visited California or Martha's Vineyard may have been exposed to Coccidioides immi tis or Francisella tularensis, respectively. Beyond simply identifying locations that a patient may have visited, the physician needs to delve deeper to learn what kinds of activities and behaviors the

patient engaged in during travel (e.g., the types of food and sources of water consumed, freshwater swimming, animal exposures) and whether the patient had the necessary immunizations and/or took the necessary prophylactic medications prior to travel; these addi tional exposures, which the patient may not think to report without specific prompting, are as important as exposures during a patient's routine daily living. Host-Specific Factors Because many opportunistic infections (e.g., with Pneumocystis jirovecii, Aspergillus species, or JC virus) affect primarily immunocompromised patients, it is of vital importance to determine the immune status of the patient. Defects in the immune system may be due to an underlying disease (e.g., malignancy, HIV infection, malnutrition), a medication (e.g., chemotherapy, gluco corticoids, monoclonal antibodies to components of the immune system), a treatment modality (e.g., total body irradiation, splenec tomy), or a primary immunodeficiency. The type of infection for which the patient is at increased risk varies with the specific type of immune defect. In concert with determining whether a patient is immunocompromised for any reason, the physician should review the immunization record to ensure that the patient is adequately pro tected against vaccine-preventable diseases (Chap. 129). PHYSICAL EXAMINATION Like the history, a thorough physical examination is crucial in evaluating patients with an infectious disease. Some elements of the physical exam (e.g., skin, lymphatics) that are often performed in a cursory manner as a result of the ever-increasing pace of medi cal practice may help identify the underlying diagnosis. Moreover, serial exams are critical since new findings may appear as the illness progresses. A description of all the elements of a physical exam is beyond the scope of this chapter, but the following components have particular relevance to infectious diseases. CHAPTER 124 Vital Signs Given that elevations in temperature are often a hall mark of infection, paying close attention to the temperature may be of value in diagnosing an infectious disease (Chap. 20). The idea that 37°C (98.6°F) is the normal human body temperature dates to the nineteenth century and was initially based on axillary measure ments. Rectal temperatures more accurately reflect the core body temperature and are 0.4°C (0.7°F) and 0.8°C (1.4°F) higher than oral and axillary temperatures, respectively. This idea of a "normal" body temperature does not consider the fact that temperatures tend to be higher later in the day, in women, and in younger people. Moreover, the average body temperature seems to have dropped ~0.03°C every decade since the early 1800s to a new normal of ~36.7°C. Although the definition of fever varies greatly throughout the medical literature, the most common definition, which is based on studies defining fever of unknown origin

(Chap. 22), uses a core temperature ≥38.3°C (≥101°F). Although fever is very commonly associated with infection, it is also documented in many other diseases (Chap. 20). For every 1°C (1.8°F) increase in core tempera ture, the heart rate typically rises by ~10 beats/min. Table 124-1 lists infections that are associated with relative bradycardia (Faget's sign), where patients have a lower heart rate than might be expected for a given body temperature. Although this pulse–temperature dissociation is not highly sensitive or specific for establishing a diagnosis, it is potentially useful in low-resource settings given its ready availability and simplicity. Approach to the Patient with an Infectious Disease Lymphatics There are ~600 lymph nodes throughout the body, and infections are an important cause of lymphadenopathy. A physical examination should include evaluation of lymph nodes in multiple regions (e.g., popliteal, inguinal, epitrochlear, axillary, multiple cervical regions), with notation of the location, size (nor mal, <1 cm), presence or absence of tenderness, and consistency (soft, firm, or rubbery) and of whether the nodes are matted (i.e., connected and moving together). Nodes that are small and firm can also be described as "shotty," referring to the size and consistency of buckshot pellets. Of note, palpable epitrochlear nodes are always

