ATS Core Curriculum 2014: Part I. Adult Pulmonary Medicine

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Diagnosis and Treatment of *Mycobacterium tuberculosis*

Melissa Nyendak and David Lewinsohn

Epidemiology

Despite advances in case finding and treatment, *Mycobacterium tuberculosis* (Mtb) remains a formidable health threat. In 2012, 8.6 million people became ill with tuberculosis (TB), with 1.3 million deaths making TB second to HIV/AIDS as one of the two major killers worldwide. Individuals with latent TB represent a significant reservoir of TB disease (1), and key challenges for definitive TB control include the identification of individuals who would benefit from prophylactic therapy for latent TB and the early identification and treatment of those with TB disease.

In countries where TB is not endemic, targeted testing for latent TB in populations at high risk of TB exposure is an effective public health intervention. Although there has been a decline in TB in the United States, the Centers for Disease Control and Prevention (CDC) report that foreign-born persons remain disproportionately affected. Specifically, the TB incidence rate in foreign-born persons is 13 times that of the U.S.-born population with California, Texas, New York, and Florida reporting half

of the TB cases. Moreover, the risk of TB reactivation among immigrants is thought to be highest in the first 5 years after arrival; however, this risk may be sustained for up to 9 years (2). Taken together, the CDC recommends additional interventions for the diagnosis and treatment of latent TB in foreign-born persons. A shorter weekly regimen for latent TB with isoniazid and rifapentine is an important advance (3) and may improve the proportion of subjects completing latent TB therapy.

Diagnosis

In TB-endemic countries, identifying individuals who will have a sustained benefit from prophylactic therapy for latent TB is a greater challenge. At present, the World Health Organization (WHO) supports prophylactic therapy with isoniazid in HIV-positive adults and children unlikely to have TB (1). In HIV-negative patients, household contact status alone does not predict the cumulative risk of TB exposure and disease, as a significant proportion of TB transmission occurs outside the home (4). In addition, current diagnostic modalities used for latent TB do not quantify the overall risk of progressing from latent TB to TB in that they do not discern recent from remote infection. Given the difficulty in the individual determination of risk in TB-endemic countries, mass screening and treatment of high-risk

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occupational cohorts has been studied, but has fallen short in terms of producing a durable effect on TB incidence (5). Collectively, additional research in biomarkers of TB bacillary burden as well as more durable pharmacologic prophylactic regimens are needed.

The broad use of molecular technology and the rapid assessment for drug resistance using nucleic acid amplification testing has greatly enhanced the diagnosis of smear-positive and smear-negative TB. To this end, the International Standards for Tuberculosis Care have been updated and offer guidance on the diagnosis and treatment for drug-susceptible and drug-resistant TB (6). In less than 2 hours, the Xpert MTB/RIF test (Cepheid [Sunnyvale, CA] and Foundation for Innovative New Diagnostics [FIND; Geneva, Switzerland]) amplifies the *Mtb* DNA of the *rpo* gene for rifampin resistance and simultaneously discerns TB and potential drug resistance (7). Since 2010, with the support of the WHO, the Xpert MTB/RIF test has been rolled out in TB-endemic countries as a point of care test to be used in the initial TB workup. In this regard, all patients, including children, with suspected TB should submit two sputum specimens for smear microscopy or a single specimen for the Xpert MTB/RIF test (6). Drug susceptibility testing is also recommended at treatment initiation for previously treated patients.

Treatment

For patients without risk factors for drug resistance, directly observed short-course therapy with a WHO-approved first-line regimen includes the initial stage of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by the continuation phase of isoniazid and rifampicin for 4 months. In patients with persistent positive-smear microscopy at 2 and 3 months of therapy, a repeat assessment for drug resistance should be undertaken with the Xpert MTB/RIF test or a line probe assay. Individuals identified with drug-resistant TB will require multi-drug prolonged therapy, and consultation with a specialist is advised to determine the second-line regimen in accordance with WHO recommendations (6).

