

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

Module 3. Internal medicine.
Contents module № 4.
Theme 3. Management of patients
with infiltrative pulmonary darkening

Guidelines for students and interns

Модуль 3. Внутрішні хвороби.
Змістовний модуль №4.
Тема 3. Ведення хворих
з затемненням в легенях

Методичні вказівки
для студентів та лікарів-інтернів

Рекомендовано
вченою радою ХНМУ.
Протокол № 11 від 21.12.2011.

Харків
ХНМУ
2012

Module. Internal medicine. Contents modul №4. Theme 3. Management of patients with infiltrative pulmonary darkening / Comp. Oleg Babak, Olexandr Bilovol, Galyna Fadeyenko et al. – Kharkiv: KNMU, 2012. – 36 p.

Compilers Oleg Babak
 Olexandr Bilovol
 Galyna Fadeyenko
 Vira Shkolnik
 Yuliya Shaposhnikova
 Valeriya Nemtsova
 Natalya Zheleznyakova

Модуль. Внутрішні хвороби. Змістовний модуль №4. Тема 3. Ведення хворих з затемненням в легенях: метод. вказ. для студентів та лікарів-інтернів / упор. О.Я. Бабак, О.М. Біловол, Г.Д. Фадеєнко та ін. – Харків: ХНМУ, 2012. – 36 с.

Упорядники Бабак О.Я.
 Біловол О.М.
 Фадеєнко Г.Д.
 Школьник В.В.
 Шапошнікова Ю.М.
 Немцова В.Д.
 Железнякова Н.М.

Module title: Current practice of internal medicine.

1. Theme title: Management of patients with with infiltrative pulmonary darkening.

2. Theme specifications.

3. Theme aims.

4. The aim of this module is to provide the student with an opportunity to keeping patient in pulmonology clinic.

5. Learning outcomes.

Students should be able to describe and define:

1. What is mean by the term fever of unknown origin.
2. The basic mechanisms of fever of unknown origin.
3. The student should have an understanding of the pathophysiology of these diseases and be able to develop a comprehensive differential diagnosis. The student will understand the appropriate diagnostic testing. The assessment, diagnosis and management the patient with fever of unknown origin.
4. Risk Factors for Infective Endocarditis.
5. Clinical manifestetions of Infective Endocarditis.
6. Diagnosis of Infective Endocarditis.
7. Treatment of Infective Endocarditis.
8. Etiology and types of lung cncer.
9. Clinical picture of lung cancer.
10. Diagnosis and treatment of lung cancer.
11. Etiology of tuberculosis.
12. Types of tuberculosis.
13. Clinical picture in tuberculosis.
14. Diagnosis in tuberculosis.
15. Treatment and prevention in tuberculosis.
16. Complications of tuberculosis.
17. Etiology and pathogenesis of sarcoidosis.
18. Clinical picture and diagnosis of sarcoidosis.
19. Treatment of sarcoidosis.
20. Etiology and clinical picture of lung abcess.
21. Diagnosis of lung abcess.
22. Differential diagnosis between lung abcess, eisoinphilic granuloma and tuberculosis.
23. Treatment of lung abcess.

**TESTS AND ASSIGNMENTS FOR SELF-ASSESSMENT BASIC LEVEL
OF KNOWLEDGE: MULTIPLE CHOICE QUESTIONS
(CHOOSE THE CORRECT ANSWER/STATEMENT)**

1. A 25-year-old male non-smoker presents with progressive shortness of breath for the past 6 months. Physical examination shows decreased breath sounds over both lower lobes. Chest X-ray demonstrates emphysematous changes in both lower lobes. Past history is insignificant except for an episode of neonatal jaundice, which resolved promptly on the 4th day with phototherapy. Routine blood count and differential counts are normal. Which of the following will help in establishing the diagnosis of his condition?

- | | |
|---|---------------------------------------|
| <i>A. Open lung biopsy.</i> | <i>C. Video assisted lung biopsy.</i> |
| <i>B. Estimating alpha -1 antitrypsin levels.</i> | <i>D. High resolution CT scan.</i> |
| | <i>E. ECG monitoring.</i> |

2. Three weeks after visiting her grandmother dying from a respiratory tract infection, a healthy 5-year-old girl develops a fever along with wheezing. On physical examination her temperature is 37.9 C. Her lung fields are clear to auscultation but there are expiratory wheezes. A chest radiograph reveals a solitary 2 cm peripheral mid-lung nodule and marked hilar lymphadenopathy. Laboratory studies show Hgb 13.6 g/dL, platelet count 183,600/microliter, and WBC count 5480/microliter. These findings are most consistent with infection by which of the following organisms?

- | | |
|---------------------------------------|--|
| <i>A. Mycobacterium tuberculosis.</i> | <i>E. Bacteroides fragilis.</i> |
| <i>B. Candida albicans.</i> | <i>F. Streptococcus pneumoniae.</i> |
| <i>C. Coccidioides immitis.</i> | <i>G. Respiratory syncytial virus.</i> |
| <i>D. Aspergillus flavus.</i> | |

3. A 65-year-old man has had no major medical problems prior to the past year, when he noted increasing malaise along with an 8 kg weight loss. He is a non-smoker. He currently does not have fever, cough, dyspnea, or any respiratory difficulties. On physical examination, he has non-tender supraclavicular lymphadenopathy. The lungs are clear to auscultation. A chest x-ray shows multiple solid nodules ranging from 1 to 3 cm scattered throughout all lung fields. No infiltrates or areas of consolidation are noted. Laboratory studies show Hgb 11.6 g/dL, Hct 34.7%, MCV 83 fL, and WBC count 6280/microliter. Which of the following pathologic processes in his lungs is most likely to account for these findings?

- | | |
|------------------------------------|--|
| <i>A. Pulmonary infarctions.</i> | <i>D. Nocardia asteroides infection.</i> |
| <i>B. Foreign body aspiration.</i> | <i>E. Silicosis.</i> |
| <i>C. Metastatic carcinoma.</i> | |

4. One fourth of patients with Upper respiratory tract infections cough is seen beyond 1 month of diseases due to if these patient have.

- A. A history of asthma, allergy or atopy (hay Fever).
- B. Immunocompromised (HIV).
- C. If the patient is on immunosuppressor medicines.
- D. A&B are correct.
- E. All of above are correct.

5. Cough is an early manifestation of many respiratory diseases and endotracheal lesion what of listed conditions may support a diagnosis of lung cancer together with chronic cough.

- A. Hemoptysis, frequent upper respiratory tract infection, very high fever and chest pain.
- B. Chest pain, hemoptysis, low grade fever and night sweats.
- C. Localized wheeze, decrease lung sounds on auscultation and high fever.
- D. Hemoptysis, frequent upper respiratory tract infections, clubbing of fingers and localized wheeze low lung sound together with unexplained weight loss.
- E. Chest pain, hemoptysis, low grade fever and night sweats. low vocal feramitus and general weekness.

6. Diffuse interstitial pneumonitis with interstitial edema, varying degrees of fibrosis, lymphoid cell infiltration, and alveolar-cell hyperplasia are pathological features typical of

- A. CMV.
- B. Influenza virus.
- C. RSV.
- D. Parainfluenza virus.
- E. Paramyxovirus.

7. A 50-year-old woman has lived in Oslo, Norway all her life and worked as a seamstress. She is a non-smoker, but she has had increasing shortness of breath, fever, weight loss, and night sweats for the past 4 months. On physical examination her temperature is 37.6 C. There are fine rales auscultated in all lung fields. A chest radiograph reveals hilar lymphadenopathy and a reticulonodular pattern of small densities in all lung fields. She demonstrates anergy by skin testing to mumps and Candida antigens. A transbronchial biopsy is performed that microscopically shows numerous small pulmonary interstitial non-caseating granulomas. Which of the following is the most likely diagnosis?

- A. Histoplasmosis.
- B. Adenocarcinoma.
- C. Sarcoidosis.
- D. Usual interstitial pneumonitis.
- E. Berylliosis.

8. A 55-year-old man with a 55 pack year history of smoking cigarettes has recently experienced an episode of hemoptysis along with his usual cough. On physical examination there are no abnormal findings. He has a sputum cytology examination performed that on microscopic examination shows atypical cells with hyperchromatic nuclei and orange-pink cytoplasm. Laboratory studies show a serum calcium of 11.3 mg/dL, with phosphorus 2.1 mg/dL. Which of the following chest radiographic findings is this man most likely to have?

- A. Large hilar mass.
- B. Pneumonia-like consolidation.
- C. Peripheral nodule.
- D. Carinal compression.
- E. Left pleural thickening.

9. A 40-year-old woman has had a high fever for a week, accompanied by a cough productive of yellowish sputum. On physical examination her temperature is 38.2 C. There are diffuse rales in all lung fields. Her chest radiograph reveals patchy infiltrates in all lung fields, and there is a 4 cm rounded area of consolidation in the left upper lobe that has an air-fluid level. Examination of her sputum reveals numerous neutrophils. Which of the following infectious agents is most likely causing her pulmonary disease?