TABLE 124-1 Causes of Relative Bradycardia Infectious Causes Intracellular organisms Gram-negative bacteria Salmonella typhi Francisella tularensis Brucella spp. Coxiella burnetii (Q fever) Leptospira interrogans Legionella pneumophila Mycoplasma pneumoniae Tick-borne organisms Rickettsia spp. Orientia tsutsugamushi (scrub typhus) Babesia spp. Other Corynebacterium diphtheriae Plasmodium spp. (malaria) Viruses/viral infections Yellow fever virus Dengue virus Viral hemorrhagic feversa Viral myocarditis Noninfectious Causes Drug fever Beta blocker use Central nervous system lesions Malignant lymphoma Factitious fever aPrimarily early in the course of infection with Marburg or Ebola virus. PART 5 Infectious Diseases pathologic. Of patients presenting with lymphadenopathy, 75% have localized findings, and the remaining 25% have generalized lymphadenopathy (i.e., that involving more than one anatomic region). Localized lymphadenopathy in the head and neck region is found in 55% of patients, inguinal lymphadenopathy in 14%, and axillary lymphadenopathy in 5%. Determining whether the patient has generalized versus localized lymphadenopathy can help narrow the differential diagnosis, as various infections present differently. Skin The fact that many infections have cutaneous manifestations gives the skin examination particular importance in the evaluation of patients (Chaps. 21, 61, 134, and A1). It is important to perform a complete skin exam, with attention to both front and back. Spe cific rashes are often extremely helpful in narrowing the differential diagnosis of an infection (Chaps. 21 and A1). In numerous anec dotal instances, patients in the intensive care unit have had "fever of unknown origin" that was actually due to unrecognized pressure ulcers. Moreover, close examination of the distal extremities for splinter hemorrhages, Janeway lesions, or Osler's nodes may yield evidence of endocarditis or other causes of septic emboli. Foreign Bodies As previously mentioned, many infections are caused by members of the indigenous microbiota. These infections typically occur when these microbes escape their normal habitat and enter a new one. Thus, maintenance of epithelial barriers is one of the most important mechanisms in protection against infection. However, hospitalization of patients is often associated with breaches of these barriers—e.g., due to placement of IV lines, surgical drains, or tubes (e.g., endotracheal tubes and Foley cath eters) that allow microorganisms to localize in sites to which they normally would not have access (Chap. 147). Accordingly, knowing what lines, tubes, and drains are in place is helpful in ascertaining what body sites might be infected. DIAGNOSTIC TESTING Laboratory and radiologic testing has advanced greatly over the past few decades and has become an important component

in the evaluation of patients. The dramatic increase in the number

of serologic diagnostics, antigen tests, and molecular diagnostics available to the physician has, in fact, revolutionized medical care. However, all of these tests should be viewed as adjuncts to the his tory and physical examination—not a replacement for them. The selection of initial tests should be based directly on the patient's history and physical exam findings. Moreover, diagnostic testing should generally be limited to those conditions that are reasonably likely and treatable, important in terms of public health consider ations, and/or capable of providing a definitive diagnosis that will consequently limit other testing. White Blood Cell (WBC) Count Elevations in the WBC count are often associated with infection, although many viral infections are associated with leukopenia. It is important to assess the WBC dif ferential, given that different classes of microbes are associated with various leukocyte types. For example, bacteria are associated with an increase in polymorphonuclear neutrophils, often with elevated levels of earlier developmental forms such as bands; viruses are associated with an increase in lymphocytes; and certain parasites are associated with an increase in eosinophils. Table 124-2 lists the major infectious causes of eosinophilia. Inflammatory Markers The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level are indirect and direct measures of the acute-phase response, respectively, that can be used to assess a patient's general level of inflammation. Moreover, these markers can be followed serially over time to monitor disease progress/resolution. It is noteworthy that the ESR changes relatively slowly, and its measurement more often than weekly usually is not useful; in contrast, CRP concentrations change rapidly, and daily measurements can be useful in the appropriate context. Although these markers are sensitive indicators of inflammation, neither is very specific. An extremely elevated ESR (>100 mm/h) has a 90% predictive value for a serious underlying disease (Table 124-3). Work is ongoing to identify other potentially useful inflammatory markers (e.g., procalcitonin, serum amyloid A protein); their clini cal utility requires further validation. Analysis of Cerebrospinal Fluid (CSF) Assessment of CSF is criti cal for patients with suspected meningitis or encephalitis. An open ing pressure should always be recorded, and fluid should routinely be sent for cell counts, Gram's stain and culture, and determination of glucose and protein levels. A CSF Gram's stain typically requires