Future Directions

Current research is focused on shortening TB therapy and novel agents for drug-resistant TB. In this regard, increasing amounts of data are being generated to assess (1) higher doses of rifamycins (2), substitution of moxifloxacin for ethambutol or isoniazid (3), the repurposing of older drugs and drug scaffolds and the development of novel agents such as bedaquiline and delamanid for drug-resistant TB, and (4) the use of adjunctive agents such as verapamil to inhibit bacterial efflux pumps to optimize intracellular drug concentrations (8, 9) (Table 1).

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Hospital-Acquired and Ventilator-Associated Pneumonia

Raj Shah and Richard Wunderink

Diagnosis

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most common lethal nosocomial infections. The diagnosis of HAP/VAP has always been difficult, because clinical criteria are sensitive but not specific. The Clinical Pulmonary Infection Score, a tool designed to assist in the diagnosis of pneumonia by enumerating usual clinical criteria, suffers from similar lack of sensitivity and specificity. Initial hope that the Clinical Pulmonary Infection Score could accurately reflect response to antimicrobial therapy has also been disappointing (1). Biomarkers specific to pneumonia, such as soluble triggering receptor expressed on myeloid cells-1 (s-TREM1), are unavailable outside the research setting. Although general inflammatory biomarkers, including procalcitonin, are also nonspecific, they may be useful to monitor the response to therapy (2).

Surveillance for ventilator-associated complications defined by worsened hypoxemia has been proposed as an alternative to clinical criteria for VAP. Ventilator-associated complications that occur with signs of infection and prescription of new antimicrobial agents are defined as infectious ventilator-associated complications. However, many noninfectious complications of mechanical ventilation mimic ventilator-associated complications and infectious ventilator-associated complications, and both criteria miss cases of VAP (3). Furthermore, “bundles” aimed at decreasing VAP will likely not address the heterogeneous causes of ventilator-associated complications and infectious ventilator-associated complications.

Empiric Treatment

Empiric antimicrobial therapy for patients with HAP/VAP should be based on risk factors for multidrug-resistant (MDR) pathogens because inadequate initial antimicrobial therapy is associated with excess mortality. Current American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines recommend initial treatment with antipseudomonal β -lactams plus antipseudomonal quinolone or aminoglycoside and linezolid or vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) coverage. Kett and colleagues (4) found that compliance with ATS/IDSA guidelines was associated with increased mortality. A major limitation to this study was noncompliance with de-escalation of initial empirical antibiotic regimens. Other investigators found that late antibiotic de-escalation for suspected VAP but negative cultures increases superinfections and may increase mortality (5).

Treatment of Specific Pathogens

Methicillin-Resistant *Staphylococcus aureus*

Linezolid should be considered the drug of choice in the treatment of MRSA HAP/VAP. A large randomized clinical trial (6) and meta-analysis (7) demonstrated superior clinical response to linezolid compared with vancomycin. Lack of a mortality difference in a study of linezolid compared with vancomycin may be due to the use of linezolid as salvage treatment in vancomycin failures. Telavancin, a newly released agent, is also more effective than vancomycin for MRSA pneumonia, particularly in organisms with a high minimal inhibitory concentration (8). Telavancin should be used with caution in patients with kidney injury because of increased rates of renal replacement therapy and mortality. Finally, ceftaroline, a cephalosporin with *in vitro* activity against MRSA, is approved by the U.S. Food and Drug Administration for community-acquired pneumonia but no clinical trial data for HAP/VAP.

Multidrug-resistant Gram Negatives

The overwhelming majority of intensive care unit patients with HAP/VAP have MDR risk factors. The incidence of MDR and extensively drug-resistant (XDR) gram-negative pneumonia is increasing, potentially compromising guideline-based therapy. Given the large variety of organisms and resistance mechanisms, antibiotic choices should be based on local patterns. MDR and XDR pathogens often require treatment with more toxic and low-efficacy drugs such as colistin and tigecycline. Aerosolized antibiotics for VAP caused by MDR pathogens may be an attractive option to increase efficacy and decrease toxicity, but significant issues with delivery device, dose, and choice of agent remain (Table 1).

