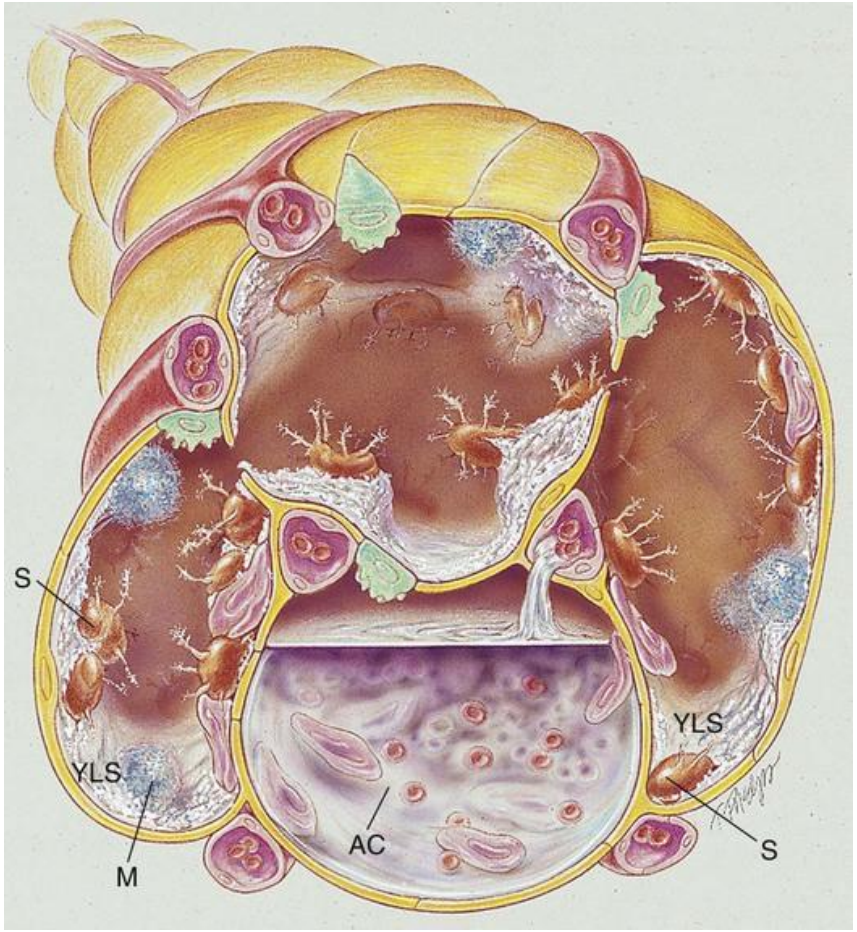


Pulmonary Fungal Infections in Immuno-compromised Patients

Introduction

- Fungal infection has emerged as a significant burden in the last decade.

- Pulmonary complications are most common cause of morbidity and mortality in immunocompromised patients.

- No. of immunocompromised patients are on the rise due to:
  - Multiple treatment options for patients with malignant diseases
  - Increasing use of organ transplantation or hematopoietic cell transplantation
  - Increased survival of patients with autoimmune diseases

Denning DW et al. Eur Respir J. 2016 Jan;47(1):45-68
Deorukhkar SC et al. Int J Curr Microbiol App Sci (2016) 5(1): 533-545

