
Pulmonary Infections

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Contents

Introduction	2	Histoplasmosis	13
Bacterial Pneumonia	2	General Principles	13
General Principles	2	Approach to the Patient	13
Approach to the Patient	3	Coccidioidomycosis	14
Prevention	6	Legionnaire's Disease	15
Atypical Pneumonias	6	General Principles	15
<i>Mycoplasma pneumoniae</i>	6	Approach to the Patient	16
Chlamydial Infection	8	References	19
Viral Pneumonia	9		
General Principles	9		
Approach to Patient	10		
Family and Community Issues	11		
Tuberculosis	11		
General Principles	11		
Approach to the Patient	11		

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Introduction

Pneumonia is a lung infection involving the alveoli and can be caused by a variety of microbes including bacteria, viruses, and fungi. It is the leading infectious cause of hospitalization and death in the United States [1]. In 2010, in the United States, pneumonia resulted in 1.1 million discharges from the hospital with an average length of stay of 5.2 days. Pneumonia accounted for 3.4 % of hospital deaths in 2006. In 2013 it accounted for 16.9 deaths per 100,000 population [2]. Pneumonia continues to be the leading killer of young children around the world, causing 14 % of all deaths in children ages 1 month to 5 years [3].

Most instances of pneumonia are attributable to self-infection with one or more types of microbes that originate in the nose and mouth. In healthy individuals, typical upper airway bacterial residents such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common bacteria causing community-acquired pneumonia. Hospital-acquired pneumonia is usually caused by more resistant bacteria such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*. In those with a serious impairment of their immune system, opportunistic microbes are more readily apparent such as fungi, viruses, and mycobacteria [1].

There are many mechanisms used by the lungs to resist infection. Physical mechanisms are structure of the upper airway, branching of the bronchial tree, sticky mucous layer lining the airways, cilia that propel mucous upward, and the cough reflex. If microbes do reach the alveoli, the immune system is usually able to destroy them [1].

A variety of strategies have been used to reduce the incidence of pneumonia. Elements of a healthy lifestyle that reduce the incidence are adequate nutrition, dental hygiene, and not smoking. For those with lung disease or impaired clearance of mucous, aerobic exercise, deep breathing maneuvers, and cough assist devices can facilitate expectoration and lung hygiene. Immunity to certain microbes can be enhanced by immunization [1].

Bacterial Pneumonia

General Principles

Definition/Background/Epidemiology

Pneumonia is a common infection in the parenchyma of the lower respiratory tract that can affect all age populations. There is significant morbidity and mortality associated with pneumonia, especially in the very young and elderly populations. Pneumonia is the leading cause of death in children younger than 5 years of age worldwide [4]. The average yearly incidence of pneumonia, specifically community-acquired pneumonia, is 5–11 per 1000, with most incident cases occurring in the winter months [5]. It is passed from person to person by viral particles on respiratory droplets.

Decisions on how to treat, whether to admit to the hospital or treat outpatient and potential prognosis, depend upon the most likely pathogen and the current clinical picture. In most cases, the pathogen is never isolated – only suspected – prior to initiation of treatment.

Classification

Pneumonia classification is based upon a variety of factors – age, clinical presentation and comorbidities, as well as history of previous hospital admissions or residence in a nursing facility. The best approach is a good history and physical exam in combination with knowledge of the most common causes of pneumonia for the presenting age patient being seen. Community-acquired pneumonia (CAP) must be distinguished from hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP), or ventilator-associated pneumonia (VAP) before treatment is started. In addition, the cause of the pneumonia must be determined to be bacterial, viral, or atypical in nature before treating.

Bacterial pneumonia, specifically *Streptococcus pneumoniae*, is the most common cause of pneumonia across all ages [4]. Certain comorbidities or risk factors (see footnote of Table 1) such as age greater than 65, alcohol abuse, recent antibiotic use (within the past 3 months), coexisting medical

diagnoses of COPD or CHF, and exposure to day care/nursing home (child or adult) increase the likelihood that the patient may have illness caused by other bacterial causes or have a pneumonia that may require additional or different treatment [5].

In children, the suspected organism that has caused the pneumonia is based upon the age of the child: [5]

Birth to 3 weeks: Group B streptococcus, *Haemophilus influenzae* type b (Hib), *Listeria monocytogenes*, and cytomegalovirus

3 Weeks to 3 months: *Streptococcus pneumoniae*, *Chlamydia trachomatis*, respiratory syncytial virus (RSV) or other respiratory viruses, and *Bordetella pertussis*

4 Months to 4 years: RSV and other respiratory viruses, *S. pneumoniae*, and group A streptococci

5–18 Years: *S. pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*

In general, the same principles apply to adults in attempting to determine the most likely organism affecting the patient. The only difference is that organism and treatment options are not based on age, but on how ill the patient is, associated risk factors (see footnote of Table 1), and the location of treatment (outpatient vs. inpatient vs. intensive care unit (ICU)): [5]

Outpatient with no risk factors: *S. pneumoniae*, *M. pneumoniae* (esp. in the 18–30-year-old age group), *C. pneumoniae*, *H. influenzae*, respiratory viruses

Outpatient with risk factors: *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, mixed bacteria + virus or atypical, *H. influenzae*, *Legionella*, respiratory viruses and fungi

Inpatient, non-ICU: *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, mixed bacteria + virus or atypical, respiratory viruses, *Legionella*, *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*

Inpatient, requiring ICU admission: *S. pneumoniae* (including drug resistant), *Legionella*, *H. influenzae*, gram-negative

enteric organisms, *S. aureus*, *M. pneumoniae*, *Pseudomonas* sp., respiratory viruses, *C. pneumoniae*, *M. tuberculosis*, and fungi.

Approach to the Patient

The most important point to consider when evaluating for pneumonia is the patient's age, the time of year, social habits, existing disease processes, travel history, or other exposure history – animals, geography, and other people. This information is best obtained from a thorough history and physical exam.

Attention must be given to determining which of the following categories the patient falls into:

- **Community-acquired pneumonia (CAP):** Pneumonia that is not associated with hospitalization, healthcare/long-term care facility, or recent medical treatment or contact with the healthcare system [5].
- **Healthcare-associated pneumonia (HCAP):** Pneumonia that occurs in patients who have recently been hospitalized within the past 90 days, reside in a nursing home or long-term care facility, or have received parenteral antimicrobial therapy, chemotherapy, or wound care within the past 30 days [5].
- **Hospital-acquired pneumonia (HAP):** Pneumonia that occurs 48 h after admission to a hospital and was not present on admission. This infection is currently the second most common nosocomial infection in the United States and is associated with high mortality and morbidity [5].
- **Ventilator-associated pneumonia (VAP):** Pneumonia that occurs 48 h or more after being intubated [5].