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Pneumonia in the Immunocompromised Host

Carl Koch and Alison Morris

Immune Function

Pneumonia in immunosuppressed hosts is a frequent cause of hospital and intensive care unit admissions (1). Various causes of immunosuppression result in dysfunction of different arms of the immune system and influence the susceptibility to different types of infections. Immune suppression can be divided into major categories such as primary immune deficiencies, acquired immune deficiencies, and therapy-associated or induced immunosuppression (2–4). Broadly, loss of cellular immunity predisposes to viral, fungal, and intracellular infections. Reduced humoral immunity increases susceptibility to encapsulated bacteria. Susceptibility to opportunistic infection is the result of net immune suppression across or within multiple arms of the immune system (2, 3). For example, HIV causes a profound loss of systemic CD4⁺ T lymphocytes, but is also associated with impaired B-cell function and abnormalities in innate and adaptive immune responses in the lung (5). The immunosuppressive regimens given in solid organ transplantation also result in broad immune defects including impairment in T- and B-cell function as well as neutrophil and macrophage abnormalities (3, 6).

Opportunistic Pathogens

Immunosuppressed hosts are at risk of a wide range of infectious organisms including common and rare bacteria, fungi, viruses, and parasites. In individuals who have undergone solid organ transplantation, the risk for specific organisms depends on time elapsed since transplantation (3, 4). For example, in the early postoperative period, typical pathogens are nosocomial, multidrug-resistant bacteria. Early donor- and recipient-derived

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infection is seen. Immunosuppression peaks in the first 3 to 6 months after transplantation, when major complications from opportunistic infections are most likely to occur (3, 6, 7). Use of prophylaxis for *Pneumocystis jirovecii*, cytomegalovirus, and *Aspergillus* decreases the risk of these infections (3). Community-acquired respiratory viruses, endemic mycoses and atypical molds, *Nocardia*, *Listeria*, as well as reactivation of latent infection from tuberculosis, cytomegalovirus, and parasites may be seen (3, 4, 7).

As immunosuppression is typically decreased at 6 months, infection favors community-acquired bacterial and viral pathogens. In HIV, risk of specific infections shifts according to the CD4⁺ cell count with increased risk of bacterial pneumonia and tuberculosis seen even with high CD4⁺ cell counts while risk for pathogens such as *Pneumocystis* and atypical *Mycobacteria* occurs at low CD4⁺ cell counts (5).

Treatment

Because the range of pathogens that can cause pneumonia in the immunocompromised host is extensive and because pneumonia in this population can be rapidly fatal, broad empiric therapy is generally started immediately (1, 7, 8). Typical signs and symptoms of inflammation such as fever and leukocytosis may not be present, and serological testing and severity scoring systems are often not reliable (7). Blood and sputum cultures should be obtained before administration of antibiotics, although this should not delay early initiation of therapy. If risk factors for tuberculosis exist, the patient should be placed in respiratory isolation. Chest computed tomography may provide diagnostic benefit as characteristic findings such as diffuse infiltrates or focal cavitation may raise suspicion for particular pathogens. Early bronchoscopy is usually warranted, with biopsies if appropriate (3, 7). Empiric antibiotic therapy should remain broad including treatment of community-acquired pneumonia as well as consideration of coverage for likely fungal, viral, or mycobacterial pathogens.

Coverage of resistant organisms is often warranted as many immunosuppressed patients have a greater risk of drug resistance based on underlying immune defects, history of antibiotic exposure, and hospitalizations (1, 4, 8). Additional coverage tailored to specific risk factors (i.e., *Pneumocystis* coverage in an HIV-infected individual with CD4⁺ cell count less than 200 cells/ μ l) should be given until a definitive diagnosis is obtained. The differential diagnosis should also include noninfectious processes (3, 7). Once a specific pathological agent is identified, therapy can be narrowed (Table 1).