Risk Factors

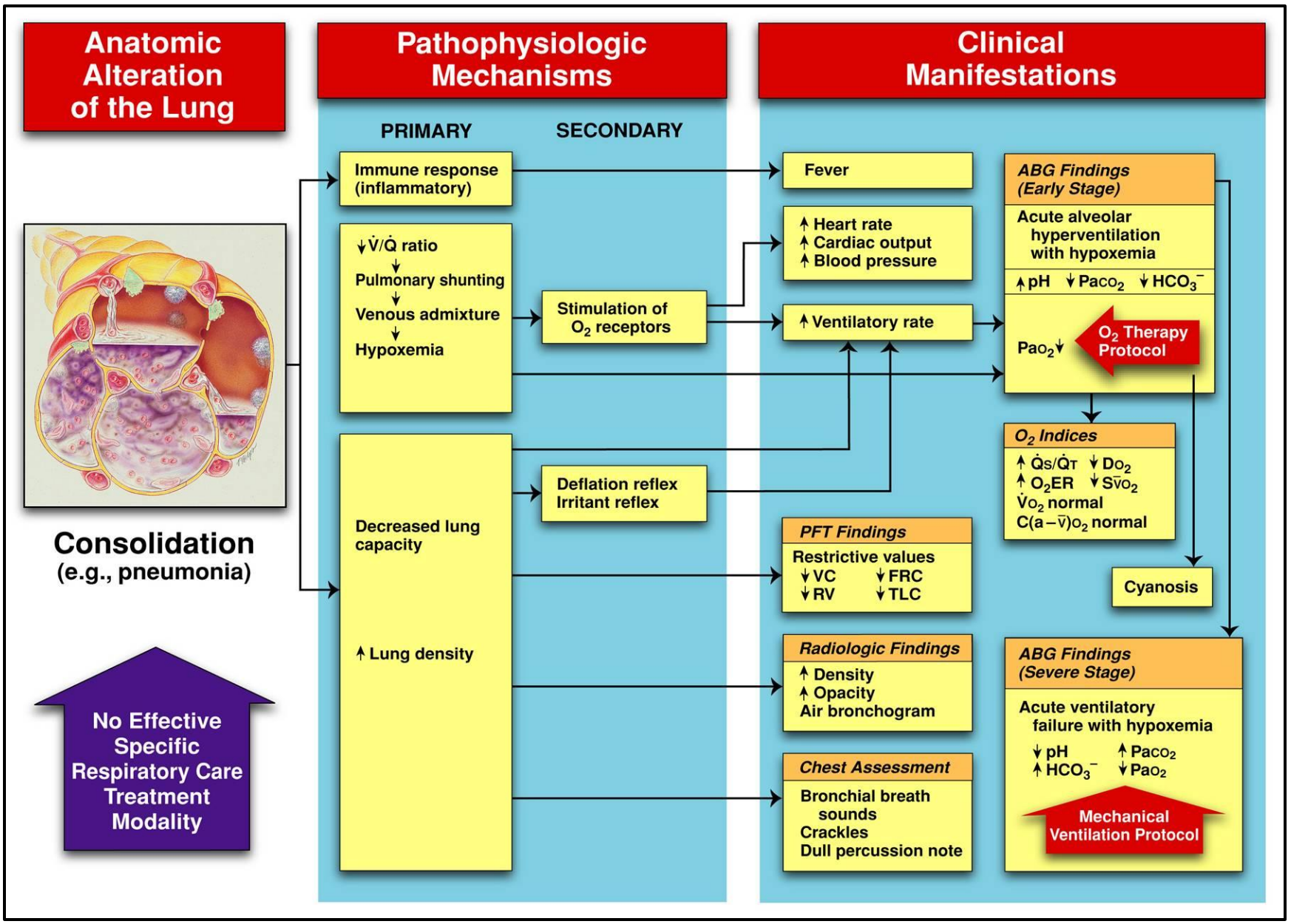
Risk factors for fungal infection		
-Neutropenia (< 500 mm^3) - Hematological malignancy - Allogeneic hematopoietic progenitor cell transplantation - Lung transplantation without prophylaxis	-Prolonged steroid treatment prior to ICU admission -Autologous hematopoietic progenitor cell transplantation - COPD, especially under inhaled steroid treatment - Hepatic cirrhosis - Solid organ malignancy - HIV infection - Lung transplantation with prophylaxis - Systemic treatment with immunosuppressants	-Severe burns - Solid organ transplantation - Treatment with steroids (<7 days) - Prolonged ICU stay (>21 days). - Malnutrition - Cardiac post-surgery - Near drowning -Multiorgan dysfunction syndrome (situation of immune paralysis) - Influenza A (H1N1) infection