Early recognition of risk factors for HCAP, HAP, or VAP with prompt empiric treatment with different antibiotic therapy than previously used is important in the prevention of significant morbidity and/or mortality associated with these illnesses [6, 7].

Diagnosis

History

The most common presenting symptoms in an immunologically competent patient include sudden or recent onset of:

- Cough with purulent sputum
- Dyspnea
- Fever +/- chills
- Pleuritic chest pain

Other important information to obtain from the patient is with regard to recent hospitalizations, current resident location (in elderly patients), medical history, and recent medication (antibiotic) use.

Physical Exam

Physical exam findings can vary from one patient to another, let alone one age population to another. The following exam findings are the most consistent findings in patients with pneumonia:

- Vital signs:
 - Temperature $>100^{\circ}\text{F}$ (37.8°C)
 - Tachypnea (>20 breaths/min)
 - Tachycardia (>100 beats/min)
 - Decreased pulse oximetry readings on room air ($<92\%$)

- General:
 - Septic appearance
- Respiratory exam:
 - Increased tactile fremitus
 - Crackles, rhonchi
 - +/- Egophony
 - Dullness to percussion
 - Decreased breath sounds/air movement

Make sure to look for red flags in patients presenting with pneumonia-type symptoms. Red flag symptoms:

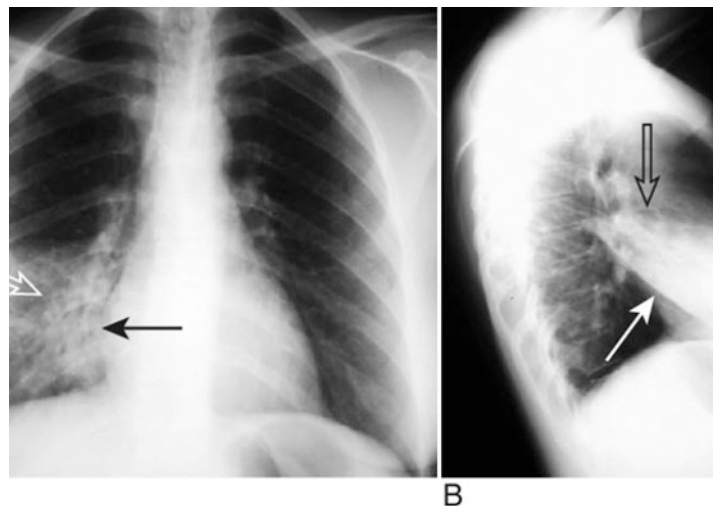
- Accessory muscle use (sternal retractions)
- Grunting
- Nasal flaring
- Altered mental status
- Apnea

The presence any of these symptoms may indicate a more severe infection requiring admission to an intensive care unit.

Laboratory and Imaging

Chest radiography is the test of choice in patients with clinically suspected CAP. The presence of an infiltrate or consolidation on X-ray is required for the diagnosis of CAP (Fig. 1).

Fig. 1 X-ray of infiltrates in pneumonia [8].



Chest radiography should be performed in:

Any patient with at least one of the following abnormal vital signs:

- Temperature $> 37.8^{\circ}\text{C}$ (100°F)
- Heart Rate > 100 beats/min
- Respiratory rate > 20 breaths/min

Or

Any patient with at least two of the clinical findings:

- Decreased breath sounds
- Crackles (rales)
- Absence of asthma

Routine laboratory testing is not required to establish diagnosis in an outpatient setting. Laboratory testing recommendations differ, though, for patients who are requiring admission to hospital or the intensive care unit for treatment. These include:

- Complete blood count (CBC)
- Basic metabolic panel (BMP)
- Sputum gram stain and culture
- Blood cultures drawn from two separate sites
- Arterial blood gas (ABG) if patient is experiencing respiratory distress

For patients who are being evaluated for HAP, HCAP, or VAP, lower respiratory tract specimens should be cultured. These specimens can come from expectorated sputum or from a bronchoalveolar lavage (BAL) [7].

Special Testing

In patients presenting with severe CAP, special testing for urinary antigens of *Streptococcus pneumoniae* and *Legionella pneumoniae* serogroup 1 has been approved [9]. These tests provide a rapid result, with high specificity and sensitivity, thereby prompting targeted treatment.

Differential Diagnosis

The following might be considered in the differential based upon the patient's signs, symptoms, and comorbidities:

- Influenza
- Viral pneumonia
- Atypical pneumonia
- Acute bronchitis
- COPD exacerbation
- Congestive heart failure (CHF)
- Pleural effusion
- Pulmonary embolism

Treatment

Medications

The most important first determination to make in treatment for a patient with pneumonia is with regard to severity of illness; this should direct the “site-of-care” decision (hospital vs. outpatient, ICU vs. medical ward). Two scoring systems for assisting with the decision on hospitalization are the Pneumonia Severity Index (PSI) and the CURB-65 (confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater). Using one of these criteria, in addition to the clinical picture of the patient, will help guide the appropriate medication and site of treatment [10].

After deciding to admit a patient to the hospital for treatment, the next decision to be made is whether or not the patient needs ICU treatment. According to the Infectious Disease Society of America/American Thoracic Society, there are several clinical criteria that should be considered for ICU admission – meeting three or more of the following:

- Tachypnea, RR > 25 – 30 breaths/min
- PaO_2 or FiO_2 ratio < 250
- Multilobar infiltrates
- Altered mental status/confusion
- BUN > 20 (Uremia)
- White blood cell count $< 4,000$
- Thrombocytopenia, platelet count < 150 k
- Temperature $< 36^{\circ}\text{C}$
- Hypotension/septic shock requiring aggressive fluid hydration [10]

Location of treatment guides antibiotic choice for treatment. In most cases, it can be difficult to establish exact organism(s) affecting a patient; therefore, empiric antibiotic therapy guidelines have been established. Table 1 reviews the most likely organisms found in adults based on patient age and treatment location and provides the recommended empiric therapy with current dosing recommendations [5, 7, 9–11].

Bacterial pneumonia is typically treated for a minimum of 5–14 days, with length of treatment being dependent upon degree of illness at presentation, age, comorbidities, initial response, and whether patient was hospitalized/ICU or not. Attention should be directed at monitoring length of intravenous therapy and recognizing when to switch to oral therapy. Once a patient is clinically improving and requiring no intervention to maintain hemodynamic stability, he/she can safely be switched to oral therapy to complete the course of treatment [10].

In addition to following the most updated guidelines, it is also important to be aware of local epidemiological data, as well as potential antibiotic-resistant changes with typical bacterial pneumonia treatment.