- A. *Staphylococcus aureus*.
- B. *Aspergillus niger*.
- C. *Mycobacterium tuberculosis*.
- D. *Mycoplasma pneumoniae*.
- E. Adenovirus.

10. A 38-year-old previously healthy woman has had a worsening non-productive cough for the past 4 days. On physical examination her temperature is 38.3 C. A chest radiograph shows patchy infiltrates and diffuse interstitial markings. Laboratory studies show a sputum gram stain with mixed flora. Her Hgb is 12.9 g/dL, platelet count 229,450/microliter, and WBC count 5815/microliter. Her cold agglutinin titer is elevated. Following a course of erythromycin therapy, she improves, with no complications. Which of the following infectious agents is most likely to cause the pulmonary disease seen in this woman?

- A. *Nocardia asteroides*.
- B. *Mycoplasma pneumoniae*.
- C. *Mycobacterium kansasii*.
- D. Respiratory syncytial virus.
- E. *Chlamydia psittici*.

6. Indicative reading list.

Kasper Dennis L., Braunwald Eugene, Fauci Anthony, Hauser Stephen, Longo Dan, Jameson J. Larry. Harrison's Principles of Internal Medicine, 16th ed. McGraw-Hill Professional, 2004. 2800 p.

7. Indicative syllabus.

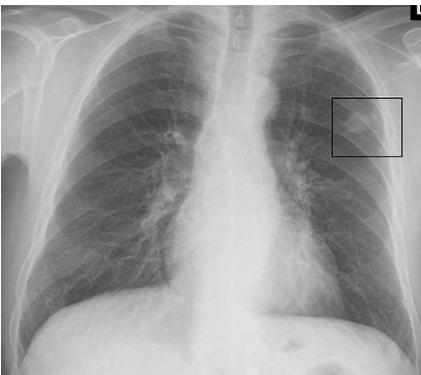
LUNG CANCER

Lung cancer is a disease of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, which is the invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are **carcinomas of the lung**, derived from epithelial cells. Lung cancer the most common cause of cancer-related death in men and women, is responsible for 1.3 million deaths worldwide annually. The most common symptoms are shortness of breath, coughing (including coughing up blood), and weight loss.

The main types of lung cancer are *small cell lung carcinoma* and *non-small cell lung carcinoma*. This distinction is important, because the treatment varies; non-small cell lung carcinoma (NSCLC) is sometimes treated with surgery, while small cell lung carcinoma (SCLC) usually responds better to chemotherapy and radiation. The most common cause of lung cancer is long-term exposure to tobacco smoke. The occurrence of lung cancer in nonsmokers, who account for as many as 15% of cases, is often attributed to a combination of genetic factors, radon gas, asbestos, and air pollution including second hand smoke.

Lung cancer may be seen on chest radiograph and computed tomography (CT scan). The diagnosis is confirmed with a biopsy. This is usually performed by bronchoscopy or CT-guided biopsy.

Treatment and prognosis depend upon the histological type of cancer, the stage (degree of spread), and the patient's performance status. Possible treatments include surgery, chemotherapy, and radiotherapy. Survival varies, depending on stage, overall health, and other factors, but the overall five-year survival rate for all persons diagnosed with lung cancer is 14%.

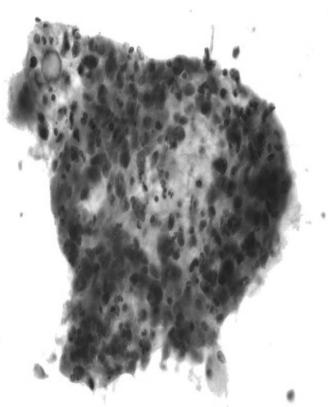
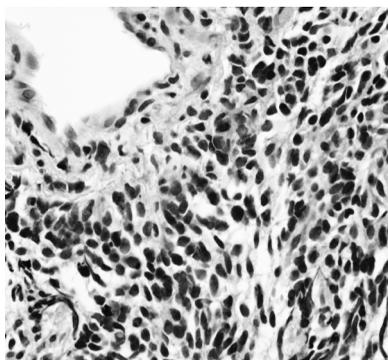


Symptoms. There are no symptoms associated with early stage lung cancer. The American Cancer Society lists the following symptoms associated with advanced stage lung cancer. A physician should be consulted if they persist. It is important to note, however, that these symptoms may be caused by factors unrelated to cancer:

- Persistent cough.
- Sputum streaked with blood.
- Chest pain.
- Voice change.
- Recurrent pneumonia or bronchitis.

Detection. Despite ongoing investigation into screening technology, research shows that lung cancer death rates have not improved. At the time they are diagnosed, the majority of lung cancers have progressed to an advanced state. Lung cancer screening is not currently routine practice. The disease is sometimes caught in its early stages by tests that are performed for other reasons. The most common methods of lung cancer detection include:

- chest x-ray;
- [chest CT](#) (computer tomography) scan;
- [bronchoscopy](#) (insertion of a tube into the bronchi), and;
- [sputum cytology](#) (examination of cells in the phlegm).



Treatment

As our focus is on the biology of the cancers and their treatments, we do not give detailed treatment guidelines. Instead,

we link to organizations in the U.S. that generate the treatment guidelines.

The National Comprehensive Cancer Network (NCCN) lists the following treatments for lung cancer:

- Surgery
- Radiation Therapy
- Chemotherapy

Chemotherapy. The term chemotherapy, or chemo, refers to a wide range of drugs used to treat cancer. These drugs usually work by killing dividing cells. Since cancer cells have lost many of the regulatory functions present in normal cells, they will continue to attempt to divide when other cells do not. This trait makes cancer cells susceptible to a wide range of cellular poisons.

The chemotherapy agents work to cause cell death in a variety of ways. Some of the drugs are naturally occurring compounds that have been identified in various plants and some are man-made chemicals. A few different types of chemotherapy drugs are briefly described below. For more information on a particular type of drug, choose from the list below.

• **Antimetabolites:** Drugs that interfere with the formation of key bio-molecules within the cell including nucleotides, the building blocks of DNA. These drugs ultimately interfere with DNA replication and therefore cell division.

• **Genotoxic Drugs:** Drugs that damage DNA. By causing DNA damage, these agents interfere with DNA replication, and cell division.

• **Spindle Inhibitors:** These agents prevent proper cell division by interfering with the cytoskeletal components that enable one cell to divide into two.

• **Other Chemotherapy Agents:** These agents inhibit cell division by mechanisms that are not covered in the three categories listed above.

• **Glossary of Chemotherapy Agents:** An easy to use table of chemotherapy drugs including trade name, generic name, and type. With links to more information.

Normal cells are more resistant to the drugs because they often stop dividing when conditions are not favorable. Not all normal dividing cells escape however, a fact that contributes to the toxicity of these drugs. Cell types that are normally rapidly dividing, such as those in the bone marrow and in the lining of the intestine, tend to be hardest hit. Death of the normal cells produces some of the common side-effects of chemotherapy.

Combination therapy, as is used for small cell lung carcinoma, has some effect in treating metastatic carcinoids. However, the response rate is only approximately 50%. Adjuvant chemotherapy along with postoperative radiation has been advocated for atypical lesions associated with mediastinal nodal extension.

Radiation therapy. Carcinoid tumors are generally radioresistant. Anecdotal reports describe tumor responses in inoperable cases. Radiation therapy is recommended for postoperative management of incompletely resected atypical lesions and in the presence of mediastinal nodal involvement. Data supporting the efficacy of this treatment are lacking.

Adenoid cystic tumors are radiosensitive and postoperative radiotherapy is of value.

Surgical Care.

Endoscopic resection: Bronchoscopic resection. This procedure is plagued by incomplete tumor removal, with frequent recurrence due to extraluminal tumor bulk, often with limited tumor visibility and accessibility via the bronchoscope. It also carries a high risk of hemorrhage.

Bronchoscopic resection is warranted to alleviate bronchial obstruction in patients in whom thoracotomy is prohibitive. Additionally, occasional preoperative use of this technique may allow assessment of the reversibility of distal parenchymal damage. Finally, the technique of argon-beam electrocoagulation may be very useful for bronchoscopic control of bleeding prior to definitive resection.

Endoscopic resection: Neodymium:Yttrium-aluminum-garnet laser. The Nd: YAG laser reduces the risk of hemorrhage-related complications by means of photocoagulation. It is not recommended as a primary mode of tumor removal. Rarely, the Nd: YAG laser is applicable to a polypoid, easily accessible lesion on a narrow, uninvolved stalk.