Denning DW et al. Eur Respir J. 2016 Jan;47(1):45-68
Garnacho-Montero J et al. Rev Esp Quimioter 2013;26(2):173-188

Overview of the Cardiopulmonary Clinical Manifestations

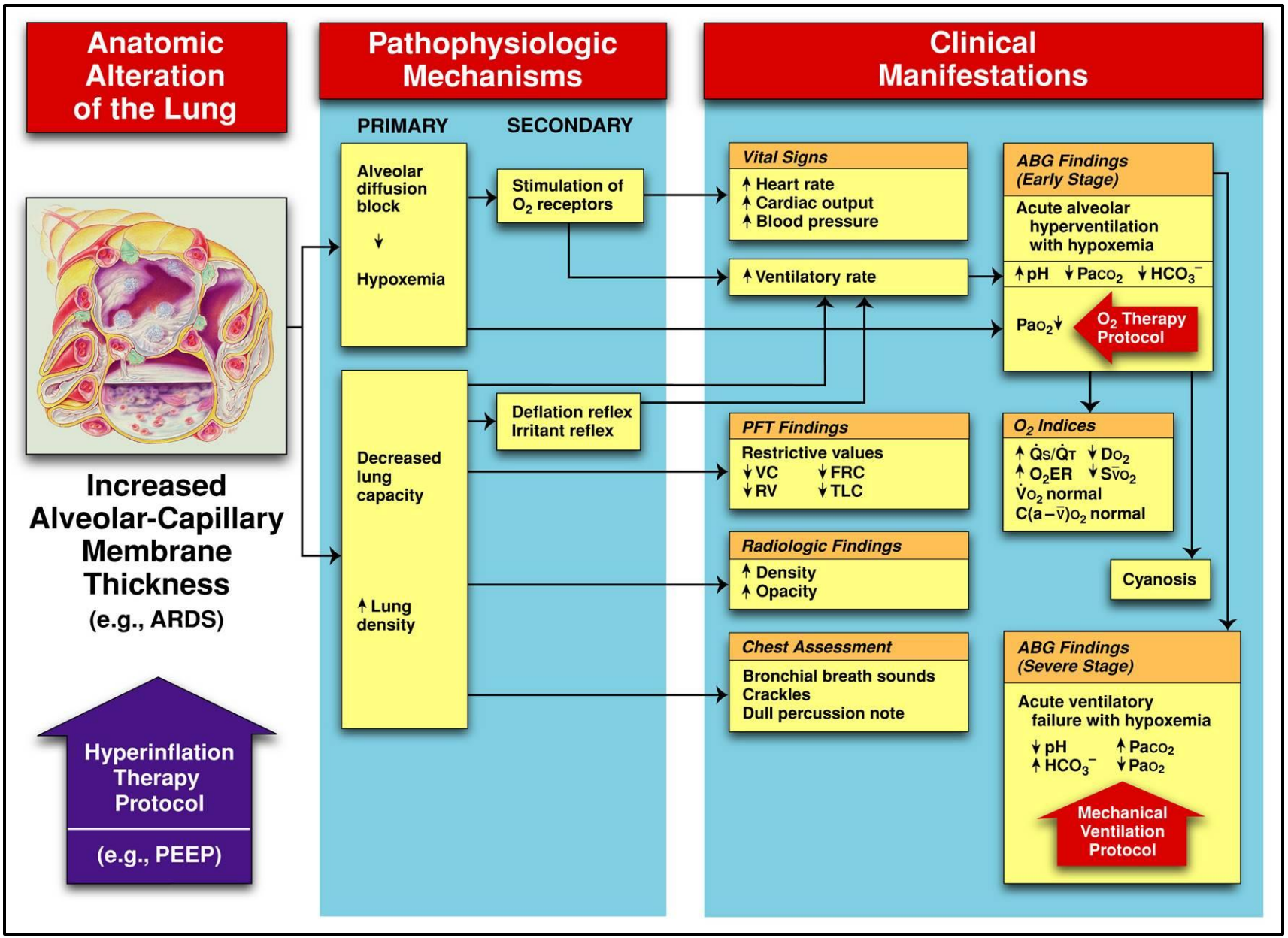
Associated with FUNGAL DISEASES OF THE LUNG

Alveolar consolidation- clinical scenario.