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Lung Cancer: Diagnosis, Staging, and CT Screening

Kolene McDade and Gaetane Michaud

Epidemiology

Lung cancer remains the leading cause of mortality in cancer patients within the United States. Unfortunately, overall 5-year survival remains only 15% despite advances. Lung cancer screening programs hope to reduce the 75% of patients who present with incurable, advanced disease. By definition they seek to identify disease at an earlier stage with subsequent improvement in mortality. Until recently, however, a suitable screening test in lung cancer had yet to be identified. Failure of prior screening trials with imaging modalities was attributed to the low resolution of chest radiography (CXR).

The National Lung Screening Trial (NLST) was a randomized controlled study involving 53,456 patients, comparing low-dose computed tomography (LDCT) with CXR annually for 3 years. Patients between the ages of 55 and 74 years with a minimum of 30 pack-years of smoking and no more than 15 years since quitting were enrolled (1). This decreased lung cancer-specific mortality by 20%, equating to 6.3 fewer lung cancer deaths per 10,000 person-years. This primarily corresponded to the number of stage I tumors identified. The American Thoracic Society currently recommends annual screening for these high-risk patients (2). Ongoing work needs to be completed to improve the selection criteria for appropriate patients to increase screening effectiveness and to reduce unnecessary cost and risk to patients.

Diagnosis and Staging

With respect to lung cancer diagnosis and staging, the American College of Chest Physicians published their revised guidelines (3). In brief, suspected lung cancer must undergo further evaluation in a timely and efficient manner to determine the pathology and the stage at presentation as this significantly impacts on management. Clinical suspicion must always be confirmed by histopathology, with the specific intention to prove the highest potential stage of malignancy. Diagnosis and staging activities are typically completely simultaneously. Initial workup includes CT of the chest with intravenous contrast, whole body positron emission

tomography (PET), integrated CT/PET, bone scan (if PET is unavailable or if there is a high rate of false positive PET scans in the population), magnetic resonance imaging (MRI), or CT of the brain.

For a new solitary peripheral lesion without evidence of mediastinal involvement with high risk for lung cancer, the primary lesion need not be sampled before definitive resection as this is unlikely to change management. Preoperative mediastinal staging in this group of patients remains controversial. In the case of larger, more central lesions or those with other high-risk features it may be reasonable to consider preoperative invasive staging as there is an increased risk of occult mediastinal extension (4).

If an advanced stage is suspected on the basis of imaging, then it is recommended that the highest stage lesion be sampled by the least invasive means. The 2013 guidelines suggest equipoise between surgical staging with mediastinoscopy and comprehensive endoscopic staging by endobronchial and/or endoscopic ultrasound. The seventh edition of the *TNM Classification of Malignant Tumors* has made several revisions in particular to the tumor size criteria, additional lung nodules in same or different lobes as well as pleural involvement (5). The revisions to the TNM classification reflect more accurately the overall prognosis and optimal management (Table 2).

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Lung Cancer: Management

Amit Mahajan and Colleen Channick

Management of lung cancer has evolved tremendously over the past decade. The advent of targeted lung cancer therapy has prolonged survival and improved the quality of life of many patients. However, before developing an appropriate treatment plan, it is essential to determine tumor cell type, subtype, genotype, and stage, in addition to assessing the patient's overall medical condition.

Stage I and II Non–Small Cell Lung Cancer

Surgical resection is clearly the preferred treatment for patients with early-stage non–small cell lung cancer (NSCLC) who are operative candidates. Lobectomy is generally preferred over sublobar resection, although the latter is being actively studied in T1a tumors. For patients deemed poor candidates for surgical resection, radiotherapy offers an efficacious alternative. Data suggest that stereotactic body radiotherapy has a high rate of primary tumor control and fewer treatment sessions than conventional radiotherapy (1). Adjuvant chemotherapy is currently recommended in stage II disease as it has demonstrated a survival advantage (2). For patients with completely resected stage I NSCLC, adjuvant chemotherapy or radiation is not currently recommended.