Different antibiotic choices should be made for patients presenting with HCAP, HAP, or VAP. Multidrug-resistant pathogens must be considered with these infections and treated accordingly [7].

Patient Education

Decreasing a patient's chance of becoming ill with pneumonia is an important part of a primary care physician's job [12]:

Counsel patients who smoke on the importance of smoking cessation.

Encourage scheduled vaccinations.

Educate patients on accepted hand hygiene standards: wash hands regularly with soap and warm water for at least 20 s.

Disinfect frequently touched surfaces.

Teach them about cough etiquette: cover the mouth and nose with a tissue when they cough or sneeze and put used tissues in the waste basket.

If they do not have a tissue, teach them to cough or sneeze into their upper sleeve or elbow, not their hands.

Prevention

Immunizations

Vaccinations against preventable illnesses have long been proven effective in overall patient and population morbidity and mortality. Risk for infection with the most common bacterial pneumonia – *Streptococcus pneumoniae* – can be decreased with immunization. According to the Centers for Disease Control, the following vaccinations are important for prevention of pneumonia:

- Pneumococcal
- *Haemophilus influenzae* type b
- Pertussis (whooping cough)
- Influenza (flu) – yearly
- Measles [4, 13]

Atypical Pneumonias

Mycoplasma pneumoniae

General Principles

M. pneumoniae is considered the most common “atypical” pathogen for community-acquired pneumonia (CAP). The prevalence of *M. pneumoniae* in adults with pneumonia can range between 1.9 % and 32.5 %. Outbreaks can occur in institutional settings such as schools and military bases [14]. It is usually transmitted from close person to person contact via respiratory droplets. The average incubation period is around 2–3 weeks [15], and infections tend to occur during the fall and winter.

Approach to the Patient

Diagnosis

History and Physical

The onset of symptoms is typically gradual over the course of several days. Common symptoms include sore throat, muscle pain, headache, malaise, and chills. Patients also complain of a cough that is initially dry, but becomes productive over the course of the infection. The cough is typically worse at night. Sinus pressure and otalgia can also

Table 1 Target treatment, location, and organisms with empiric antibiotic recommendations

Age	Treatment location	Organisms being targeted	Antibiotic
<65, with no risk factors	Outpatient	<i>S. pneumoniae</i> <i>M. pneumoniae</i> <i>C. pneumoniae</i> <i>H. influenzae</i>	Macrolide: <i>Azithromycin</i> , 500 mg orally on day 1 and then 250 mg on days 2–5 <i>Clarithromycin</i> , 250 mg orally twice daily <i>Erythromycin</i> , 250 mg orally every 6 h or 500 mg orally every 12 h <i>Doxycycline</i> , 100 mg orally every 12 h for day 1 and then 100 mg orally daily
>65 +/- risk factors/ comorbidities ^a	Outpatient	<i>S. pneumoniae</i> <i>H. influenzae</i>	Respiratory fluoroquinolone: <i>Levofloxacin (Lеваquin)</i> , 500 mg orally every 24 h for 7–14 days or 750 mg orally every 24 h for 5 days <i>Moxifloxacin</i> , 400 mg orally daily <i>Gemifloxacin</i> , 320 mg orally daily B-lactam plus macrolide: <i>High-dose amoxicillin</i> , 1 g orally three times daily + macrolide (as dosed above) <i>Augmentin</i> , 2,000 mg orally every 12 h + macrolide (as dosed above) Alternatives to B-lactam include: <i>Cefuroxime</i> , 500 mg twice daily Alternative to macrolide: <i>Doxycycline</i> , 100 mg orally twice daily
All ages	Inpatient, non-ICU	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>S. aureus</i>	B-lactam plus macrolide: <i>Cefotaxime (Claforan)</i> , 1–2 g IV/IM every 8 h + azithromycin 500 mg IV for 2 days and then followed by 500 mg orally daily (as dosed above) <i>Ceftriaxone (Rocephin)</i> , 1–2 g IV/IM every 24 h, divided into two doses with max of 4 g/day + azithromycin (as dosed above) <i>Ampicillin</i> , 250–500 mg IV/IM every 6 h + azithromycin (as dosed above) Alternative to macrolide: <i>Doxycycline</i> , 100 mg orally twice daily Respiratory fluoroquinolone: <i>Levofloxacin (Lеваquin)</i> , 500 mg orally every 24 h or 750 mg orally every 24 h <i>Moxifloxacin</i> , 400 mg orally daily <i>Gemifloxacin</i> , 320 mg orally daily
All ages	Inpatient, ICU	<i>S. pneumoniae</i> (including drug-resistant) <i>Legionella</i> <i>H. influenzae</i> Gram-negative enteric organisms	B-lactam plus macrolide: <i>Cefotaxime (Claforan)</i> , 1–2 g IV/IM every 8 h <i>Ceftriaxone (Rocephin)</i> , 1–2 g IV/IM every 24 h, divided into two doses with max of 4 g/day <i>Ampicillin-sulbactam (Unasyn)</i> , 250–500 mg IV/IM every 6 h Plus: <i>Azithromycin</i> 500 mg IV for 2 days, then followed by 500 mg orally every day <i>Levofloxacin (Lеваquin)</i> , 750 IV every 24 h Penicillin allergy: levofloxacin (as dosed above) + aztreonam 1–2 g IV every 8 h

(continued)

Table 1 (continued)

Age	Treatment location	Organisms being targeted	Antibiotic
All ages	Inpatient, ICU	Methicillin-resistant <i>S. aureus</i> (MRSA)	Above treatment for ICU patients plus: Vancomycin 2 g IV daily divided every 6–12 h Linezolid (Zyvox) 600 mg IV or orally every 12 h
All ages	Inpatient/ICU	<i>Pseudomonas aeruginosa</i> , suspected	Antipneumococcal, anti-pseudomonal B-lactam: Piperacillin-tazobactam (Zosyn) 3.375 mg IV every 6 h for 7–10 days Cefepime 1–2 g IV every 8–12 h for 10 days Imipenem 500 mg – 1 g IV every 6 h Plus, either Ciprofloxacin 750 mg IV every 24 h Levofloxacin 750 mg IV every 24 h Penicillin allergy: <i>Aztreonam 1–2 g IV every 6–8 h can be substituted for B-lactam</i>

From Mandell et al. [10]

^aRisk factors and comorbidities

Chronic heart, lung, liver, or renal disease

Diabetes mellitus

Alcoholism

Malignancies

Asplenia

Immunosuppression or use of immunosuppressing drugs

Antimicrobial therapy within previous 3 months

occur. The lung exam can be normal on initial examination, but can develop into scattered rales or wheezes during its progression. Extrapulmonary complications can include maculopapular rashes, arthralgia, aseptic meningitis, transverse myelopathy, and Guillain-Barré syndrome. Since the progression is gradual, a patient may not seek medical attention until a few days to a week.