> 105 bacteria/mL for reliable positivity; its specificity approaches 100%. Table 124-4 lists the typical CSF profiles for various infec tions. In general, CSF with lymphocytic pleocytosis and a low glucose concentration suggests either infection (e.g., with Listeria, M. tuberculosis, or a fungus) or a noninfectious disorder (e.g., neo plastic meningitis, sarcoidosis). Bacterial antigen tests of CSF (e.g., latex agglutination tests for Haemophilus influenzae type b, group B Streptococcus, S. pneumoniae, and Neisseria meningitidis) are not recommended for screening, given that these tests are no more sensitive than Gram's stain; however, these assays can be helpful in presumptively identifying organisms seen on Gram's stain. In con trast, other antigen tests (e.g., for Cryptococcus) and some CSF sero logic testing (e.g., for Treponema pallidum, Coccidioides) are highly sensitive and are useful for select patients. In addition, polymerase chain reaction (PCR) analysis of CSF is increasingly being used for the diagnosis of bacterial (e.g., N. meningitidis, S. pneumoniae, mycobacteria)

> and viral (e.g., herpes simplex virus, enterovirus) infections; while these molecular tests permit rapid diagnosis with a high degree of sensitivity and specificity, they often do not allow determination of antimicrobial resistance profiles. Cultures The mainstays of infectious disease diagnosis include the culture of infected tissue (e.g., surgical specimens) or fluid (e.g., blood, urine, sputum, pus from a wound). Samples can be sent for culture of bacteria (aerobic or anaerobic), fungi, or viruses. Ideally, specimens are collected before the administration of antimicrobial therapy; in instances where this order of events is not clinically

TABLE 124-2 Major Infectious Causes of Eosinophiliaa ORGAN INVOLVED ORGANISM EXPOSURE GEOGRAPHIC DISTRIBUTION DEGREE OF EOSINOPHILIAb Central nervous system Angiostrongylus Raw seafood Asia Mild Gnathostoma Raw poultry and seafood Asia Moderate to extreme Eye Loa loa Insect bite Africa Moderate (expatriates), mild (patients living in endemic areas) Onchocerca Insect bite Africa Mild (expatriates), moderate (patients living in endemic areas) Lung Chlamydia trachomatis Sexual transmission Worldwide Mild Strongyloides Soil Tropical Moderate (acute), mild (chronic) Toxocara canis/Toxocara catic Dogs, soil Worldwide Moderate to extreme Paragonimus Crabs and crayfish Asia Moderate (acute), mild (chronic) Coccidioides immitis Soil Southwestern United States Mild (acute), extreme (disseminated) Brugia malayi Insect bite Asia Mild to moderate Pneumocystis jirovecii Air Worldwide Mild Liver Schistosoma japonicum Freshwater swimming Asia Moderate (acute), mild (chronic) Schistosoma mansoni Freshwater swimming Africa, Middle East, Latin America Fasciola Watercress Worldwide Moderate Clonorchis Raw seafood Asia Mild to moderate Opisthorchis Raw seafood Asia Mild to moderate Intestines Ascarisd Raw fruits and vegetables, contaminated water Hookworm Soil Worldwide Mild to moderate Trichuris Raw fruits and vegetables, contaminated water Cystoisospora belli Contaminated water and food Worldwide Mild Dientamoeba fragilis Unclear; spread via fecal–oral route Capillaria Raw seafood Asia Extreme Heterophyes Raw seafood Asia, Middle East Mild Anisakis Raw seafood Worldwide Mild Baylisascaris procyonise Soil North America Moderate to extreme Hymenolepis nana Contaminated water, soil Worldwide Mild Bladder Schistosoma haematobium Freshwater swimming Africa, Middle East Moderate (acute), mild (chronic) Muscle Trichinella Pork Worldwide Moderate to extreme Lymphatics Wuchereria bancroftid Insect bite Tropical Moderate to extremef Bartonella henselae Cats Worldwide Mild Other Recovery from bacterial or viral infections — — Mild HIV Contaminated bodily fluid Worldwide Mild Cryptococcus neoformans Soil Worldwide Moderate to extreme (disseminated) aThere are numerous noninfectious causes of eosinophilia, such as atopic disease, DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, and pernicious anemia, which can cause mild eosinophilia; drug hypersensitivity and serum sickness, which can cause mild to moderate eosinophilia; collagen vascular disease, which can cause moderate eosinophilia; and malignancy, Churg-Strauss syndrome, and hyper-IgE syndromes, which can cause moderate to extreme eosinophilia. bMild: 500–1500 cells/μL; moderate: 1500–5000 cells/μL; extreme: >5000 cells/μL. cCan also affect the liver and the eyes. dCan also affect the lungs. eCan also affect the eyes and the central nervous system. fLevels are typically higher with pulmonary infections. feasible, microscopic examination of the specimen (e.g., Gram-stained or potassium hydroxide [KOH]–treated preparations) is particularly important. Culture of the organism(s) allows identification of the etiologic agent(s), determination of the antimicrobial susceptibil ity profile,