Stage III and IV Non–Small Cell Lung Cancer

Stage IIIA NSCLC constitutes a heterogeneous group ranging from occult micrometastatic N2 involvement detected at surgery to unresectable, bulky nodal disease. For patients with good performance status and minimal weight loss, treatment with combination platinum-based chemotherapy and radiotherapy results in greater survival than radiation alone. The debate continues regarding the value of surgery in this group. For Stage IIIB disease, treatment with concurrent chemoradiotherapy is the preferred approach.

In patients with stage IV NSCLC, a platinum-based chemotherapy regimen is recommended based on data showing a survival advantage and improved quality of life over best supportive care (3). The choice of the particular regimen is guided by the histological cell type, with the use of pemetrexed limited to patients with nonsquamous NSCLC. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), improves survival combined with carboplatin and paclitaxel in patients with stage IV NSCLC nonsquamous histology, good performance status, lack of brain metastases, and no hemoptysis (4).

Epidermal Growth Factor Therapies

Epidermal growth factor receptor (EGFR) mutations and the ELM-4ALK translocation mutation are the most established targets of management of advanced-stage NSCLC. First-line therapy for patients with EGFR mutations currently involves use of the tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib. The incidence of EGFR mutations in never-smokers is 50% in Western populations and as high as 80% in individuals of East Asian descent. Patients with stage IV NSCLC with EGFR mutations treated with tyrosine kinase inhibitors versus platinum-doublet were found to have improved progression-free survival, increased response rates, more favorable side effect profiles, and improved quality of life (4). Crizotinib, a small molecule tyrosine kinase inhibitor, is specific for the inhibition of ALK and was approved for the treatment of patients with EML4-ALK mutations.

Small Cell Lung Cancer

Small cell lung cancer is categorized as either limited or extensive stage. Combination therapy with platinum-based chemotherapy

and concurrent radiation therapy in limited-stage disease doubles the 5-year survival compared with chemotherapy alone (13.3 vs. 5.7%) (5). Although concurrent chemoradiation is associated with increased hematological toxicity and esophagitis, this approach has been shown to yield a superior survival advantage over a sequential regimen. Platinum-based chemotherapy is the treatment of choice for extensive-stage small cell lung cancer. Prophylactic cranial irradiation is offered if the patient achieves at least a partial response to therapy and has been shown to prolong survival in this group.

Palliative care plays a critical role in the management of the physical symptoms and emotional distress inherent in lung cancer. Data show improved quality of life and longer survival when palliative care is integrated early in conjunction with standard oncologic care (6) (Table 2).

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Pleural Effusions and Hemothorax

A. Christine Argento and Momen Wahidi

Epidemiology

Pleural effusions pose a common problem, with more than 1.5 million pleural effusions being diagnosed each year in the United States. There are many causes of pleural effusion including diseases of the pleura or underlying lung, systemic conditions, organ dysfunction, and drugs (1). Pleural fluid normally originates from the capillaries of the parietal pleura, is filtered into the pleural space, and then absorbed by the parietal pleural lymphatics. Effusions accumulate whenever the rate of pleural fluid formation exceeds that of its reabsorption, usually the result of simultaneous malfunction of both processes creating an imbalance (2).

Diagnosis and Treatment

Pleural effusions can cause dyspnea, cough, and chest pain. Virtually all patients who are found to have a new effusion should undergo a diagnostic and/or therapeutic thoracentesis. The pleural fluid should be analyzed to differentiate transudates from exudates using Light's criteria to help narrow the differential diagnosis. The most common causes of transudative pleural effusions are congestive heart failure, hepatic hydrothorax, and nephrosis for which treatment consists of managing the underlying disease. Exudative effusions are most commonly parapneumonic or malignant.