Laboratory and Imaging, Special Testing

Obtaining a chest radiograph may reveal an infiltrate and may be more prominent if the illness has been present for at least 2 weeks [15]. Cultures from throat, nasopharyngeal, or pleural fluid are considered the “gold standard” for diagnosis. A cold agglutinin test can be used as well and usually appears by the end of the first week of illness. Around 72–92 % of patients with pneumonia and positive cold agglutinins (>1:32) will develop a serologic response to *M. pneumoniae*. Serology can be obtained by complement fixation (CF) or enzyme immunoassay (EIA) [14].

Treatment

Macrolides (erythromycin, azithromycin), tetracyclines (doxycycline), and fluoroquinolones (levofloxacin, moxifloxacin) are the typical therapies used to treat *M. pneumoniae*. Macrolides, particularly azithromycin, tend to be the most active against *M. pneumoniae* in in vitro studies [14]. The duration of antibiotic treatment is typically 5 days of azithromycin or 7–14 days with a tetracycline or fluoroquinolone.

Prevention

Use of appropriate hand hygiene and cough etiquette.

Chlamydial Infection

General Principles

Chlamydia is a gram-negative obligate intracellular organisms. It includes *Chlamydia trachomatis*, *Chlamydia pneumoniae* (formerly *Chlamydia pneumoniae*), and *Chlamydia psittaci*.

C. trachomatis generally presents as a genital tract or ocular infection, but the latter two can present itself as an atypical pneumonia. Around 10 % of cases of community-acquired pneumonia (CAP) are related to *C. pneumoniae* [16].

Approach to the Patient

Diagnosis

History and Physical

Along with other atypical pneumonias, patients can present with productive cough, sore throat [17], sinus congestion, and malaise.

Patients who have psittacosis, caused by *C. psittaci*, tend to have a history with exposure to infected birds. It often presents in young to middle-aged adults. Symptoms include abrupt fever, headache, dry cough, myalgia, and malaise.

Laboratory and Imaging: Special Testing

Chest radiographs may show infiltrates. For diagnosis, oropharyngeal swabs can be used to culture *Chlamydophila* species. Serology tests, EIA, and polymerase chain reaction (PCR) can be used as well [17]. A chest radiograph can reveal interstitial or lobar infiltrates [18]. As with *C. pneumoniae*, *C. psittaci* can be diagnosed with serologic testing.

Treatment

Doxycycline (100 mg orally twice daily) for 10–14 days is the treatment of choice for both *C. pneumoniae* and *C. psittaci*. Macrolides (azithromycin) can be used as well and are usually the choice for empiric treatment for atypical pneumonia [17, 18].

Prevention

Counsel patients about the importance of hand hygiene and cough etiquette [19].

Viral Pneumonia

General Principles

In immunocompetent adults with pneumonia, 18 % had a viral etiology and in 9 % a respiratory virus was the only pathogen identified. Studies that included outpatients found viral pneumonia rates as high as 36 % [10]. In children, viral etiologies for community-acquired pneumonia have been documented in up to 80 % of children younger than 2 years of age. Older children, ages 10–16, have a much lower percentage of viral pathogens [10].

Epidemiology

In immunocompetent adults, the most commonly seen virus is influenza and in children respiratory syncytial virus (RSV). Influenza affects 5–20 % of the US population annually, resulting in 226,000 hospitalizations and 36,000 deaths. RSV accounts for 25–40 % of pneumonia and bronchiolitis in infants [20].

Other common viruses are adenovirus and parainfluenza. Less common viruses include human metapneumovirus, herpes simplex virus, varicella-zoster virus, SARS-associated coronavirus, and measles virus [10].

Transmission

For influenza and RSV droplet and fomite transmission are the most common methods of transmission.

Influenza has an incubation period of 1–3 days, and viral shedding begins before the appearance of symptoms and within the first 24 h of inoculation. Viral shedding peaks on the second day and in healthy adults is no longer detectable 6–10 days later. In children and immunocompromised adults, prolonged viral shedding occurs up to 21 days [21]. RSV viral shedding has a mean of 6.7 days with a range of up to 21 days [20].

Approach to Patient

Diagnosis

History

Infants with RSV initially present with rhinorrhea and decreased appetite followed by a cough within 1–3 days. Soon after the cough, sneezing, fever, and wheezing occur. In very young infants, the only symptoms may be irritability, decreased activity, and apnea [20].

In adults the presentation is similar to that of community-acquired pneumonia, but they may have symptoms of an upper respiratory infection for less than 5 days prior. The symptoms of an upper respiratory infection are rhinorrhea, sore throat, cough, headache, fatigue, and fever [10].

Physical Examination

The physical examination should target the following areas: general appearance and vital signs, head, eyes, ears, nose, and throat, cardiac, and pulmonary and thorax.

General appearance and vital signs are important in discerning the severity of illness. Is the patient lethargic, or confused? Is the patient tachycardic or hypotensive? These are signs of more severe illness and most likely will require hospitalization.

Examination of the head, eyes, ears, nose, and throat can provide evidence for a preceding upper respiratory infection which would indicate a more viral etiology.

On cardiac examination, if there is a new gallop or murmur, then that can indicate increased severity of illness.

Pulmonary and thorax examination are done to look for abnormal breath sounds and evidence of a consolidation or effusion which again can indicate a higher level of severity (Table 2) [10].

Treatment

Medications are given based on etiology of viral pneumonia. Influenza is treated with oseltamivir. Herpes simplex and varicella-zoster are treated with acyclovir. No antiviral treatment of proven

Table 2 Laboratory and imaging recommendations for viral pneumonia [22]

Office-based	
RSV	Antigen detection test supplemented by cell culture Sensitivity of antigen detection tests range from 80 % to 90 % and is reliable in young children Real-time polymerase chain reaction (RT-PCR) assays are more sensitive in older children and adults who may have a lower viral load
Influenza	Rapid influenza diagnostic tests Sensitivity tests range from 50 % to 70 % and specificity tests range from 90 % to 95 %
Hospital-based	
Serology	Complete blood count with differential – to assess severity of infection Electrolytes – to assess hydration, kidney function, and glucose Blood culture for bacterial pathogens
Sputum	Culture and sensitivity for bacterial pathogens
Nasopharyngeal	For RSV and influenza
Chest X-ray	Initially, to assess for presence of consolidation or effusion
CT of chest	For those not responding to initial therapy
Specialized testing	
Serology	Titers for acute and convalescent phase – more important for seroprevalence and epidemiological studies

value is available for other viral pneumonias and a high clinical suspicion for bacterial superinfection should be maintained. For RSV infection, high-risk infants and young children likely to benefit from immunoprophylaxis based on gestational age, certain underlying medical conditions, and RSV seasonality, palivizumab is available. This is a monoclonal antibody given in monthly intramuscular injections during RSV season [22].