Des Jardins T, Burton GG. Clinical Manifestations & Assessment of Respiratory Disease. Elsevier Health Sciences; 2015 Mar 12.

Increased alveolar-capillary membrane thickness clinical scenario.



Des Jardins T, Burton GG. Clinical Manifestations & Assessment of Respiratory Disease. Elsevier Health Sciences; 2015 Mar 12.

Common Fungal Infections

- The diagnosis of fungal infections in critically ill patients is an extremely difficult task.
- The symptoms are invariably masked by the presence of dominant primary pathology.
- The etiology of fungal infections can be broadly subdivided into:
  - Systemic infections caused by true pathogenic fungi , Eg.: Histoplasmosis, Blastomycosis, Coccidioidomycosis etc.
  - Infections caused by opportunistic saprophytic fungi. E.g., Candidiasis, Aspergillosis etc.

Aspergillosis

Aspergillosis

- Most common opportunistic mould causing pulmonary infection
- In India, A. flavus is the most common species, followed by A. fumigatus, and A. niger is the third most common species implicated.
- Risk factors for invasive pulmonary aspergillosis include
  - haematopoietic cell transplant (HCT)
  - solid organ transplant
  - Neutropenia.

    especially when prolonged, corticosteroids and cytomegalovirus infection

Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244.

Aspergillosis Clinical Features

- Patients usually have symptoms of fever and cough initially; chest pain and haemoptysis follow as the infection progresses.
- Other symptoms ensue if dissemination to skin, brain or other organs occurs.
- The clinical presentation varies based on host risk factors.
- Spread to the CNS is a dreaded complication because of the very high mortality rate

Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244.

Diagnosis of Aspergillosis

- **Culture and histopathology**: Identification of the fungus in culture and tissue specimens is the gold standard for diagnosing aspergillosis, but may not be feasible in the intensive care setting due to the long time required and difficulty in obtaining tissue samples in these patients.

- **Galactomannan test:** It is an important constituent of the cell wall and it can be detected in the serum or bronchoalveolar lavage fluid; however, brochoalveolar lavage is considered to be more sensitive.

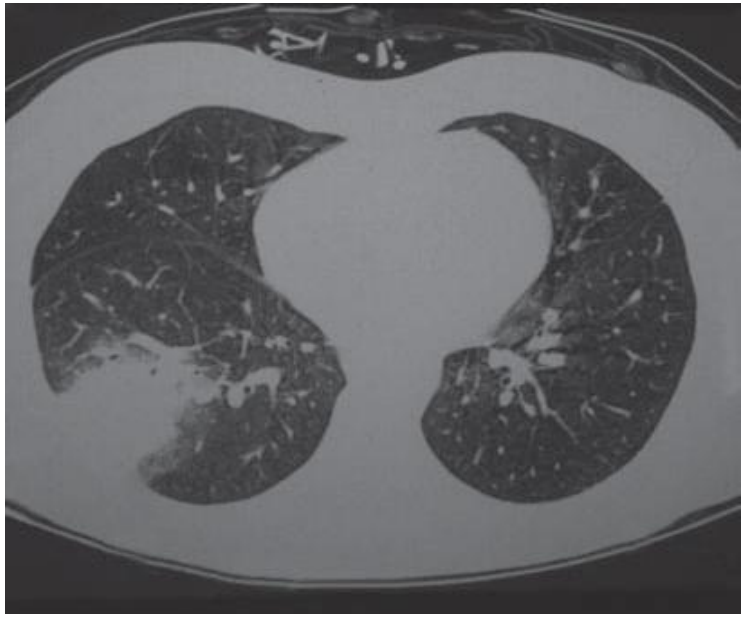
- **PCR**: It detects the fungal nucleic acid and is sensitive when combined with other tests.