Surgical resection. In the past, as many as 62% of patients with bronchial adenomas underwent lobectomy or pneumonectomy. They frequently had significant delays in their diagnosis and had complete obstruction of a bronchus with distal parenchymal destruction. Complete tumor removal, removal of all destroyed lung parenchyma, nodal dissection, and preservation of functional parenchyma are the goals of resectional therapy

Surgical procedures overview. Preoperative endobronchial resection may be used as part of the preparation of the patient for surgical resection

Bronchotomy/bronchial wedge resection. Polypoid tumors are accessible by bronchotomy and excision, including the involved bronchial wall. Bronchotomy ensures complete resection (as compared to endoscopic removal, which may not), and wedge resection may be appropriate for small lesions lacking atypia. These procedures may be accompanied by nodal sampling.

Lobectomy with or without sleeve resection. This is the most commonly used technique because most tumors occur in or near the origin of lobar bronchi. Concomitant sleeve resection of the main stem is required if the orifice of the lobar bronchus or the adjacent main stem bronchus is involved. Bron-

choplastic adjuncts may permit preservation of normal distal parenchyma and are preferred over pneumonectomy when possible

Pneumonectomy. Pneumonectomy may be required if all lobes on the involved side are destroyed because of a proximal obstructing lesion

Preoperative risk assessment. Preoperative testing is done to assist in risk assessment and to identify areas of concern that can be mitigated prior to surgical intervention. Tests and evaluations other than those listed below may be appropriate as suggested by history, physical examination, and laboratory testing findings, but all of the listed tests are not routinely required.

History (focusing on factors known to affect operative risk) may include the following:

- Chronic obstructive pulmonary disease.
- Chronic renal failure.
- Cor pulmonale.
- Diabetes mellitus.
- Myocardial infarction within 6 months or unstable ischemic disease.
- Severe cardiac valvular disease.
- Congestive heart failure.

Sarcoidosis. Sarcoidosis is idiopathic, and the trigger antigen inciting granuloma formation is unknown. The prominent involvement of the pulmonary system has raised the possibility of inciting airborne agents, but to date no infectious organism has been definitely linked.

Primarily, the lymphoreticular system is affected with prominent cervical and mediastinal lymphadenopathy (eg, perihilar and peritracheal nodes) and also involvement of the smaller scattered lymphatic collections in solid organs (eg, spleen, liver) and lymphoid tissue surrounding glandular organs such as the parotid and lacrimal glands.

Debate continues as to whether sarcoidosis results from a dysfunctional immune system or a secondary response to environmental antigens. Sarcoid granulomas may be seen in solid organs such as liver, kidney, and spleen. Neurosarcoidosis results from nervous system involvement by sarcoid granulomas.

The clinical features of neurosarcoidosis depend on the site of neuraxis involved. While neurosarcoidosis most commonly affects the central nervous system, a subset of patients demonstrate predominantly peripheral nervous system involvement. This may manifest as a myopathy and/or a peripheral neuropathy depending on the distribution of the granulomas.

The true incidence of peripheral neuropathy in sarcoidosis is unknown, as a significant number of asymptomatic patients with sarcoidosis have subclinical peripheral nerve involvement.

Neuropathy occurs via 2 mechanisms. The tissue can be involved directly: in muscle, a slow and indolent myositis results, and in the nerve, a neu-

ropathy results. Granulomas in the nerve are seen most often in the perineurium and the epineurium, with local effects leading to axonal damage.

Some studies reveal sparing of the endoneurium, but others show prominent infiltration of the endoneurium, suggesting that all 3 nerve layers may be involved. Occasionally, myelin loss is prominent, with appearance of myelin ovoids. Whether the latter are due to compression from the granulomas, a result of regional toxic effects, or a result of specific targeting of the myelin sheath is unclear.

Tajima suggested a predominance of helper T cells in the sarcoid granulomas. Inflammation of the vasa nervorum or the arterioles to the muscles can result in ischemic injury or severe vasculitic neuropathy. A significant increase of the HLA allele DQB 1 0602 has been reported in sarcoidosis patients with small fiber neuropathy and this allele has been associated with severe course of disease.

Peripheral nerve injury from these mechanisms may result in a diffuse polyneuropathy, mononeuritis multiplex, focal mononeuropathies, or polyradiculopathy from involvement of spinal root sheaths. The spinal root sheaths are an extension of the pachymeninges and a tissue for which sarcoid granulomas have a particular predilection.

Differential Diagnoses

Acute Inflammatory Demyelinating Polyradiculoneuropathy	Metabolic Neuropathy
Alcohol (Ethanol) Related Neuropathy	Neuropathy of Leprosy
Cauda Equina and Conus Medullaris Syndromes	Neurosarcoidosis
HIV-1 Associated Acute/Chronic Inflammatory Demyelinating Polyneuropathy	Neurosyphilis
HIV-1 Associated Distal Painful Sensorimotor Polyneuropathy	Peroneal Mononeuropathy
HIV-1 Associated Multiple Mononeuropathies	Ulnar Neuropathy
Lyme Disease	
Metabolic Myopathies	

Laboratory Studies. The diagnosis of peripheral neuropathy as a result of sarcoidosis is determined by establishing in the first instance the presence of a peripheral neuropathy; excluding the common causes of peripheral neuropathy, such as hyperglycemic states, deficiencies of vitamins, and presence of toxins such as heavy metals; and establishing a pathological diagnosis of noncaseating granulomas, in neural or extraneural sites.

- A complete blood (CBC) count with differential may show a variety of changes, as follows.

- Normochromic normocytic anemia.
- Megaloblastic changes.
- Basophilic stippling.
- Other dyshematopoietic states.
- Lymphopenia.

- Erythrocyte sedimentation rate (ESR) may be elevated in systemic sarcoidosis.

- Blood tests are needed to look at hyperglycemic states, which include fasting glucose and glycosylated hemoglobin. If these results are normal, then a 2-hour oral glucose tolerance test is needed.

- Serum B-12 level: If on the low side, this should be pursued by serum homocysteine and methylmalonic acid levels (expected to be high in B-12 deficiency).

- Serum protein immune electrophoresis.

- Angiotensin-converting enzyme (ACE) level is rarely elevated in isolated neuropathy but may be elevated in systemic sarcoidosis.

- Blood urea nitrogen (BUN), creatinine, and serum calcium should be checked to rule out long-standing metabolic derangements, which can result in neuropathy. Hypercalcemia is a known feature of systemic sarcoidosis, and abnormalities of renal functions may reflect a wider involvement of the primary disease process.

- Liver function tests (eg, alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase), if abnormal, may reflect systemic involvement by either sarcoidosis or other diseases.

Imaging Studies.

Chest radiography.

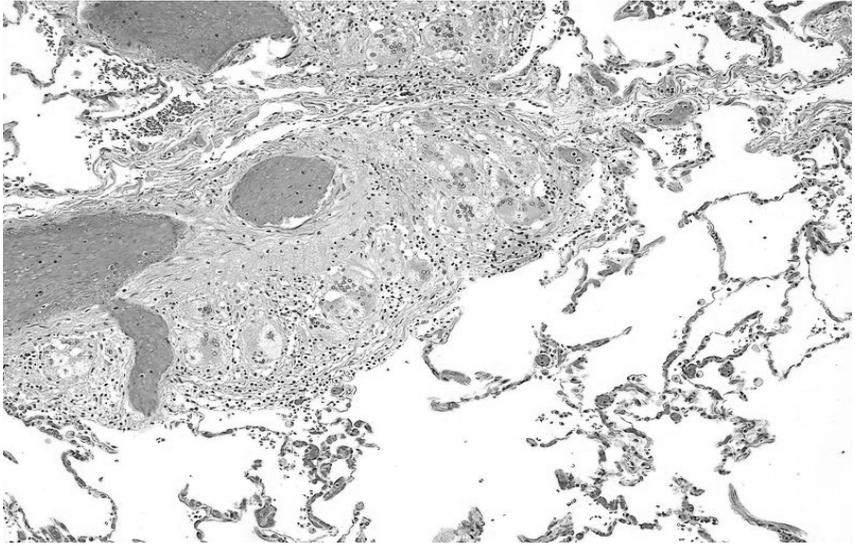
- Chest radiography often demonstrates perihilar lymphadenopathy or the interstitial lung disease of sarcoidosis. These abnormalities also may suggest lymphoma or other systemic diseases.

- Whole-body gallium scan or fluorodeoxyglucose positron emission tomographic (FDG-PET) scan may reveal otherwise occult/subclinical areas of involvement, demonstrate the extent of disease, and suggest possible biopsy sites.

- Magnetic resonance imaging (MRI) with gadolinium is helpful in identifying T2 enhancement of nerve roots, plexuses, and limb nerves.

MR peripheral nerve imaging may occasionally show a diffusely enlarged nerve as a soft tissue mass.

- Imaging studies of specific regions or organ systems may be appropriate if clinically indicated or if laboratory testing suggests involvement of that organ system.