Family and Community Issues

Prevention using standard precautions and droplet precautions for at least 5 days is recommended. Wash hands frequently and correctly with soap and water for at least 20 s or use alcohol-based hand gels. Use respiratory hygiene measures such as masks or tissues to cover the mouth for patients with respiratory illness. Avoid sharing cups and utensils. Clean contaminated surfaces.

For influenza yearly vaccination is recommended, and for those whom vaccination is contraindicated, antiviral chemoprophylaxis is recommended. Encourage patients to alert providers when they present for a visit and have symptoms of respiratory infection [20, 21].

Tuberculosis

General Principles

Definition

Tuberculosis is caused by mycobacterium tuberculosis (MTB). This is a large nonmotile rod-shaped obligate aerobic bacterium requiring oxygen for survival. It is commonly introduced to the body through inhalation of droplet nuclei. MTB is usually found in well-aerated upper lobes of the lungs. MTB is a facultative intracellular parasite that is engulfed by macrophages. MTB is released into the alveoli upon death of the macrophage, and the health of the host's immune system is the key factor in expression of TB disease [23].

Epidemiology

One-third of the world's populations is infected with tuberculosis (TB). In 2012, nearly nine million people around the world became sick with TB disease, and there were approximately 1.3 million TB-related deaths worldwide. TB is a leading killer of people who are HIV infected. A total of 9,582 TB cases (or 3.0 per 100,000 persons) were reported in the United States in 2013 [24].

Classification

MTB may be cleared by the host immune system or may progress to latent TB infection or to primary TB. Latent tuberculosis infection (LTBI) means that the host immune system has used the cellular immune system mediated by T-helper cells to contain MTB in a granuloma. 5–10 % of persons with LTBI are at risk of progressing to active TB disease. Immunocompromised persons (HIV, cancer, on immunosuppressing medications) are at greater risk for progression to active TB disease [23].

Approach to the Patient

Diagnosis

Screening

The Centers for Disease Control (CDC) recommends that high-risk populations be screened for latent infection. This includes HIV patients, IV drug users, healthcare workers who serve high-risk populations, and contacts of individuals with pulmonary tuberculosis. A validated risk-assessment questionnaire may be used to identify children who are likely to benefit from screening.

History/Physical Examination

Classic clinical features of pulmonary tuberculosis include chronic cough, sputum production, appetite loss, weight loss, fever, night sweats, and hemoptysis. Extrapulmonary tuberculosis occurs in 10–42 % of patients. In HIV-infected persons, the risk of active tuberculosis increases soon after infection with HIV. Those with a CD4 count of less than 200 cells/mm³ may have an atypical presentation of tuberculosis with subtle infiltrates, pleural effusion, hilar lymphadenopathy, and other forms of extrapulmonary tuberculosis. At CD4 counts of less than 75 cells/mm³, pulmonary findings may be absent and disseminated tuberculosis is more frequent. Disseminated tuberculosis presents as a nonspecific chronic

febrile illness with widespread organ involvement [25].

Laboratory/Imaging

Latent infection is diagnosed using the tuberculin skin test (TST) or interferon-gamma release assay (IGRA). In the TST a small amount of tuberculin is injected into the dermis of the skin creating a small, pale bump. In 2–3 days the TST must be read by a trained healthcare worker. A positive reaction is induration measured in millimeters. Those people who have previously been vaccinated with bacillus Calmette-Guérin (BCG) may have a false-positive TST [26]. IGRA measures a person's immune reactivity to MTB. White blood cells from most persons infected with MTB will release interferon gamma when mixed with antigens derived from MTB. IGRA requires a single patient visit and results can be available within 24 h. Vaccination with BCG does not cause a false-positive IGRA test. However, IGRA is more expensive than TST [26].

Active tuberculosis infection is diagnosed using sputum microscopy and culture along with chest radiography. Three sputum samples are obtained for acid-fast bacilli (AFB). In addition a nucleic acid amplification test (NAAT), a complete blood count, and electrolytes are also ordered. Sputum culture is more sensitive than smear staining, facilitates identification of the mycobacterium species by nucleic acid amplification, and evaluates drug sensitivity. Cultures may take 4–8 weeks [23]. 40–50 % of TB cases are AFB smear-negative and 15–20 % have negative cultures [23]. Chest X-ray is often normal but hilar adenopathy is the most common abnormality found in as much as 65 % of cases. Hilar changes can occur 1–8 weeks after skin test conversion. The findings often resolve within the first year of detecting a positive skin test for primary TB [23]. Pleural effusions are also common in active TB infection.

Treatment

Treatment depends on whether latent or active infection is diagnosed.

Latent infection is treated with isoniazid 300 mg daily for at least 6 months and preferably

for 9 months. Alternative regimens include isoniazid 900 mg and rifapentine 900 mg weekly for 3 months, rifampin 600 mg daily for 4 months, isoniazid 300 mg plus rifampin 600 mg daily for 3 months, or isoniazid 900 mg plus rifampin 600 mg twice weekly for 3 months. All treatment regimens require directly observed therapy – a person employed by the state health department administers and ensures that the patient diagnosed with latent infection takes their medication [25].

Active TB is treated with a four-drug regimen: isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (intensive phase) followed by isoniazid and rifampin for 4 months (continuation phase). Pyridoxine supplementation is recommended to prevent isoniazid-induced neuropathy [25]. If there is multidrug-resistant disease, then initial treatment is based on local disease patterns and pending drug-susceptibility results; later-generation fluoroquinolones are preferred (e.g., moxifloxacin or levofloxacin) [25].

For those with active TB, sputum analysis should be done weekly until sputum conversion is documented. Patients who receive pyrazinamide should undergo baseline and periodic serum uric acid assessments. Those who receive long-term ethambutol therapy should undergo baseline and periodic visual acuity and red-green color perception testing. Also patients should be monitored for toxicity with baseline and periodic liver enzymes, complete blood cell count, and serum creatinine [23].

Currently 17 % of newly diagnosed MTB cases are resistant to one or more first-line agents; isoniazid is the most commonly associated with resistance (10 %). There are strains resistant to both isoniazid and rifampin. In 2009 the World Health Organization estimated that 3.3 % of new TB cases were multidrug resistant [23].

Family and Community Issues

Tuberculosis is required to be reported to local public health authorities. For control of pulmonary tuberculosis, control of infectivity is most efficiently achieved through prompt specific drug treatment. It takes 2–4 weeks for vital organisms to disappear in the sputum and 4–8 weeks to be cleared in the sputum.