and—when there is concern about an outbreak—isolate typing. While cultures are extremely useful in the evaluation of patients, determining whether culture results are clinically meaning ful or represent contamination (e.g., a non-aureus, non-lugdunensis staphylococcal species growing in a blood culture) can sometimes be challenging and requires an understanding of the patient's immune status, exposure history, and microbiota. In some cases, serial cultures to demonstrate clearance of the organism may be helpful. Pathogen-Specific Testing Numerous pathogen-specific tests (e.g., serology, antigen testing, PCR testing) are commercially

Moderate (acute), mild (chronic) Worldwide Mild to extreme Tropical Mild CHAPTER 124 Worldwide Mild Approach to the Patient with an Infectious Disease available, and many hospitals now offer some of these tests in-house to facilitate rapid turnaround that ultimately enhances patient care. The reader is directed to relevant chapters on the pathogens of interest for specific details. Some of these tests (e.g., universal PCRs, shotgun metagenomic sequencing) identify organisms that currently are not easily cultivable and have unclear relationships to disease, thereby complicating diagnosis. As these tests become more com monplace, the relevance of some of these previously unrecognized bacteria to human health will likely become more apparent. Radiology Imaging provides an important adjunct to the physical examination, allowing evaluation for lymphadenopathy in regions that are not externally accessible (e.g., mediastinum, intraabdomi nal sites), assessment of internal organs for evidence of infection, and facilitation of image-guided percutaneous sampling of deep spaces. The choice of imaging modality (e.g., CT, MRI, ultrasound,

TABLE 124-3 Causes of an Extremely Elevated Erythrocyte Sedimentation Rate (>100 mm/h) ETIOLOGIC CATEGORY (% OF CASES) SPECIFIC CAUSES Infectious diseases (35–40) Subacute bacterial endocarditis Abscesses Osteomyelitis Tuberculosis Urinary tract infection Inflammatory diseases (15–20) Giant cell arteritis Rheumatoid arthritis Systemic lupus erythematosus Malignancies (15–20) Multiple myeloma Leukemias Lymphomas Carcinomas Other (20–35) Drug hypersensitivity reactions (drug fever) Ischemic tissue injury/trauma Renal diseases nuclear medicine, use of contrast) is best made in consultation with a radiologist to ensure that the results will address the physician's specific concerns. TREATMENT Physicians often must balance the need for empirical antibiotic treat ment with the patient's clinical condition. When clinically feasible, it is best to obtain relevant samples (e.g., blood, CSF, tissue, purulent exudate) for culture prior to the administration of antibiotics, as antibiotic treatment often makes subsequent diagnosis more difficult. Although a general maxim for antibiotic treatment is to use a regimen with as narrow a spectrum as possible (Chap. 149), empirical regi mens are necessarily somewhat broad, given that a specific diagnosis has not yet been made. Table 124-5 lists empirical antibiotic treatment regimens for commonly encountered infectious presentations. These regimens should be narrowed as appropriate once a specific diagno sis is made. In addition to antibiotics, there is sometimes a role for adjunctive therapies, such as intravenous immunoglobulin G (IVIG) pooled from healthy adults or hyperimmune globulin prepared from PART 5 Infectious Diseases TABLE 124-4 Typical Cerebrospinal Fluid Profiles for Meningitis and Encephalitisa BACTERIAL MENINGITIS VIRAL MENINGITIS NORMAL WBC count (per µL) <5