Other Tests

- Skin tests: Cutaneous anergy can be seen in systemic or active pulmonary sarcoidosis. However, it almost never occurs in pure neurosarcoidosis.
 - Lumbar puncture
 - Cerebrospinal fluid (CSF) examination shows pleocytosis and elevated protein if the root sheaths or meninges are involved.
 - In these situations, glucose levels also may be reduced.
 - When the involvement is purely peripheral (eg, diffuse peripheral neuropathy or myopathy), the CSF findings are normal.
 - Small fiber neuropathy may be evaluated by thermal threshold testing (TTT). On the other hand, sympathetic skin responses and cardiac autonomic testing (by Ewing test and ¹²³I-MIBG myocardial scanning) have been reported to have limited diagnostic value for evaluation of small fiber neuropathy.
 - Electrophysiologic studies
- Nerve conduction studies (NCS) and electromyography (EMG) demonstrate the presence of a diffuse, focal, or multifocal neuropathy or polyradiculopathy.
- EMG often shows features of an axonal polyneuropathy.
 - Studies investigating the involvement of small diameter unmyelinated fibers have revealed a higher prevalence of small-fiber neuropathy than previously recognized.

Medical Care

- Several treatment regimens have been proposed. However, no definitive treatment exists.
- Corticosteroids remain the standard treatment, although response may be slow. Patients resistant to oral steroids may improve with pulsed intravenous methylprednisone.
- Immunosuppressants such as cyclosporine, methotrexate, and cyclophosphamide have been used with varying results. Almost all of the studies completed to date have involved treatment of CNS sarcoidosis as opposed to peripheral neuropathy. A case report of a biopsy-proven axonal sensorimotor polyneuropathy responding to intravenous immunoglobulin while unresponsive to steroid therapy is described.
- There have been anecdotal reports of improvement with intravenous immunoglobulin therapy in patients who have failed conventional therapy. The response may be related to amelioration of vasculitic neuropathy.
- Anecdotally, small fiber neuropathy has been reported to show improvement following treatment with infliximab.
- Local radiation therapy may resolve nerve swelling.

Medications used in peripheral neuropathy in sarcoidosis are the same as those used for systemic sarcoidosis and neurosarcoidosis. Immunosuppressants are used to dampen or alter the inflammatory activity. Corticosteroids are preferred. Nonresponders may be tried on cyclosporine, azathioprine, and/or methotrexate.

Immunosuppressants. Corticosteroids alter the immune response and may lead to resolution of the granulomas in sarcoidosis.

Prednisone. Most commonly used oral corticosteroid, works by altering immune system and decreasing inflammatory reaction that is responsible for granuloma formation. Tuberculin skin test required prior to commencing high daily dose of steroids. Improvement has been reported in patients with sarcoid polyneuropathy who received methylprednisolone (1 g/wk for 8 wk) when oral prednisone failed. Disagreement exists about optimal treatment dose, but doses listed here are typical.

Often, high dose required for period of 2-4 wk before tapering; taper may need to be continued for several months before discontinuing treatment altogether.

Occasionally, patients respond to methylprednisolone pulses when high-dose oral prednisone fails.

Adult. Starting dose: 1-1.5 mg/kg/d PO; maintain this dose until clinical response seen; taper dose steadily over several months, titrating according to clinical response

Pediatric. 1-1.5 mg/kg/d PO; if possible, taper dose more quickly in children because of adverse metabolic and growth retardation effects of steroids

Cytotoxic drug/immunosuppressants. These agents suppress the auto-immune response, which is responsible for granuloma formation.

Cyclosporine. Used extensively in patients who have undergone transplant. Beneficial effects in neurosarcoidosis have been reported, although most clinical scenarios have been central and not peripheral nervous system sarcoidosis. Has been found to have benefit when used as adjunct to steroids in 6 patients with CNS involvement of neurosarcoidosis.

Adult. 3-6 mg/kg/d PO.

Pediatric. Administer as in adults.

Azathioprine. Cytostatic drug that has been used in numerous immune-mediated diseases. Active component, 6-mercaptopurine, thought to have immune-suppressing properties.

Adult. 50 mg/d PO initial dose; increase by 50 mg/d weekly to desired dose 3-5 mg/kg PO usual dose for all age groups.

Pediatric. Administer as in adults.

Methotrexate. Antimetabolite used as immunosuppressant, often in rheumatoid arthritis, severe psoriasis, and certain neoplastic diseases. Its use for neurosarcoidosis has not been tested sufficiently.

Adult. Dosage varies depending on indication; one patient with CNS neurosarcoidosis has been described as benefiting from 25 mg/wk PO Starting dose varies from 25-30 mg/d PO; maintenance dose usually 7.5 mg/d

Pediatric. Not established except for cancer therapy

Lung abscess

Lung abscess is necrosis of the pulmonary tissue and formation of cavities (more than 2 cm) containing necrotic debris or fluid caused by microbial infection.

This pus-filled cavity is often caused by aspiration, which may occur during altered consciousness. Alcoholism is the most common condition predisposing to lung abscesses.

Lung abscess is considered primary (60%) when it results from existing lung parenchymal process and is termed secondary when it complicates another process e.g. vascular emboli or follows rupture of extrapulmonary abscess into lung.

Causes

Conditions contributing to lung abscess

- Aspiration of oropharyngeal or gastric secretion
- Septic emboli
- Necrotizing pneumonia
- Vasculitis: Wegener granulomatosis
- Necrotizing tumors: 8% to 18% are due to neoplasms across all age groups, higher in older people; primary squamous carcinoma of the lung is the commonest.

Organisms. In the post-antibiotic era pattern of frequency is changing. In older studies anaerobes were found in up to 90% cases but they are much less frequent now.

- Anaerobic bacteria: Peptostreptococcus, Bacteroides, Fusobacterium species;
- Microaerophilic streptococcus : Streptococcus milleri
- Aerobic bacteria: Staphylococcus, Klebsiella, Haemophilus, Pseudomonas, Nocardia, Escherichia coli, Streptococcus, Mycobacteria;
- Fungi: Candida, Aspergillus
- Parasites: Entamoeba histolytica,

Symptoms. Onset of symptoms is often gradual, but in necrotizing staphylococcal or gram-negative bacillary pneumonias patients can be acutely ill. Cough, fever with shivering and night sweats are often present. Cough can be productive with foul smelling purulent sputum ($\approx 70\%$) or less frequently with blood (i.e. hemoptysis in one third cases) Affected individuals may also complain of chest pain, shortness of breath, lethargy and other features of chronic illness.

Patients are generally cachectic at presentation. Finger clubbing is present in one third of patients¹. Dental decay is common especially in alcoholics and children. On examination of chest there will be features of consolidation such as localised dullness on percussion, bronchial breath sound etc.

Diagnosing



Chest X ray and other imaging studies. Abscess is often unilateral and single involving posterior segments of the upper lobes and the apical segments of the lower lobes as these areas are gravity dependent when lying down. Presence of air-fluid levels implies rupture into the bronchial tree or rarely growth of gas forming organism.

Laboratory studies. Raised inflammatory markers (high ESR, CRP) are usual but not specific. Examination of sputum is important in any pulmonary infections and here often reveals mixed flora. Transtracheal (via bronchoscopy) aspirates can also be cultured. Fibre optic bronchoscopy is often performed to exclude obstructive lesion; it also helps in bronchial drainage of pus.

Management. Broad spectrum antibiotic to cover mixed flora is the mainstay of treatment. Pulmonary physiotherapy and postural drainage are also important. Surgical procedures are required in selective patients for drainage or pulmonary resection.

Antibiotic Therapy. Standard treatment of an anaerobic lung infection is clindamycin (600 mg IV q8h followed by 150-300 mg PO qid). This regimen has been shown to be superior over parenteral penicillin in published trials. Several

anaerobes may produce beta-lactamase (eg, various species of *Bacteroides* and *Fusobacterium*) and therefore develop resistance to penicillin.

Although metronidazole is an effective drug against anaerobic bacteria, the experience with metronidazole in treating lung abscess has been rather disappointing because these infections are generally polymicrobial. A failure

- Rate of 50% has been reported.
- In hospitalized patients who have aspirated and developed a lung abscess, antibiotic therapy should include coverage against *S aureus* and *Enterobacter* and *Pseudomonas* species.
- Ampicillin plus sulbactam is well tolerated and as effective as clindamycin with or without a cephalosporin in the treatment of aspiration pneumonia and lung abscess.
- Moxifloxacin is clinically effective and as safe as ampicillin plus sulbactam in the treatment of aspiration pneumonia and lung abscess.

Duration of therapy

- Although the duration of therapy is not well established, most clinicians generally prescribe antibiotic therapy for 4-6 weeks.
- Expert opinion suggests that antibiotic treatment should be continued until the chest radiograph has shown either the resolution of lung abscess or the presence of a small stable lesion.
- The rationale for extended treatment maintains that risk of relapse exists with a shorter antibiotic regimen.

Response to therapy

- Patients with lung abscesses usually show clinical improvement, with improvement of fever, within 3-4 days after initiating the antibiotic therapy. Defervescence is expected in 7-10 days. Persistent fever beyond this time indicates therapeutic failure, and these patients should undergo further diagnostic studies to determine the cause of failure.