Patients with sputum smear-positive TB who live in congregate settings should be placed in an airborne infection isolation room with negative pressure ventilation. Patients should cover their nose and mouth while sneezing. Persons entering rooms where TB patients reside should wear personal respiratory protective devices capable of filtering particles less than 1 μm in diameter. Patients whose sputum is negative for bacteria and who do not cough and who are known to be on adequate drug treatment do not require isolation. Handwashing and good housekeeping practices must be maintained according to policy [19].

Histoplasmosis

General Principles

Definition/Background and Epidemiology

Histoplasmosis is a pulmonary infection caused by *Histoplasma* – a fungus found in soil with large amounts of bird and bat guano [27]. People acquire histoplasmosis after breathing in the microconidia (microspores) from the air, often after participating in activities that disturb the soil. Although most people who breathe in the spores become mildly ill, moderate infection may present with a fever, cough, and/or fatigue. Not every person infected with this spore becomes ill; but in patients with weakened immune systems, the infection can become severe, especially if it becomes a systemic infection [27].

Anyone is susceptible to histoplasmosis if they live or have traveled to an area where *Histoplasma* lives in the soil. In the United States, *Histoplasma* mainly lives in soil in the central and eastern states, especially in the Ohio and Mississippi River valleys. *Histoplasma* has been reported worldwide, with localized foci located in Central America, Europe, Africa, and Asia [28]. Outdoor activities often associated with this fungus include cave spelunking, mining, construction/demolition, excavation, chimney cleaning, and farming/gardening.

There are specific populations who are at higher risk for developing the severe forms of histoplasmosis. This population includes patients who have weakened immune response (HIV/AIDS, previous organ transplant, or who are on chronic immune-suppressing medications), infants, and older adults (55 and older).

Approach to the Patient

Diagnosis

History

A majority of patients either will have no symptoms or will present with subacute influenza-like symptoms – dry cough, fever, myalgias, and fatigue – possibly weeks to months after exposure. In patients with acute illness, presenting symptoms can include high fever, headache, non-productive cough, chills, weakness, pleuritic chest pain, and fatigue. Patients who are immunocompromised are at increased risk for systemic dissemination.

For patients not living in the areas of highest incidence, travel and activity history are important factors in diagnosing this illness.

Physical Examination

In general, the physical exam findings for any acute pulmonary infection will be similar to those for bacterial pneumonia:

- Tachycardia
- Tachypnea, +/- hypoxia
- Decreased or adventitious breath sounds
- Fever $>40\text{ }^{\circ}\text{C}$ ($102\text{ }^{\circ}\text{F}$)
- Possible septic appearance

Laboratory and Imaging

Initial presentation resembles community-acquired pneumonia; therefore, the typical lab tests and imaging are completed at that time. These include a CBC and chest X-ray. Based on initial exam and diagnostic findings alone, most patients will likely be treated for a bacterial CAP; not until the patient's condition has worsened or

initial antibiotic therapy has failed will additional special testing completed.

Chest X-ray findings with acute pulmonary histoplasmosis include patchy or diffuse reticulonodular infiltrates; CT scans show +/- mediastinal or hilar lymphadenopathy [29]. At this point, further testing with treatment plan adjustments is recommended.

Special Testing

Definitive testing for histoplasmosis requires cultured growth of the organism, but this can take 4–6 weeks. Several tests are available for diagnosis of histoplasmosis once it is considered the cause of illness. Table 3 provides a list of testing available [28, 29].

For patients who present with diffuse disease or chronic disease with cavitating lesions, HIV testing or differentiation of cause of immunocompromised state should be completed.

Differential Diagnosis

- Pneumonia – bacterial, atypical, viral
- Sarcoidosis
- Other pulmonary fungal infections – blastomycosis, aspergillosis, coccidioidomycosis
- Lung cancer

Treatment

Medications

Table 4 summarizes the most recent recommendations on treatment of histoplasmosis. There has been a recent change in the treatment recommendations, with increased use of itraconazole.

Table 3 Testing methods for histoplasmosis

Diagnostic method	Comments
Antigen detection Urine Serum	Most sensitive if both urine and blood are tested Acute and chronic infection <i>CON:</i> Not as useful in immunocompromised patients – unable to mount antibody response
Culture	Diagnostic <i>CON:</i> Takes 4–6 weeks for culture to grow

Amphotericin B is still highly recommended for patients with severe pulmonary histoplasmosis and for immunosuppressed patients [11, 28–30].

Prevention and Patient Education

For patients who are immunocompromised, education on high-risk behavior in endemic areas – cave exploration/spelunking, for example – should be provided.

Coccidioidomycosis

General Principles

Definition/Background and Epidemiology

Coccidioides is a dimorphic fungus that is found in the soil of the southwest region of the United States. Coccidioidomycosis is an infection caused by *Coccidioides immitis* or *Coccidioides posadasii* and it is due to the inhalation of spores [31]. The incidence of reported coccidioidomycosis has increased, from 5.3 per 100,000 population in 1998 to 42.6 per 100,000 in 2011 [32]. The reports were from the endemic areas of Arizona, California, Nevada, New Mexico, and Utah. Due to population increases in Arizona and California, the number of infections has risen to about

Table 4 Treatment recommendations for histoplasmosis [28]

Disease acuity	Medications
Mild to moderate	Itraconazole 200 mg orally three times a day for first 3 days and then 200 mg orally once or twice daily for 6–12 weeks
Moderate to severe	Amphotericin B (lipid formulation) 3–5 mg/kg daily IV for 1–2 weeks, followed by itraconazole 200 mg orally three times daily for 3 days and then 200 mg twice daily, for a total of 12 weeks Plus Methylprednisolone 0.5–1 mg/kg daily IV for the first 1–2 weeks of therapy, in patients with ARDS ^a

^aARDS acute respiratory distress syndrome

150,000 per year. It is also known as “valley fever” [33].

Approach to the Patient

Diagnosis

History and Physical Examination

Infection is usually acquired by inhalation of the spores and living around the endemic regions of the southwestern United States. Most commonly, coccidioidomycosis usually presents itself as a self-limiting acute or subacute community-acquired pneumonia. This can develop around 1–3 weeks after infection. The patient can present with respiratory complaints, fatigue, or arthralgia. For some patients, fatigue can last from weeks to months. A few patients (0.5 %) infected may develop a progressive pulmonary or disseminated infection (skin, meninges, and bones). Persons of African or Filipino descent and pregnant, diabetic, and immunosuppressed patients have a higher risk of extrapulmonary complications.