Parapneumonic effusions occur in about 40% of patients with pneumonia. These pleural effusions should be drained and the fluid analyzed quickly to discern simple from complicated parapneumonic effusions and empyema. A complicated parapneumonic effusion is defined as having a pH less than 7.2, glucose less than 60, or lactate dehydrogenase greater than 3 times the upper limit of normal. An empyema is defined as having purulence or an organism on gram stain.

If either a complicated parapneumonic effusion or an empyema is present, drainage via chest tube is indicated to prevent lung entrapment and need for surgical intervention. In an effort to fully evacuate the pleural space in patients with complicated parapneumonic effusions, Rahman and colleagues found that intrapleural administration of tissue plasminogen activator (tPA) and DNase together was superior to double placebo, tPA alone, or DNase alone at improving drainage, resulting in improved chest X-ray (CXR) on Day 7 and reduced frequency of surgical referrals and length of hospital stay (3).

Malignant Pleural Effusions

Malignant pleural effusions are due to lung cancer, breast cancer, or lymphoma in about 75% of cases. The presence of malignant pleural effusion upstages lung cancer to stage IV and portends a poor prognosis compared with those without it. Although up to 25% of patients are initially asymptomatic from the effusion, nearly all patients will eventually experience significant dyspnea. Despite management of the underlying malignancy with chemotherapy and/or radiation therapy, malignant pleural effusions tend to persist or recur and require local palliative procedures to control symptoms (4).

Treatment options for these patients include repeated thoracentesis, pleurodesis, or placement of an indwelling tunneled pleural catheter. Pleurodesis is commonly performed through a small- or large-bore chest tube with talc or doxycycline, with success rates of 68–97 and 61–88%, respectively (5). Pain and fever are the most common side effects of chemical pleurodesis. Indwelling tunneled pleural catheters have become instrumental for the treatment of malignant pleural effusions. They are well tolerated and approximately half will effectively cause spontaneous pleurodesis at 56 days (6). In 2011, Reddy and colleagues published a pilot protocol combining talc poudrage administered during medical thoracoscopy with placement of an indwelling tunneled pleural catheter to promote rapid pleurodesis. They achieved successful pleurodesis at a mean of 16.65 days and shortened length of hospital stay (4).

Hemothorax

Hemothorax is a pleural effusion whereby the hematocrit of the pleural fluid is greater than 50% of the hematocrit of peripheral blood. Hemothorax is most commonly seen with trauma or secondary to thoracic procedures and is present in about 20% of patients with traumatic pneumothorax (5). On occasion, hemothorax can accumulate from malignancy, endometriosis, or supratherapeutic anticoagulation. Blood entering the pleural space coagulates rapidly, which causes loculations and organization, making them difficult to evacuate and treat. Timely insertion of a chest tube is important; the tube can be small bore if the patient is stable or must be large bore if the patient is unstable. Chest tubes remove blood, can stop bleeding by improving pleural apposition, allow accurate volume assessment, and decrease risk of infection/empyema and fibrothorax formation. If the fluid accumulation is greater than 1,500 ml or more than 200 ml/hour then surgical intervention is recommended (Table 3).

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Environmental Lung Diseases, Hypersensitivity Pneumonitis, and Workplace Disability

William Beckett and Gautam George

Pneumoniconioses

Pneumoniconioses are lung diseases caused by inorganic dust. They can cause obstructive, restrictive, or mixed patterns of pulmonary dysfunction; and can increase the risk of bronchogenic carcinoma.

Crystalline silica causes silicosis and is associated with mining, construction, sandblasting, and rock dust exposure. Clinical manifestations include bronchitis, nodular fibrosis, lymphadenopathy, and restrictive or obstructive changes. Bilateral rounded opacities with apical predominance and calcified lymph nodes may be seen on imaging. Silicosis has no specific treatment and increases the risk of tuberculosis (1).