- Considerations in patients with poor response to antibiotic therapy include bronchial obstruction with a foreign body or neoplasm or infection with a resistant bacteria, mycobacteria, or fungi.

- Large cavity size (ie, > 6 cm in diameter) usually requires prolonged therapy. Because empyema with an air-fluid level could be mistaken for parenchymal abscess, a CT scan may be used to differentiate this process from lung abscess.

- A nonbacterial cause of cavitory lung disease may be present, such as lung infarction, cavitating neoplasm, and vasculitis. The infection of a preexisting sequestration, cyst, or bulla may be the cause of delayed response to antibiotics.

Surgical Care. Surgery is very rarely required for patients with uncomplicated lung abscesses. The usual indications for surgery are failure to respond to medical management, suspected neoplasm, or congenital lung malformation. The surgical procedure performed is either lobectomy or pneumonectomy.

When conventional therapy fails, either percutaneous catheter drainage or surgical resection is usually considered. Endoscopic lung abscess drainage is considered if an airway connection to the cavity can be demonstrated. Success of this treatment represents an additional option other than percutaneous catheter drainage or surgical resection.

TUBERCULOSIS

Tuberculosis or **TB** (short for *tubercles bacillus*) is a common and often deadly infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* in humans. Tuberculosis usually attacks the lungs but can also affect other parts of the body. It is spread through the air when people who have the disease cough, sneeze, or spit. Most infections in humans result in anasymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of its victims.

The classic symptoms are a chronic cough with bloodtinged sputum, fever, night sweats, and weight loss. Infection of other organs causes a wide range of symptoms. Diagnosis relies on radiology (commonly chest X-rays), a tuberculin skin test, blood tests, as well as microscopic examination and microbiological culture of bodily fluids. Treatment is difficult and requires long courses of multiple antibiotics. Contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in (extensively) multi-drug-resistant tuberculosis. Prevention relies on screening programs and vaccination, usually with Bacillus Calmette-Guérin vaccine.

One third of the world's population are thought to be infected with *M. tuberculosis*, and new infections occur at a rate of about one per second. The proportion of people who become sick with tuberculosis each year is stable or falling worldwide but, because of population growth, the absolute number of new cases is still increasing. In 2007 there were an estimated 13.7 million chronic active cases, 9.3 million new cases, and 1.8 million deaths, mostly in developing countries. In addition, more people in the developed world are contracting tuberculosis because their immune systems are compromised by immunosuppressive drugs, substance abuse, or AIDS. The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5-10% of the US population test positive.

Tuberculosis classification

The current clinical classification system for tuberculosis (TB) is based on the pathogenesis of the disease.

Classification System for TB

Class	Type	Description
0	No TB exposure Not infected	No history of exposure Negative reaction to <u>tuberculin</u> skin test
1	TB exposure No evidence of infection	History of exposure Negative reaction to tuberculin skin test <u>Ghon complex</u>
2	TB infection No disease	Positive reaction to tuberculin skin test Negative bacteriologic studies (if done) Fibrocaceous cavitary lesion (usually in upper lobe of lungs)
3	TB, clinically active	<i>M. tuberculosis</i> cultured (if done) Clinical, bacteriologic, or radiographic evidence of current disease
4	TB Not clinically active	History of episode(s) of TB or Abnormal but stable radiographic findings Positive reaction to the tuberculin skin test Negative bacteriologic studies (if done) and No clinical or radiographic evidence of current disease
5	TB suspect	Diagnosis pending TB disease should be ruled in or out within 3 months

When the disease becomes active, 75% of the cases are pulmonary TB, that is, TB in the lungs. Symptoms include chest pain, coughing up blood, and a productive, prolonged cough for more than three weeks.

Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, pallor, and often a tendency to fatigue very easily.

In the other 25% of active cases, the infection moves from the lungs, causing other kinds of TB, collectively denoted extrapulmonary tuberculosis. This occurs more commonly in immunosuppressed persons and young



children. Extrapulmonary infection sites include the pleura in tuberculosis pleurisy, the central nervous system in meningitis, the lymphatic system in scrofula of the neck, the genitourinary system in urogenital tuberculosis, and bones and joints in Pott's disease of the spine. An especially serious form is disseminated TB, more commonly known as miliary tuberculosis. Extrapulmonary TB may co-exist with pulmonary TB as well.

Signs and symptoms

History

• Patients with miliary tuberculosis (TB) may experience progressive symptoms over days to weeks or occasionally over several months. Symptoms include the following:

- Weakness, fatigue (90%)
- Weight loss (80%)
- Headache (10%)

Physical

- Signs of miliary TB include the following:
- Subtle signs, such as low-grade fever (20%)
- Fever (80%)
- Cough (60%)
- Generalized lymphadenopathy (40%)
- Hepatomegaly (40%)
- Splenomegaly (15%)
- Pancreatitis (<5%)

Multiorgan dysfunction, adrenal insufficiency

Causes

• Risk factors for miliary TB involve immunosuppression and include, but are not limited to, the following:

- Cancer
- Transplantation

HIV infection

- Malnutrition
- Diabetes

Silicosis

- End-stage renal disease
- Major surgical procedures - Occasionally may trigger dissemination

Differential diagnoses

Acute Respiratory Distress Syndrome	Hyponatremia
Addison Disease	Influenza
Alcoholism	Lactic Acidosis
Ascites	Pneumocystis Carinii Pneumonia
Blastomycosis	Pneumonia, Bacterial
Bone Marrow Failure	Pneumonia, Community-Acquired
Cardiac Tamponade	Pneumonia, Fungal
Disseminated Intravascular Coagulation	Pneumonia, Viral
Eosinophilic Pneumonia	Sarcoidosis
Epididymal Tuberculosis	Silicosis
Histoplasmosis	
Hypersensitivity Pneumonitis	

Other Problems to Be Considered

Fungal infection

Histiocytosis X (Langerhans cell histiocytosis)

HIV-related pulmonary opportunistic infections

Lymphangitic spread of cancer (eg, thyroid carcinoma, malignant melanoma)

Measles

Pancreatic abscess

Pulmonary alveolar microlithiasis

Talc granulomatosis

Laboratory Studies

- Chemistry

- Hyponatremia: A decrease in sodium levels may correlate with disease severity. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or hypoadrenalism may complicate tuberculosis (TB).

- Alkaline phosphatase levels are elevated in approximately 30% of cases.

- Elevated levels of transaminases suggest liver involvement or, if treatment has been initiated, drug toxicity.

- CBC count

- Leukopenia/leukocytosis may be present.

- Leukemoid reactions may occur.

Patients may have anemia.

- Thrombocytopenia or, rarely, thrombocytosis may be present.

- The erythrocyte sedimentation rate is elevated in approximately 50% of patients.

- Cultures for mycobacteria (sputum, blood, urine, cerebral spinal fluid [CSF], and other body fluids, as available): Sensitivity testing is essential for all

positive isolates. Consider investigation for multidrug-resistant TB (MDR-TB) in all cases.

- Coagulation studies: Measure the prothrombin time/activated partial thromboplastin time (PT/aPTT) prior to biopsy.

- The tuberculin skin test with purified protein derivative (PPD) often yields negative results in patients with miliary TB. This may be explained by the large number of TB antigens throughout the body.

- Nucleic acid probes

Specificity for smear-negative and culture-negative specimens is lower than 100% (false-negative results).

- False-positive TB cultures are of concern, and the rate is estimated to be approximately 5%. This may be due to laboratory contamination.

- Polymerase chain reaction testing of the blood may yield positive results in most cases of HIV-related disseminated TB; the yield is low in non-HIV miliary TB.

- Mycobacterial blood cultures

- Findings are positive in approximately 5% of patients who do not have HIV infection.

- Findings are positive in many patients who have HIV infection. One study yielded an 85% positivity rate.

Imaging Studies

- Chest radiography

- Findings are typical in 50% of cases.

- A bright spotlight helps to reveal miliary nodules.

Bilateral pleural effusions indicate dissemination versus localized and unilateral pleural TB. This may be a useful clinical clue.

- Nodules characteristic of miliary TB may be better visualized on lateral chest radiography (especially in the retrocardiac space).

- Chest CT scanning

- This has higher sensitivity and specificity than chest radiography in displaying well-defined randomly distributed nodules. High-resolution CT scanning with 1-mm cuts may be even better.

- It is useful in the presence of suggestive and inconclusive chest radiography findings.

- Ultrasonography may reveal diffuse liver disease, hepatomegaly, splenomegaly, or para-aortic lymph nodes.

- Head CT scanning with contrast and/or MRI of the brain

- Use this to assess for suspected TB lesions.

- Hydrocephalus or cerebral mass lesion (tuberculoma) may increase the risk of herniation if lumbar puncture is performed.

- Abdomen CT scanning may reveal para-aortic lymph nodes, hepatosplenomegaly, or tuberculous abscess.