Obtaining an accurate travel history is important. The patient should have been exposed in a region where exposure is possible (southwestern United States). The most common symptom is a respiratory illness, particularly if it involves the lower respiratory tract (i.e., pneumonia). The severity of illness varies from a mild respiratory infection to progressive pulmonary lesions or dissemination. The diagnosis of coccidioidomycosis from other causes is difficult without further testing.

Laboratory and Imaging: Special Testing

A sputum culture growing *Coccidioides* species establishes the diagnosis; however, it could take weeks for the culture to grow. *Coccidioides* species is considered by the Centers for Disease Control (CDC) as a select agent, so there are specific guidelines to oversee its handling [34]. Usually a culture is reserved for patients who require hospitalization. For most patients in an ambulatory setting, serologic testing can be used to diagnose coccidioidomycosis. IgM and IgG anti-coccidioidal antibodies are usually the screening test of choice. The most common chest radiograph

abnormality is airspace opacity (58 % of patients), followed by pulmonary nodules (22.8 %) and a cavitary lesion (13.2 %) [35].

Treatment

If there are no risk factors or no evidence of extensive coccidioidal infection, a majority of patients do not need any antifungal medication. Follow-up visits every 3–6 months for up to 1–2 years are recommended with serial chest radiographs. This is done to document radiographic resolution or to identify extrapulmonary complications. For patients presenting with a severe illness or have risk factors (i.e., pregnancy), it is recommended to start antifungal therapy. Common antifungals used are ketoconazole 400 mg PO (per os/by mouth) daily, fluconazole 400–800 mg by PO daily, and itraconazole 200 mg PO two to three times per day. For pregnant patients, amphotericin B deoxycholate (0.5–1.5 mg/kg intravenously daily or alternate day) or amphotericin B lipid formulation (2.0–5.0 mg/kg or greater intravenously daily) is used as the antifungal of choice. Depending on the severity, the duration of therapy can range from 3 to 6 months to years.

Prevention

Dust control measures in endemic areas such as face masks, air-conditioned cabs, and wetted soil are recommended. Concurrent disinfection of discharges and soiled surfaces and terminal cleaning must be accomplished [19].

Legionnaire’s Disease

General Principles

Definition/Background

Legionnaire’s disease is a waterborne, pulmonary infection caused by a gram-negative, nonspore-forming, aerobic bacterium, *Legionella pneumophila*. This pulmonary infection was coined Legionnaire after an outbreak of pneumonia that occurred in people who had attended a convention of the American Legion in

Philadelphia in 1976. *Legionella* is the third most common cause of pneumonia in immunocompetent patients [36].

The bacteria, *Legionella pneumophila*, loves warm water and can be found naturally in the environment. This bacterium can live in and be spread to humans from hot tubs, cooling towers, hot water tanks, large plumbing systems, or fountains. The bacteria reside on droplets of water (vapor or mist) and are inhaled from environments containing water features as described above. The incubation period is usually 2–14 days before patients notice any symptoms.

This organism should be suspected in a patient who has had progressive pneumonia-like symptoms and is resistant to standard treatment for CAP.

Epidemiology

Since being discovered, an estimated 8,000–18,000 people are hospitalized yearly in the United States with this infection [37]. It is considered the second most common pathogen detected in cases of pneumonia requiring admission to ICUs and is the third most common cause of pneumonia in immunocompetent patients [36, 37]. In the past 10–12 years, there has been a notable increase in the number of cases reported. This infection is most often reported in the fall and summer, peaking in August [37].

Approach to the Patient

Factors to consider in a patient presenting with a pneumonia-type picture and potential diagnosis of *Legionella* are:

- Older age, >65 years of age
- Smoking status
- Male
- COPD or other chronic lung diseases
- Immunosuppressed or immunocompromised
- Lung cancer
- Diabetes mellitus

Diagnosis

Prompt diagnosis and early initiation of therapy are important for adequate treatment of Legionnaire's disease [10].

History and Physical Examination

Many symptoms are associated with Legionnaire's disease, but symptoms that are consistently reported include fever, loss of appetite, dyspnea, cough, headaches, and malaise. Some patients have reported diarrhea, confusion, phlegm, and/or blood-streaked sputum/hemoptysis. In most cases, symptoms have an abrupt start. If not recognized and treated appropriately, a mild infection can rapidly turn fatal.

Additional information to glean from a patient is recent travel history (including hotel or cruise ship stay) within 2 weeks of onset of symptoms [4].

Physical exam findings might include:

- Tachypnea, RR >20
- Temperature >40 °C (102 °F)
- Mental status changes, confusion
- Rales on auscultation
- Relative bradycardia
- Generalized abdominal tenderness

Use of special scoring systems, like the Modified Winthrop-University Hospital Infectious Disease Division's Weighted Point System for Diagnosing Legionnaire's Disease in Adults, can be crucial in early infection to diagnose correctly for treatment of Legionnaire's disease.

Laboratory and Imaging

Chest X-rays of patients with *Legionella pneumoniae* can appear identical to X-rays from other types of bacterial pneumonia; therefore, additional testing is required. In general, if these patients are admitted to the hospital, standard blood work should be collected (CBC, BMP, blood cultures × 2, sputum culture/g stain). If *Legionella* is being suspected, there are several options in testing for this organism – the choice of test will likely be driven by what is available within the clinic or hospital laboratory.

Special Testing

When Legionnaires' disease is suspected, both a urinary antigen test and *Legionella* culture of a respiratory specimen should be ordered. The culture requires a special medium, buffered charcoal yeast extract agar (BCYE). The "gold standard" and most sensitive test is the isolation of the organisms by culture from sputum or BAL. The disadvantage to culturing *Legionella* is that it can take 5–10 days for results and is a meticulous process. Cultures can yield a sensitivity of 20–80 %, with a specificity of 100 % [36, 37].

A serum test has been developed utilizing immunofluorescent assay (IFA) and enzyme-linked immunosorbent assay (ELISA). These tests evaluate and aid in diagnosis when the antibody titer increases greater than fourfold [30]. The time required for adequate testing using this method can take up to 3–8 weeks. Sensitivity and specificity of blood serum testing are 70–100 % and 100 %, respectively [36, 37].

A newer test being used in hospitals is the urinary antigen test. An advantage to this test is a fast turnaround time (<1 h) allowing a shorter time from presentation to diagnosis to targeted treatment. The main disadvantage to using this test for detection of *Legionella* is that it is specific for *L. pneumophila* serogroup 1 only [37]. The urinary antigen test yields a sensitivity and specificity of 80–90 % and >99 %, respectively [36, 37].