Patterson KC et al. Chest. 2014 Nov;146(5):1358-68.

Radiology Findings- Aspergillosis

- Radiographic techniques have improved over the last several decades and findings highly suggestive of invasive aspergillosis have been established in neutropenic patients; these include

- Nodules surrounded by ground glass, the so-called 'halo sign', caused by haemorrhage, and later, in the course of illness, cavitation of the nodules, causing the so-called 'air crescent sign.'



Patterson KC et al. Chest. 2014 Nov;146(5):1358-68.

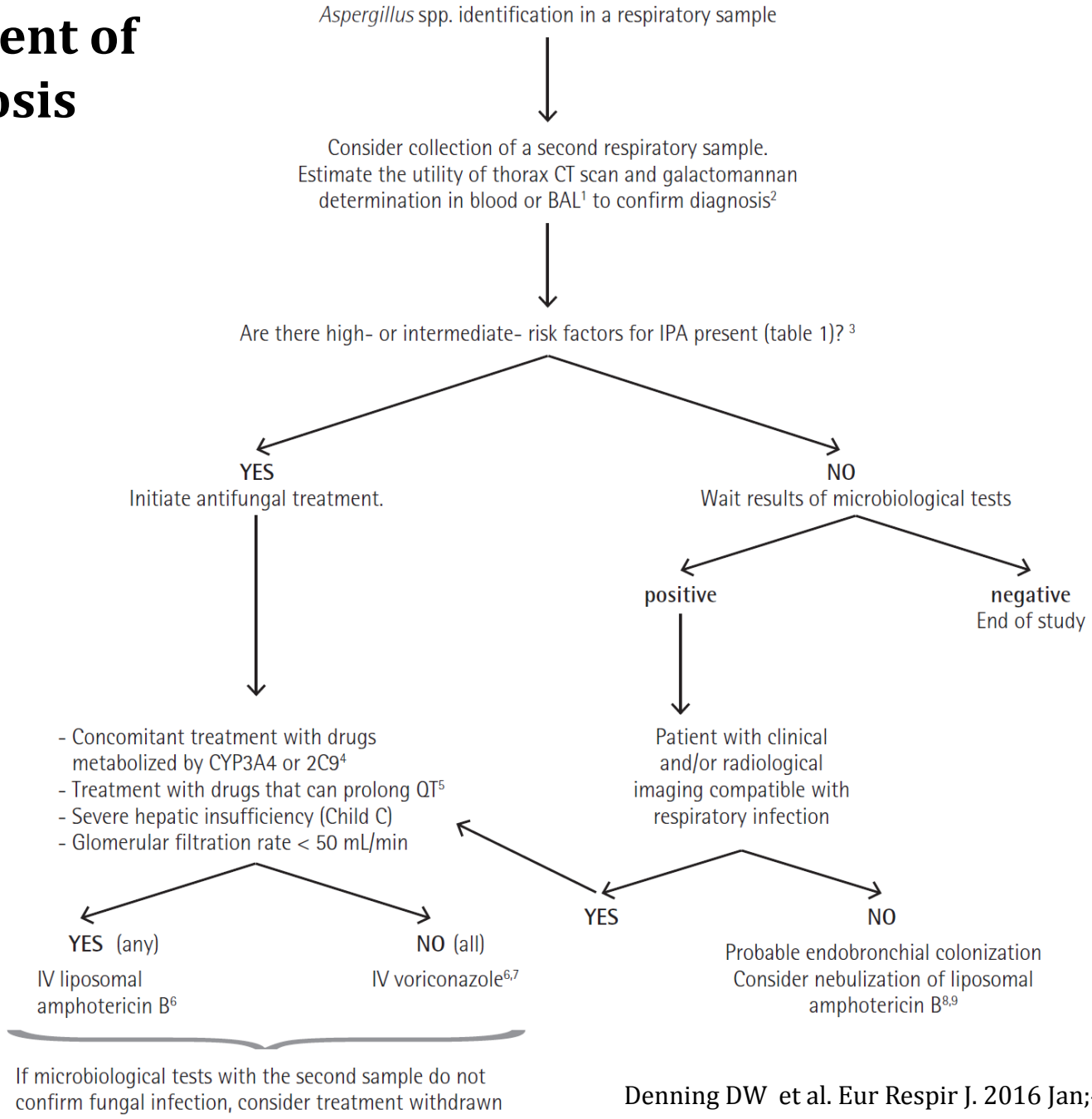
Management

- **Primary therapy:**
  - I.V. Voriconazole : 6 mg/kg every 12 hourly followed 24 h later by 4 mg/kg every 12 hourly.
  - Followed by oral voriconazole 200 mg twice daily until clinical and radiological stabilization occurs.
  - Alternatively, I.V. amphotericin B (liposomal) 3-5 mg/kg/day can be used followed by oral voriconazole (200 mg twice daily)

- **Salvage therapy:**
  - Echinocandins are utilized when the primary therapy fails.
  - I.V. Caspofungin -70 mg on Day 1, followed by 50 mg/day.
  - I.V. micafungin can also be used.
  - Oral posaconazole in a dose of 200 mg every 6 hourly, followed by 400 mg twice daily, has been found to be equally effective.

Walsh TJ. Aspergillosis. In: Goldman L, Schafer AI, eds. Goldman's Cecil Medicine. 25th ed. Philadelphia, PA: Elsevier Saunders; 2016:chap 339.
Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244.