> " 1000 25–500 40–600 150–2000 25–100 50–500 Differential of WBC 60–70% lymphocytes, ≤30% monocytes/ macrophages ↑↑PMNs (≥80%) Predominantly

> lymphocytesc Lymphocytes or PMNs, depending on specific organism Gram's stain Negative Positive (in >60% of cases) Negative Rarely positive Negative Occasionally positivee Negative Glucose (mg/dL) 40–85 <40 Normal ↓ to normal Normal <50 in 75% of cases Protein (mg/dL) 15–45 100 20–80 150–300 50–200 100–200 50–100 Opening pressure (mmH2O) 50–180 300 100–350 160–340 Normal 150–280 Normal to ↑ Common causes — Streptococcus pneumoniae, Neisseria meningitidis Enteroviruses Candida, Cryptococcus, and Aspergillus spp. aNumbers indicate typical results, but actual results may vary. bCerebrospinal fluid characteristics depend greatly on the specific organism. cNeutrophils may predominate early in the disease course. dPatients typically have striking eosinophilia as well. eSensitivity can be increased by examination of a smear of protein coagulum (pellicle) and the use of acid-fast stains. Abbreviations: PMNs, polymorphonuclear neutrophils; WBC, white blood cell.

the blood of individuals with high titers of specific antibodies to select pathogens (e.g., cytomegalovirus, hepatitis B virus, rabies virus, vaccinia virus, Clostridium tetani, varicella-zoster virus, Clostridium botulinum toxin). Although the data suggesting efficacy are limited, IVIG is sometimes used for patients with suspected staphylococcal or streptococcal toxic shock syndrome. INFECTION CONTROL When evaluating a patient with a suspected infectious disease, the physician must consider what infection control methods are nec essary to prevent transmission of any possible infection to other people. In 2007, the U.S. Centers for Disease Control and Prevention published guidelines for isolation precautions that are available for download at www.cdc.gov/infectioncontrol/guidelines/isolation/. Per sons exposed to certain pathogens (e.g., N. meningitidis, HIV, Bacillus anthracis) should receive postexposure prophylaxis to prevent disease acquisition. (See relevant chapters for details on specific pathogens.) WHEN TO OBTAIN AN INFECTIOUS DISEASE CONSULT At times, primary physicians need assistance with patient manage ment from a diagnostic and/or therapeutic perspective. Multiple studies have demonstrated that an infectious disease consult is asso ciated with improved outcomes, shorter length of hospital stay, and decreased costs for patients with various diseases. For example, in a prospective cohort study of patients with S. aureus bacteremia, infec tious disease consultation was independently associated with a 56% reduction in 28-day mortality. While artificial intelligence–based chatbots are beginning to be utilized in healthcare settings, they are not yet sophisticated enough to supplant an actual infectious dis ease consultation. In addition, infectious disease specialists provide other services (e.g., infection control, antimicrobial stewardship, management of outpatient antibiotic therapy, occupational exposure programs) that have been shown to benefit patients. Whenever such assistance would be advantageous to a patient with a possible infection, the primary physician should opt for an infectious disease consult. Specific situations that might prompt a consult include (1) difficult-to-diagnose patients with presumed infections, (2) patients who are not responding to treatment as expected, (3) patients with a complicated medical history (e.g., organ transplant recipients, patients immunosuppressed due to autoimmune or inflammatory conditions), and (4) patients with "exotic" diseases (i.e., diseases that are not typically seen within the region). FUNGAL MENINGITISb PARASITIC MENINGITIS TUBERCULOUS MENINGITIS ENCEPHALITIS Predominantly lymphocytesc Predominantly lymphocytesc ↑↑ Eosinophils (≥50%)d Normal Angiostrongylus cantonensis, Gnathostoma spinigerum, Baylisascaris procyonis

Mycobacterium tuberculosis Herpesviruses, enteroviruses, influenza virus, rabies virus

TABLE 124-5 Initial Empirical Antibiotic Therapy for Common Infectious Disease Presentationsa CLINICAL SYNDROME COMMON ETIOLOGIES ANTIBIOTIC(S) COMMENTS SEE CHAPTER(S) Septic shock Staphylococcus aureus, Streptococcus pneumoniae, enteric gram-negative bacilli Vancomycin, 15 mg/kg q12hb plus A broad-spectrum antipseudomonal β-lactam (piperacillin-tazobactam, 4.5 g q6h; imipenem,