Differential Diagnosis

- Bronchitis
- Q-fever
- Acute respiratory distress syndrome
- Pneumonia – viral, atypical, bacterial
- Pleural effusion

Treatment

Medications

First-line treatment for *Legionella pneumoniae* follows the guidelines for bacterial CAP – utilizing either a respiratory fluoroquinolone or azithromycin [4, 11, 37] (Table 5).

Immunizations and chemoprophylaxis

There are no vaccines available for prevention of *Legionella* infections.

Table 5 Antimicrobial therapy for *Legionella pneumoniae*

First line	Levofloxacin 500 mg IV or orally every 24 h for 7 days or 750 mg IV orally every 24 h for 5 days Azithromycin 500 mg IV or 500 mg IV daily for 7–10 days
Second line	Doxycycline 100 mg orally twice daily for 5–7 days

Prevention

The most important factor in preventing infection is continued maintenance of water areas, such as hot tubs and heating/cooling water systems.

Family and Community Issues

Awareness of outbreaks and potential contaminants should be considered when multiple cases within a community are diagnosed with *Legionella*.

Mycobacterium Avium Complex

General Principles

Definition/Background, Epidemiology

Mycobacterium avium complex (MAC) is considered to be a non-tuberculous mycobacteria. MAC includes several subspecies: *Mycobacterium avium* subsp. *avium*, *M. avium* subsp. *silvaticum*, *M. avium* subsp. *hominissuis*, *M. avium* subsp. *paratuberculosis*, *M. avium* subsp. *intracellulare*, *M. arosiense*, *M. chimaera*, *M. colombiense*, *M. marseillense*, *M. timonense*, *M. bouchedurhonense*, and *M. ituriense* [38].

Non-tuberculous mycobacteria (NTM) are normal inhabitants of soil and water. Infections occur because their occupied habitats are shared with humans, animals, fish, and poultry. The habitats include drinking water distribution systems and household plumbing [38].

Patients who receive TNF- α blockers are susceptible to NTM infections and MAC was the most commonly implicated [39].

Approach to the Patient

Diagnosis

History and Physical Examination

Symptoms are nonspecific. Most patients present with a chronic cough, with or without sputum production or hemoptysis, and slowly progressive fatigue or malaise. Constitutional symptoms such as weight loss, fever, and night sweats are less frequent, occurring in 30–50 % of patients, and often indicate advanced disease. Physical examination would be the same as for other types of pneumonia [40].

Laboratory and Imaging

Radiographic abnormalities are more specific and generally follow two distinct patterns. The first is bronchiectasis and nodular lesions mostly involving the lingual and middle lobe. The second is fibrocavitary lesions that mostly involve the upper lobes and resemble pulmonary tuberculosis [40].

Differential diagnoses for cavitary lesions include pulmonary malignancy, sarcoidosis, and infections by non-mycobacterial pathogens such as fungi and *Nocardia* species [40].

Special Testing

Sputum culture is required to make the diagnosis. This can be from at least two separate expectorated sputum samples or at least one bronchial wash or lavage.

Management

Treatment regimens should consist of a rifamycin (rifampin or rifabutin), ethambutol, and a macrolide (azithromycin or clarithromycin). Therapy can be given daily or intermittently depending on the disease type and severity. Nodular bronchiectasis patterns can usually be treated by three times weekly therapy. Cavitary MAC disease involves daily three-drug therapy in addition to IM streptomycin or IM/IV amikacin usually given three times weekly [39].

Pneumocystis Pneumonia

General Principles

Definition/Background, Epidemiology

Pneumocystis pneumonia (PCP) is an opportunistic infection that occurs in immunocompromised patients, such as persons infected with the human immunodeficiency virus (HIV). Patients who are on chronic immunosuppressive therapy are also at risk [41]. Traditionally the nomenclature of the organism was *Pneumocystis carinii pneumonia* (*P. carinii pneumonia*), but the name has been changed to *Pneumocystis jiroveci* to distinguish the species that affects humans. The acronym “PCP” is still used today (*Pneumocystis pneumonia*) to avoid confusion in medical literature [42]. For patients with acquired immunodeficiency syndrome (AIDS), PCP is the most common opportunistic infection, but since the introduction of highly active antiretroviral therapy (HAART), the prevalence of PCP has decreased [43].

Approach to the Patient

Diagnosis

History and Physical

Patients typically have to be in an immunocompromised state to develop *Pneumocystis pneumonia*. The risk of PCP increases as the T-helper cell count (CD4) decreases in a patient. PCP usually occurs when the CD4 count is less than 200 cells/mm³. Symptoms can include a low-grade fever, progressive dyspnea, or a nonproductive cough. Upon physical examination, a patient may have tachycardia and tachypnea. Auscultating the lung can be within normal limits, but may reveal nonspecific crackles.

Laboratory and Imaging, Special Testing

With PCP, a chest radiograph can show perihilar interstitial infiltrates, which may become more dispersed as the disease process worsens. One may also see lung nodules. If the chest radiograph is normal, a high-resolution computed tomography (CT) scan may show ground-glass attenuation

or lesions cystic in nature. For diagnosis of PCP, an induced sputum (with hypertonic saline) culture should be the initial test of choice. If the culture is negative and still suspected, bronchoscopy with bronchoalveolar lavage is indicated [42].

Treatment

In not acutely ill patients with PCP ($\text{PaO}_2 > 70$ mmHg), the treatment of choice is trimethoprim-sulfamethoxazole (TMP-SMX) 15–20 mg/kg PO daily in divided doses. For patients who are acutely ill ($\text{PaO}_2 < 70$ mmHg, unable to take PO), a 3-week corticosteroid taper should be added in conjunction with TMP-SMX. The patient should take prednisone 40 mg twice daily for 5 days, followed by 40 mg daily on days 6–11, and then 20 mg daily on days 12–21. For those patients who cannot tolerate TMP-SMX, alternative regimens include oral primaquine (30 mg daily) plus clindamycin (600 mg three times daily), atovaquone 750 mg orally twice a day [14], trimethoprim (5 mg/kg orally three times daily) plus dapsone (100 mg orally daily) [44], or pentamidine 4 mg/kg intravenously daily. Glucose-6-phosphate dehydrogenase (G6PD) deficiency must be checked prior to using primaquine or dapsone [43]. The duration of treatment should be 21 days. Following therapy, it is recommended for the patient to start on PCP prophylaxis.

Prevention and Community Issues

For patients with HIV, primary prophylaxis should be started when the CD4 count is less than 200 cells/mm³. The prophylactic treatment of choice is TMP-SMX at one tablet (single or double strength) by mouth daily. Other options can include dapsone 100 mg PO daily, atovaquone 1,500 mg PO daily, or pentamidine 300 mg PO nebulized every 4 weeks. With the introduction of HAART, prophylaxis can be discontinued if the CD4 levels go above 200 cells/mm³ [41].

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