Management of Aspergillosis



Denning DW et al. Eur Respir J. 2016 Jan;47(1):45-68

Mucormycosis

Introduction

- Mucormycosis refers to several different diseases caused by infection with fungi in the order of Mucorales.
- Second most common cause of pulmonary invasive mould infections.
- Approximately 75% of mucormycosis cases are caused by three genera, *Rhizopus, Mucor* and *Rhizomucor.*
- *Mucormycosis* has been increasing in the last two decades

Smith JA et al. Respirology. 2012 Aug;17(6):913-26

Burden

- Mucormycosis carries a mortality rate of 50-85%.
- The mortality rate associated with rhinocerebral disease is 50-70%.
- Pulmonary and gastrointestinal (GI) diseases carry an even higher mortality rate, because these forms are typically diagnosed late in the disease course.
- Disseminated disease carries a mortality rate that approaches 100%.
- Cutaneous disease carries the lowest mortality rate (15%).

Bozorgi V et al. The Pan Af Med J. 2016;24:232

Risk Factors

- Pulmonary mucormycosis occurs in patients with profound degree of immune dysfunction.

- Especially in patients with
  - haematological malignancy complicated by prolonged neutropenia
  - HCT receipients

- Other less common predisposing factors for development of mucormycosis include
  - Immunomodulating viral infections, such as cytomegalovirus,
  - Trauma,
  - Iron overload and
  - Intravenous drug use