1 g q8h; meropenem, 1 g q8h; or cefepime,

1–2 g q8–12h) Meningitis S. pneumoniae, Neisseria meningitidis Vancomycin, 15 mg/kg q12hb plus Ceftriaxone, 2 g q12h CNS abscess Streptococcus spp., Staphylococcus spp., anaerobes, gram-negative bacilli Vancomycin, 15 mg/kg q12hb plus Ceftriaxone, 2 g q12h plus Metronidazole, 500 mg q8h Acute endocarditis (native valve) S. aureus, Streptococcus spp., coagulase-negative staphylococci Vancomycin, 15 mg/kg q12hb plus Cefepime, 2 g q8h Pneumonia CommunityS. pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae, Chlamydia pneumoniae No comorbiditiesh: Azithromycin, 500 mg PO? 1, then 250 mg PO qd 4 days With comorbiditiesh: Levofloxacin, 750 mg PO qd acquired, outpatient Inpatient, non-ICU Above plus Legionella spp. A respiratory fluoroquinolone (moxifloxacin,

400 mg IV/PO qd; gemifloxacin, 320 mg PO qd; or levofloxacin, 750 mg IV/PO qd) or A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus azithromycin Inpatient, ICU Above plus S. aureus A β-lactam plus Azithromycin or a respiratory fluoroquinolone Hospital-acquired pneumoniad S. pneumoniae, H. influenzae, S. aureus, gram-negative bacilli (e.g., Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter spp.) An antipseudomonal β-lactam (cefepime, 2 g q8h; ceftazidime, 2 g q8h; imipenem, 500 mg q6h; meropenem, 1 g q8h; or piperacillin-tazobactam, 4.5 g q6h) plus An antipseudomonal fluoroquinolone (levofloxacin, 700 mg qd, or ciprofloxacin,

400 mg q8h) or an aminoglycoside (amikacin, 15–20 mg/kg q24hc; gentamicin, 5–7 mg/kg q24he; or tobramycin, 5–7 mg/kg q24he) Complicated intraabdominal infection Mild to moderate Anaerobes (Bacteroides spp., Clostridium spp.),

gram-negative bacilli (Escherichia coli), Streptococcus spp. Cefoxitin, 2 g q6h or A combination of metronidazole (500 mg q8–12h) plus one of the following: cefazolin (1–2 g q8h), cefuroxime (1.5 g q8h), ceftriaxone (1–2 g

q12–24h), cefotaxime (1–2 g q6–8h), ciprofloxacin (400 mg q12h), levofloxacin

(750 mg qd) severity High-risk patient or high degree of severity Same as above A carbapenem (imipenem, 500 mg q6h; meropenem, 1 g q8h; doripenem, 500 mg q8h) or Piperacillin-tazobactam, 3.375 g q6hf or A combination of metronidazole (500 mg q8h) plus an antipseudomonal cephalosporin (cefepime, 2 g q8h; ceftazidime, 2 g q8h)

If a pseudomonal species is likely, a second antipseudomonal agent should be added.

Dexamethasone (0.15 mg/kg IV q6h for 2–4 d) should be added for patients with suspected or proven pneumococcal meningitis, with the first dose administered 10–20 min before the first dose of antibiotics. 143 and pathogenspecific chapters —

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If MRSA is a consideration, add vancomycin (15 mg/kg q8–12hb) or linezolid (600 mg q12h); daptomycin should not be used in patients with pneumonia. 131 and pathogenspecific chapters CHAPTER 124 Approach to the Patient with an Infectious Disease If MRSA is a consideration, add vancomycin (15 mg/kg q8–12hb) or linezolid (600 mg q12h); daptomycin should not be used in patients with pneumonia. If MRSA is a consideration, add vancomycin (15 mg/kg q12hb) 137, 182, and

pathogen-specific chapters (Continued)

Revision #1
Created 2026-01-06 16:32:29 UTC by Omar Ayman
Updated 2026-01-06 16:32:29 UTC by Omar Ayman