Asbestos pleural diseases include benign pleural plaques, rounded atelectasis, benign exudative effusions, and diffuse malignant mesothelioma. Asbestos bodies indicate exposure but not disease. Mesothelioma is not associated with tobacco use and may first present as pleural thickening or exudative effusion. Tissue

(or sometimes pleural fluid cytology) is necessary for diagnosis. Plasma fibulin-3 is under study as a biomarker. Asbestosis is usually a patchy fibrosis with bibasilar preponderance (2). Special iron staining may be needed to reveal asbestos bodies on biopsy, bronchoalveolar lavage (BAL), or sputum.

Chronic beryllium disease occurs in less than 10% of those exposed. Exposure occurs in aerospace, nuclear, ceramics, metal recycling, and machining industries. Disease may present decades after exposure. Imaging shows reticulonodular changes, adenopathy, and ground glass opacities. Biopsy typically yields noncaseating granulomas. Granulomatous pulmonary disease with potential exposure history should lead to beryllium lymphocyte proliferation assays on BAL and/or serum, which tests for T-lymphocyte sensitization to beryllium. Treatment includes systemic steroids and immunosuppressants (3).

Work-related Asthma

Work-related asthma comprises work-exacerbated asthma—defined as previously existing asthma made worse by workplace exposure—and occupational asthma, caused by exposure at the workplace. Occupational asthma is classified as either sensitizer-induced or irritant-induced asthma (4). Sensitizer-induced occupational asthma is caused by exposure to a known immunologically sensitizing substance. Irritant induced asthma and reactive airway dysfunction syndrome (RADS) are nonimmunologic and result from inhaling irritants, including strong acids or bases. RADS and irritant-induced asthma are on the same spectrum. RADS is usually considered to result from a single very heavy inhalation exposure, whereas irritant asthma may result from multiple, repeated lower level exposures. Episodic wheeze, reversible airflow obstruction, and positive methacholine challenge may be seen. Peak flows lower at work than at home, and specific IgE by skin prick or blood testing, can aid in diagnosis of sensitizer-induced asthma. Patients respond to usual asthma medications, but the mainstay of treatment is removal of the patient from exposure.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is an immune parenchymal disease caused by repeated inhalation of biologic or chemical substances in a susceptible individual. Examples include thermophilic *Actinomyces* in hay, nontuberculous mycobacteria in hot tubs, fungi in humidifiers, and proteins from birds. Symptoms include fever, chills, cough, and dyspnea. Imaging shows alveolar filling or inflammation and reticulonodular opacities. Leukocytes and acute-phase reactants may be high. Biopsy typically shows cellular bronchiolitis and lymphocytic infiltrates. The notable pulmonary function abnormality is a reduced diffusing capacity. The treatment is removal of the offending antigen and administration of corticosteroids. Recurrent episodes can lead to chronic fibrotic disease (5).

Disability

A disability evaluation should address the specific criteria of the disability program (e.g., Social Security disability, state or provincial

Worker Compensation, or Veterans Administration) and include the following: diagnosis, description on how symptoms affect work and daily living, and copies of spirometry/pulmonary function tests results measured after optimal medical therapy (6) (Table 3).

Author disclosures are available with the text of this article at www.atsjournals.org.

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Table 1. Key updates: pulmonary infections

Tuberculosis

- The diagnosis and treatment of latent tuberculosis (TB) among foreign-born persons residing in the United States is recommended because of the elevated incidence rates of TB disease in this population
- In TB-endemic countries, the WHO supports prophylactic therapy for latent TB with isoniazid in HIV-positive adults and children unlikely to have TB disease
- Molecular technology for the rapid assessment of TB and drug resistance has greatly enhanced TB diagnosis and therapy
- Drug-resistant TB remains a concern and when identified, should be managed with multidrug prolonged therapy in consultation with a specialist