Bozorgi V et al. The Pan Af Med J. 2016;24:232

Clinical Features

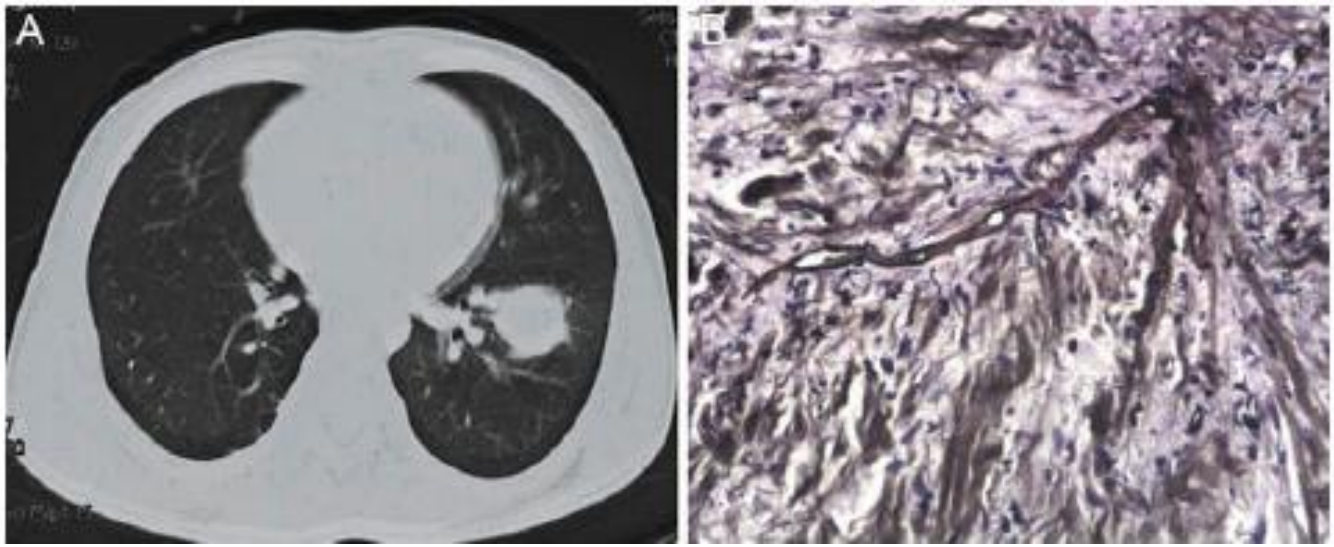
- Most mucormycosis infections are life-threatening, and risk factors, such as diabetic ketoacidosis, neutropenia, are present in most cases.
- Patients complain of dyspnoea, cough, haemoptysis and chest pain, and they usually appear quite ill.
- Massive haemoptysis can occur.
- Less often, and mostly in less immunocompromised patients, the disease can be more indolent, presenting with mass-like lesions that can cavitate.
- Involvement of adjacent structures, including pleura, pericardium and mediastinum is common.

Bozorgi V et al. The Pan Af Med J. 2016;24:232

Diagnosis

- **Computed tomography (CT):** should be obtained

- The definitive diagnosis of mucormycosis requires the identification of characteristic broad, non-septate hyphae invading tissues (fig)



A) Chest CT scan showed a mass in lower lobe of the left lung. (B) Broad, irregularly branched and non-septate hyphae with positive methenamine silver stain observed in lung tissue (magnification,×40).

- In an immunosuppressed patient positive CT scan or sputum or BAL culture yielding a Mucorales is adequate to initiate empiric treatment

Bozorgi V et al. The Pan Af Med J. 2016;24:232

Management

- The mainstay of therapy remains amphotericin B.
- Many clinicians advocate higher doses of amphotericin B for the treatment of mucormycosis.
- There have been several adjunctive measures in the treatment of mucormycosis brought forth in the last decade.
- These include the addition of echinocandins, the iron chelator, deferasirox and several different immunomodulatory agents to amphotericin B therapy
- Immunotherapy with interferon-gamma and/or granulocyte macrophage colony-stimulating factor has been a promising possibility for the last decade but has not gained widespread acceptance.