- Echocardiography is the most sensitive test for pericardial effusion.

Other Tests

- Funduscopy: This may reveal retinal tubercles.

- Electrocardiography

 - This test helps evaluate for pericardial effusion.

 - Right ventricular hypertrophy may indicate pulmonary hypertension prior to lung biopsy.

- Contact investigation

- Miliary TB in a child indicates recent transmission. Contact investigation could identify the source case and associated susceptibilities.

- Contact investigation of child index cases should be conducted quickly.

- Thoroughly evaluate household contacts by means of tuberculin skin testing and, if the test results are positive, chest radiography.

Procedures:

- Sputum induction has low sensitivity. Findings are smear-negative and culture-negative in 80% of patients because of hematogenous spread.

- Fiberoptic bronchoscopy is the most effective procedure for obtaining

 - cultures (bronchoalveolar lavage).

 - The culture yield for transbronchial biopsies is 90%.

- Lumbar puncture should be strongly considered, even with normal brain MRI findings.

- Leukocytes: Approximately 65% of patients have WBC counts with 100-500 mononuclear cells/ μ L.

 - Lymphocytic predominance (70%)

 - CSF lactic acid levels are mildly elevated.

 - Elevated protein levels (90%).

 - Low glucose levels (90%).

 - RBCs are common.

 - Acid-fast bacilli ($\geq 40\%$ with serial spinal taps).

- Gastric lavage: This requires 3 prebreakfast samples, especially in children, with a yield of approximately 60%.

- Nucleic acid amplification techniques may aid in the diagnosis, but negative findings do not rule out TB.

- Bone marrow biopsy has no serious adverse effect. The yield is approximately 50%.

- Liver biopsy: Liver bleeding is a serious and potentially life-threatening complication estimated to occur in approximately 10% of cases.

- For abdominal involvement, laparoscopy is useful to obtain tissue and material for culture.

Histologic Findings. Necrotizing granulomas are the hallmark of TB, and staining for acid-fast bacilli reveals rodlike structures in approximately 80% of specimens. The disseminated nodules consist of central caseating necrosis and peripheral epithelioid and fibrous tissue. Radiographically, the nodules are not calcified.

Staging. Miliary TB with meningeal involvement may require prolonged treatment (up to 12 mo).

Medical Care. Early treatment of patients with suspected miliary tuberculosis (TB) decreases the likelihood of mortality and improves outcome.

Surgical Care. Surgical treatment is rarely necessary. Occasionally, a ventriculoatrial shunt is indicated for hydrocephalus.

Consultations

- Pulmonary and critical care specialists

- Infectious disease specialist

Neurologist - Steroids for meningitis or paradoxically increasing

- tuberculomas

- TB expert

- Health department notification

- Appropriate infection control measures

Diet. Adequate attention to nutrition is important. Many patients with miliary TB are debilitated by the disease, and malnutrition can contribute to a weakened immune system.

Activity. Once the patient receives several weeks of effective therapy, experiences significant clinical improvement, and has negative sputum acid-fast bacillus smears, restrictions are minimal. However, one must be certain that the patient truly is no longer contagious. The absence of sputum positivity does not guarantee others protection against exposure. Directly observed therapy is optimal for assuring compliance and preventing relapse.

Early empirical therapy for suspected miliary tuberculosis (TB) is prudent. A delay of even 1-8 days contributes to a high mortality rate.

Steroids are warranted for hypotension due to presumed adrenal insufficiency after an adrenocorticotrophic hormone (ACTH) stimulation test.

For susceptible organisms, the treatment period is 6-9 months. For meningitis, it is 9-12 months. For miliary TB with meningeal involvement, daily medications for the entire length of therapy are recommended.

Three basic rules apply in the prevention of entirely "doctor-made" resistant TB, which cost more than \$180,000 in the United States in 1991. First, rifampin is the drug of choice for treatment. In most cases, the treatment duration is at least 18 months without rifampin. Second, ethambutol (EMB) is used

to prevent rifampin resistance if the organism is resistant to isoniazid (INH). EMB can be discontinued as soon as the organism is found to be susceptible to rifampin and INH. Third, pyrazinamide is used for the first 2 months of treatment to decrease the treatment duration from 9 months to 6 months if the organism is susceptible to rifampin and INH.

For MDR-TB, use a minimum of 1 susceptible injectable and at least 3 additional susceptible drugs to prevent the development of additional resistance. Treat MDR-TB with the consultation of an expert in the care of TB.

Intermittent-type therapies have not been established. If MDR-TB test results are pending, increasing the number of drugs is reasonable. For example, use 6 or 7 initial drugs, including an injectable.

Antitubercular agents. Any regimen must contain multiple drugs to which TB is susceptible. In addition, drug therapy must be taken regularly and continued for a sufficient period.

Miliary TB has a high number (load) of organisms; thus, the initial number of medications should be high.

Rifampicin

One of most important TB drugs. Used in combination with other anti-tuberculous drugs in the treatment of all forms of TB. Without rifampin, the treatment duration is at least 18 mo.

Inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, interacts with bacterial RNA polymerase but does not inhibit mammalian enzyme. Cross-resistance has been shown only with other rifamycins.

Continue therapy for 6-9 mo or until at least 6 mo have elapsed from conversion to sputum culture negativity.

Restart with different schedule if rifampin was discontinued because of adverse effects (eg, 20 min after a light meal, in divided doses).

Adult. 600 mg/d IV if patient unable to tolerate PO or if reasons exist to suspect that PO medication will not achieve desired absorption

Often can be changed to 600 mg PO 2 d/wk after the first 2 wk

Pediatric. 10-20 mg/kg PO/IV; not to exceed 600 mg/d

Isoniazid. Best combination of effectiveness, low cost, and minor adverse effects. First-line drug unless known resistance or another contraindication. Therapeutic regimens of <6 mo demonstrate unacceptably high relapse rate.

Coadministration with pyridoxine recommended if peripheral neuropathies develop secondary to INH therapy. Prophylactic doses of 6-50 mg/d of pyridoxine are recommended.

Adult. 5 mg/kg/d (usually 300 mg/d) PO/IV and 10 mg/kg/d PO/IV in 1-2 divided doses in patients with disseminated disease; not to exceed 300 mg/d In directly observed therapy, administer 15 mg/kg 2 times/wk PO/IV; not to exceed 900 mg/d.

Pediatric. 10-20 mg/kg/d PO/IV; not to exceed 300 mg/d.

Pyrazine analog of nicotinamide that may be bacteriostatic or bactericidal against *M tuberculosis*, depending on concentration of drug attained at site of infection; mechanism of action is unknown.

Administer for initial 2 mo of a 6-mo or longer treatment regimen for drug-susceptible cases. Treat drug-resistant cases with individualized regimens.

Adult. 15-30 mg/kg/d PO; not to exceed 2 g/d.

Alternatively, 1.5 g/d PO; increase to 2 g for body weight >75 kg, and decrease to 1 g for body weight <50 kg.

Pediatric. Administer as in adults.

Ethambutol

Diffuses into actively growing mycobacterial cells, such as tubercle bacilli. Impairs cell metabolism by inhibiting synthesis of one or more metabolites, which, in turn, causes cell death. No cross-resistance demonstrated. Mycobacterial resistance is frequent with previous therapy. Use in these patients in combination with second-line drugs that have not been previously administered.

Administer q24h until permanent bacteriological conversion and maximal clinical improvement is seen. Absorption is not significantly altered by food.

Adult. No previous antituberculous therapy: 15 mg/kg/d (7 mg/lb/d) PO

Previous antituberculous therapy: 25 mg/kg/d (11 mg/lb/d) PO

Absorption not significantly altered by administration with food

Pediatric. <12 years: Not recommended

>12 years: Administer as **in adults**

Streptomycin sulphate

For treatment of susceptible mycobacterial infections.

Use in combination with other antituberculous drugs (eg, INH, EMB, rifampin). Total period of treatment for TB is a minimum of 1 y; however, indications for terminating streptomycin therapy may occur at any time.

Recommended when less potentially hazardous therapeutic agents are ineffective or contraindicated.

May be used in patients with severe liver dysfunction (transaminases >3- to 5-fold normal).

Adult.

2 times/wk dosing: 15 mg/kg/d IM; not to exceed 1 g/d.

3 times/wk dosing: 25-30 mg/kg/d IM; not to exceed 1.5 g/d.

Pediatric.

2 times/wk dosing: 20-40 mg/kg/d IM; not to exceed 1 g/d.

3 times/wk dosing: 25-30 mg/kg/d IM; not to exceed 1.5 g/d.

Levofloxacin

Second-line drug with low risk of liver toxicity. Useful in TB in combination with rifampin and other antituberculosis agents. Other quinolones also may be useful, especially newer quinolones.

Adult. 500 mg/d PO.

Pediatric.