Hospital- and ventilator-associated pneumonia

- Use of the Clinical Pulmonary Infection Score or the ventilator-associated complications algorithm has not substantially improved the accuracy of the difficult diagnosis of hospital-acquired and ventilator-associated pneumonia
- Biomarkers such as procalcitonin can complement clinical assessments to assess adequacy of response to therapy for serious infections such as hospital- and ventilator-associated pneumonia
- Empiric antimicrobial therapy for patients with HAP/VAP should be based on risk factors for multidrug-resistant pathogens and local epidemiology because inadequate initial antimicrobial therapy is associated with excess mortality
- De-escalation of antibiotics based on culture results is critical to avoid complications of broad-spectrum empirical treatment of HAP/VAP

Opportunistic Infections

- Immune suppression confers susceptibility to pneumonia via loss in cellular immunity, humoral immunity, and physical barriers due to primary, acquired, and therapy-associated immune deficiencies and treatments
- Specific pathogenic susceptibilities vary in immunosuppressed hosts related to variations in net immune suppression, such as time elapsed posttransplantation or CD4⁺ cell count in HIV
- A high index of suspicion is critical in the early diagnosis and treatment of pneumonia in the immunosuppressed host because of a lack of typical signs and symptoms of infection
- Early empiric antibiotic therapy should remain broad and must consider individual risk for atypical and resistant organisms, as well as fungal, viral, and atypical mycobacterial pathogens

Definition of abbreviations: HAP/VAP = hospital-acquired pneumonia/ventilator-associated pneumonia; HIV = human immunodeficiency virus; WHO = World Health Organization.

Table 2. Key updates: lung cancer

Diagnosis

- Lung cancer screening saves lives in high-risk patients. The data support screening for patients who are 55–74 yr old and who are current or former smokers (quit within the past 15 yr) with a minimum 30 pack-year smoking history
- For a new solitary peripheral lesion without evidence of mediastinal involvement with high risk for lung cancer, the primary lesion need not be sampled before definitive resection as this is unlikely to change management
- If an advanced stage is suspected on the basis of imaging, then it is recommended that the highest stage lesion be sampled by the least invasive means. There is equipoise between full endoscopic staging and mediastinoscopy for advanced-stage disease
- Consider all patients for comprehensive staging regardless of age, comorbid illness, or limited cardiopulmonary reserve

Management

- Surgical resection is the gold standard treatment for early-stage non-small cell lung cancer, but alternative therapies include focused radiation therapy, or stereotactic body radiotherapy (SBRT) for individuals who are not surgical candidates
- Molecular analysis for determining EGFR and EML4-ALK mutations provides essential information in determining therapy
- Small cell lung cancer categorized as limited stage shows a doubling in 5-yr survival when combination therapy with platinum-based chemotherapy and concurrent radiation therapy are used

Definition of abbreviation: EGFR = epidermal growth factor receptor.

Table 3. Key updates: pleural and environmental disease**Pleural disease**

- For complicated parapneumonic effusions and empyema, combination of intrapleural tPA and DNase was found to be superior to either drug alone at improving drainage leading to decreased length of hospital stay and need for surgical intervention
- Tunneled pleural catheters relieve dyspnea for malignant pleural effusions as effectively as pleurodesis, and in half of patients, the tunneled pleural catheter with drainage alone will induce spontaneous pleurodesis by Day 56
- Rapid pleurodesis using a combination of talc poudrage and insertion of a tunneled pleural catheter reduces time to pleurodesis to 16.65 d

Environmental lung disease

- Silicosis, caused by inhaled mineral dust containing crystalline silica, can lead to nodular fibrotic interstitial disease with enlarged lymph nodes
- Occupational asthma may be caused by inhaled sensitizing agents or severe or recurrent exposures to irritants and can be caused by work or may represent a workplace exacerbation of underlying asthma
- A person with hypersensitivity pneumonitis may present with fever and an abnormal chest radiograph. Common causes are indoor birds or hot tubs

Definition of abbreviation: tPA = tissue plasminogen activator.