<18 years: Not recommended, although it has been used in MDR-TB when options are limited

>18 years: Administer as in adults

Eosinophilic Granuloma

Background. Eosinophilic granuloma, also known as pulmonary histiocytosis X (PHX) or pulmonary Langerhans cell histiocytosis X (PLCH), is an uncommon interstitial lung disease that is epidemiologically related to tobacco smoking. It chiefly affects young adults, primarily occurring in the third or fourth decades of life.

Pathophysiology. Pulmonary Langerhans cell histiocytosis X (PLCH) is histologically characterized by parenchymal infiltration of the lungs by activated Langerhans cells. Langerhans cells are differentiated cells of the dendritic cell system and are closely related to the monocyte-macrophage line. These antigen-presenting cells are normally found in the skin, reticuloendothelial system, heart, pleura, and lungs. They may be identified by immunohistochemical staining or by the presence of Birbeck granules via electron microscopy.

PLCH is similar to pediatric histiocytic disorders (Letterer-Siwe disease and Hand-Schüller-Christian disease). However, in contrast to pediatric histiocytoses, which involve multiple organs, PLCH usually manifests in a single organ — the lung. About 4-20% of patients with PLCH also have cystic lesions in the bones. Other organ systems are only rarely affected.

The accumulation of Langerhans cells in the lungs is hypothesized to occur in response to exposure to cigarette smoke. Supporting this hypothesis is the finding that the initial histologic and radiographic findings are peribronchiolar. In addition, the disease is most prominent in the upper and middle lung zones, as seen in other smoking-related lung diseases. The granulomatous infiltrates seen in PLCH are composed of Langerhans cells, eosinophils, lymphocytes, macrophages, plasma cells, and fibroblasts, which form nodules centered on the terminal and respiratory bronchioles, causing destruction of the airway walls. In late stages of the disease, fibrotic stellate scarring occurs, and end-stage PLCH is characterized by this scarring along with cystic spaces and honeycombing.

History. Presentations of pulmonary Langerhans cell histiocytosis X (PLCH) are variable. Approximately 25% of patients are asymptomatic, and their disease is diagnosed after an evaluation of incidental findings on chest

radiographs. Others present with respiratory or constitutional symptoms. In order of decreasing frequency, common presenting symptoms are as follows:

- Nonproductive cough (56-70%)
- Dyspnea (40%)
- Fatigue (30%)
- Weight loss (20-30%)
- Chest pain (21%)
- Spontaneous pneumothorax, which may be recurrent, is a classic presentation found in 10-20% of patients.
- Fever (15%)
- Cystic bone lesions (4-20%): These may be painful and may predispose the patient to pathologic fracture.

Physical. Patients with pulmonary Langerhans cell histiocytosis X (PLCH) present with nonspecific physical findings. Neither inspiratory rales (crackles) nor clubbing is common. Cor pulmonale may develop; therefore, the following related findings may be present:

- Loud second heart sound with accentuated pulmonic component
- Tricuspid regurgitation murmur
- Right ventricular lift
- Peripheral edema

Causes

No occupational causes or geographic predispositions are recognized for pulmonary Langerhans cell histiocytosis X (PLCH). People with PLCH, almost invariably, are cigarette smokers. Antigenic stimulation from 1 or more components of tobacco smoke is likely responsible for the disease. Because only a few tobacco smokers develop the disease, other susceptibility factors, such as host genetics and environmental exposures, most likely play an important role in pathogenesis. Some reports in the literature also describe PLCH developing following radiation and/or chemotherapy for lymphoma. Additional investigation is needed to further our understanding of this disease process.

Differential diagnoses

Chronic Obstructive Pulmonary Disease	Pulmonary Fibrosis, Idiopathic
Cystic Fibrosis	Pulmonary Fibrosis, Interstitial (Nonidiopathic)
Emphysema	Sarcoidosis
Hypersensitivity Pneumonitis	Wegener Granulomatosis
Lymphangioliomyomatosis	
Pneumocystis (carinii) jiroveci Pneumonia	

Other Problems to Be Considered

- Tuberosus sclerosis

• Lymphangioliomyomatosis (LAM): Patients with pulmonary Langerhans cell histiocytosis X (PLCH) frequently present to medical attention with spontaneous pneumothoraces. Lymphangioliomyomatosis is a disorder that exclusively affects young women and is characterized by cystic, emphysematous dilation of the terminal airways and shares this predisposition. It may be mistaken for PLCH on a chest radiograph or high-resolution CT (HRCT) scan of the chest.

- Pulmonary histiocytic sarcoma

Laboratory Studies

• Results from routine laboratory testing in patients with pulmonary Langerhans cell histiocytosis X (PLCH) are nonspecific.

- Peripheral eosinophilia is not observed.

Imaging Studies

• Chest radiographs in patients with pulmonary Langerhans cell histiocytosis X (PLCH) characteristically reveal bilateral, symmetric, ill-defined nodules and reticulonodular infiltrates. As the disease progresses, cystic lesions appear. An upper-zone predominance of radiographic findings with sparing of the costophrenic angles is typically observed.

- Cystic lesions can be of various sizes and thin or thick walled.

- Lung volume is normal or increased.

- Honeycombing indicates advanced disease.

- Bony lesions may occur on the ribs or any other site.

• Hilar or mediastinal adenopathy is rare and should prompt the consideration of sarcoidosis or malignancy.

- Pleural effusion is uncommon.

- HRCT of the chest may be virtually diagnostic in the appropriate

clinical setting. Pathognomonic findings include nodules and cysts, predominantly in the mid and upper lung zones, with sparing of the costophrenic regions. The nodules may be cavitory and variable in size. Likewise, the cysts may be of various diameters and wall thicknesses. A broad differential diagnosis must be considered in the following situations:

• If only nodules are present on HRCT, the findings are nonspecific, and a number of other granulomatous disorders cannot be excluded radiographically.

• When cysts are an isolated finding, LAM must be considered as well. Unlike PLCH, LAM is usually uniformly distributed throughout the lungs. Sparing of the costophrenic angles supports a diagnosis of PLCH.

• Emphysema is usually distinguishable, as walls do not surround the cystic spaces found in emphysema. However, extensive emphysema is sometimes difficult to differentiate from PLCH.

Other Tests

- Pulmonary function testing in pulmonary Langerhans cell histiocytosis X (PLCH) patients can demonstrate all patterns of abnormality: Normal, restrictive, obstructive, or mixed.

- Most patients have normal or near-normal total lung capacity with near-normal spirometry findings.

- Gas exchange, as measured by the diffusing capacity for carbon monoxide, is generally reduced.

In rare cases, patients have reversible airflow limitation.

- Gas exchange abnormalities may be present at rest. Although such abnormalities are most pronounced with exercise, most patients have a normal gradient of alveolar-arterial partial pressures.

- Pulmonary exercise testing may demonstrate decreased exercise capacity with reduced oxygen utilization. Gas exchange, ventilatory, and pulmonary vascular abnormalities may also be present. Therefore, exercise limitation is generally multifactorial.

Procedures

- Analysis of bronchioalveolar lavage (BAL) fluid is sometimes diagnostic in pulmonary Langerhans cell histiocytosis X (PLCH).

- A greater than 5% increase in the number of Langerhans cells in BAL specimens is almost pathognomonic for PLCH. Although this finding is highly specific, it is not particularly sensitive.

- Langerhans cells can be recognized by their characteristic staining for S-100 protein or peanut agglutination antigen.

- These cells are CD1a-positive, and may also be identified by a specific monoclonal antibody (MT-1).

- Although the disease is present in a patchy distribution, sometimes transbronchial biopsy may be diagnostic if sampling is done in a number of areas and sufficient tissue is obtained.

- Immunostaining for Langerhans cells (CD1a) improves the sensitivity and specificity of the biopsy sample.

The diagnostic yield is approximately 10-40%.

- Open or thoracoscopic lung biopsy is the most sensitive and specific diagnostic modality, and is generally recognized as the criterion standard.

- In addition to immunostaining, electron microscopy of tissue samples may be performed.

- Langerhans cells demonstrate the characteristic intracytoplasmic Birbeck granules. These are found in all Langerhans cells, but they are present in increased numbers in the pathologic Langerhans cells found in the lesions of PLCH.

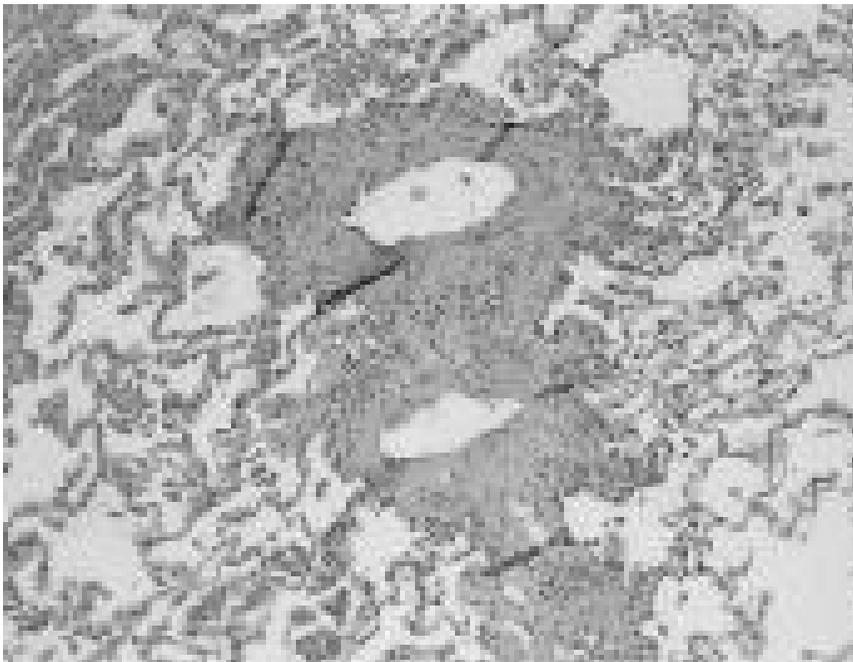
Histologic Findings. The earliest lesions of pulmonary Langerhans cell histiocytosis X (PLCH) consist of Langerhans cells grouped around the small airways. These inflammatory lesions expand to form granulomatous nodules composed of Langerhans cells as well as eosinophils, macrophages, lymphocytes, plasma cells, and fibroblasts.

In addition to looking for the typical morphologic features of Langerhans cells, immunostaining for S-100 and CD1a may also be useful. Electron microscopy helps in identifying Langerhans cells by demonstrating the presence of diagnostic pentilaminar cytoplasmic inclusion bodies, or Birbeck granules (x-bodies).

Of note, eosinophils may not always be present. Therefore, the name eosinophilic granuloma, despite being a commonly accepted term, is a misnomer.

Granulomas are centered on distal bronchioles. Evidence of pulmonary vascular involvement and respiratory bronchiolitis are often present, as well as infiltration and destruction of airway walls. As the disease progresses, cavitation occurs as a result of this destruction. The nodule fibroses, eventually forming a stellate scar.

Hematoxylin-eosin staining is demonstrated in the image below:



Medical Care. Smoking cessation is the most important medical intervention for pulmonary Langerhans cell histiocytosis X (PLCH). Smoking cessation often stabilizes the disease and sometimes leads to regression. It is also helpful in preventing bronchogenic carcinoma. Largely because of the rarity of PLCH, well-designed, prospective, randomized data regarding therapy are lacking. Treatment considerations are as follows:

- The use of corticosteroids is controversial. Corticosteroids may be considered in patients with a persistence of clinically significant pulmonary or constitutional symptoms or those with documented progression of disease. Corticosteroid therapy is not indicated in patients with normal lung function. Recommendations for the use of corticosteroids are based largely on retrospective data and expert opinion.

- Investigational therapies include interleukin-2 (IL-2) and anti-tumor necrosis factor-alpha (anti-TNF-alpha). Both agents have been reported to improve outcomes in pediatric disseminated histiocytosis. This finding may lead to the investigation of their use in adult PLCH.

- Useful adjunctive therapies include the following:

- Supplemental oxygen therapy for those with clinically significant hypoxemia ($\text{SaO}_2 < 89\%$ or $\text{PaO}_2 < 55 \text{ mmHg}$) at rest or with exertion

- Aggressive treatment for pulmonary infections with prompt initiation of antibiotic therapy

- Bronchodilator therapy in the presence of an obstructive ventilatory defect

Surgical Care. Lung transplantation is an option for select patients with advanced disease. Recurrence of pulmonary Langerhans cell histiocytosis X (PLCH) has been reported in the transplanted lung.

Consultations. Refer patients with suspected pulmonary Langerhans cell histiocytosis X (PLCH) to a pulmonary disease specialist.

Activity. Exercise and pulmonary rehabilitation are encouraged in pulmonary Langerhans cell histiocytosis X (PLCH). These activities may improve the patient's functional status, even if they have no effect on disease progression.

Medication. The mainstays of treatment for pulmonary Langerhans cell histiocytosis X (PLCH) are smoking cessation and supportive therapy. The use of corticosteroids in the treatment of PLCH is controversial. Their efficacy has not been proven in well-designed, prospective, randomized, controlled trials. Some experts recommend a trial of corticosteroids for those patients with persistent symptomatic disease or evidence of progression.

Corticosteroids. These agents have anti-inflammatory properties and cause profound and varied metabolic effects. Corticosteroids modify the body's immune response to diverse stimuli.

Prednisolone

Used as immunosuppressant to treat autoimmune disorders. By reversing increased capillary permeability and suppressing activity of polymorphonuclear cells, may decrease inflammation. Oral corticosteroid with relatively limited mineralocorticoid activity. Best prescribed in consultation with pulmonary disease specialist.

Adult

0.5-1.0 mg/kg/d PO initially, followed by 6- to 12-mo taper

Pediatric

Not established

Literature

○ Goodman & Gilman's The Pharmacological Basis of Therapeutics / Laurence L. Brunton, Keith L. Parker, Donald K. Blumenthal, Iain L.O. Buxton / 11th edition / 2007

○ Basic & Clinical Pharmacology / Bertram G. Katzung / 10th edition / 2006

○ Katzung & Trevor's Pharmacology: Examination & Board Review / Trevor AJ, Katzung BG, & Masters SB / 7th edition / 2005

○ USMLE Road Map: Pharmacology / Katzung BG, Trevor AJ / 2nd edition / 2006.

○ Current Medical diagnosis and treatment/ Edited by Lawrence M Tierney/ 2010

○ Harrison's principles of internal medicine-17th edition.

Навчальне видання

**Модуль 3. Внутрішні хвороби.
Змістовний модуль №4.
Тема 3. Ведення хворих
з затемненням в легенях**

*Методичні вказівки
для студентів та лікарів-інтернів*

Упорядники Бабак Олег Якович
 Фадєєнко Галина Дмитрівна
 Біловол Олександр Миколайович
 Школьник Віра Владиславівна
 Шапошнікова Юлія Миколаївна
 Немцова Валерія Данилівна
 Железнякова Наталя Мерабівна

Відповідальний за випуск Бабак О.Я.

Комп'ютерний набір
Ю.М. Шапошнікова

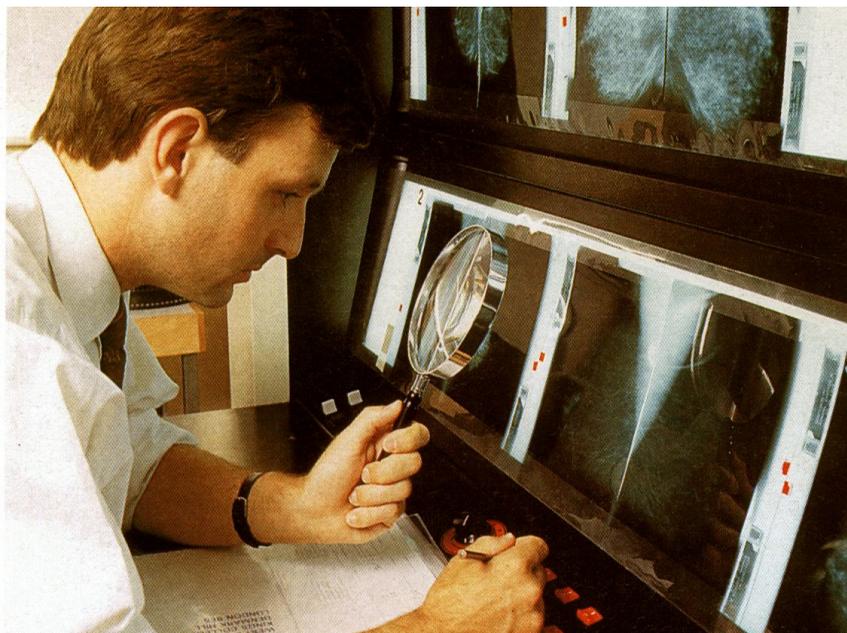
План 2012, поз. 27.
Підп. до друку 12.06.2012. Формат А5. Папір типогр. Різографія.
Умов. друк. арк. 2,25. Тираж 150 прим. Зам. № 12-2929.

**Редакційно-видавничий відділ
ХНМУ, пр. Ленина, 4, г. Харків, 61022
izdat@knhmu.kharkov.ua**

Свідоцтво про внесення суб'єкта видавничої справи до Державного реєстру видавництв, виготовників і розповсюджувачів видавничої продукції серії ДК № 3242 від 18.07.2008 р.

Module 3. Internal medicine.
Contents module № 4.
Theme 3. Management of patients
with infiltrative pulmonary darkening

Guidelines for students and interns



Модуль 3. Внутрішні хвороби.
Змістовний модуль №4.
Тема 3. Ведення хворих
з затемненням в легенях

*Методичні вказівки
для студентів та лікарів-інтернів*