ChowdharyA et al. PLoS Pathog. 2016 Apr; 12(4): e1005491.
Smith JA et al. Respirology. 2012 Aug;17(6):913-26

Cryptococcosis

Introduction

- Pulmonary cryptococcosis occurs in ‘normal’ hosts as well as those who are immunocompromised patients
- Generally more severe in those who have defects in immunity and often accompanied by disseminated infection, including CNS disease.
- In immunocompetent hosts, cryptococcosis is more likely to be limited to the lung and occurs more commonly in patients with chronic lung disease

Fisher JF et al. Open Forum Infect Dis 2016. 1-12

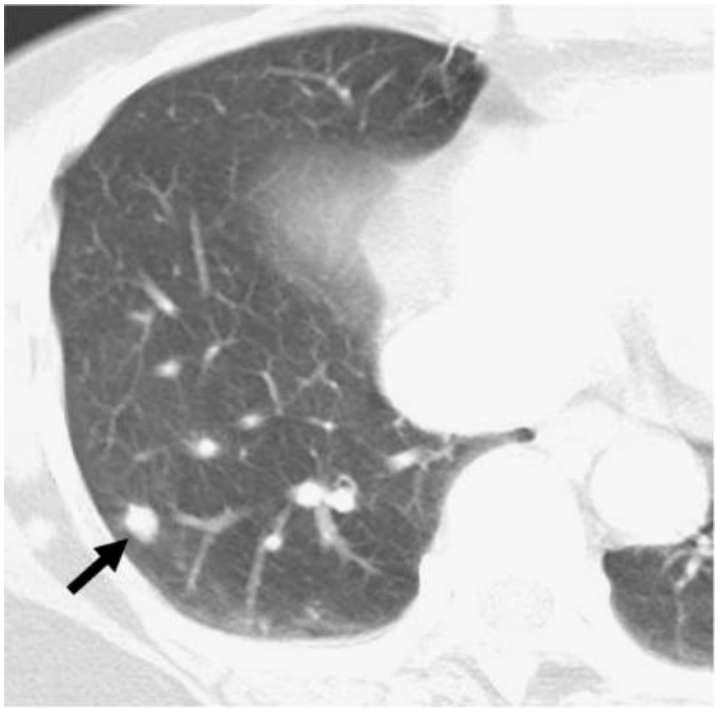
Clinical Features

- Immunocompetent subjects with pulmonary cryptococcosis usually are asymptomatic or have mild symptoms that include
  - fever,
  - malaise,
  - cough with sputum production and
  - dyspnoea.
- Immunocompromised patients are much more likely to present with fulminant infection with fever, dry cough and dyspnoea that can progress to acute respiratory distress syndrome (ARDS).

Fisher JF et al. Open Forum Infect Dis 2016. 1-12

Diagnosis

- Imaging studies show solitary pulmonary nodules, often pleural-based, diffuse nodules, consolidation or diffuse bilateral infiltrates.
- Lymphadenopathy and cavitation occur but are uncommon
- In a patient who has no radiographic findings, isolating *C. neoformans* from sputum may reflect colonization.
- A stain specific for *Cryptococcus,* the mucicarmine stain, should always be performed to establish identity of yeast-like structures seen in tissues.



Pulmonary cryptococcosis of solitary pulmonary nodular pattern

Fisher JF et al. Open Forum Infect Dis 2016. 1-12
Smith JA et al. Respirology. 2012 Aug;17(6):913-26

Diagnosis

- The cryptococcal antigen test is highly sensitive and specific and is routinely used to help establish the diagnosis of cryptococcal meningitis and disseminated cryptococcosis.

- Because of the frequency of disseminated infection in immunocompromised patients, a systematic evaluation, including cultures from blood and cerebrospinal fluid and measurement of serum and cerebrospinal fluid cryptococcal antigen, should be performed in all immunosuppressed patients who present with seemingly isolated pulmonary cryptococcosis.

Fisher JF et al. Open Forum Infect Dis 2016. 1-12
Smith JA et al. Respirology. 2012 Aug;17(6):913-26

Management

- For mild to moderate isolated pulmonary infection, oral fluconazole for 6–12 months is recommended.

- For severe pulmonary involvement:
  - initial treatment with amphotericin B lipid formulation
  - Combined with flucytosine for 2–4 weeks,
  - Followed by consolidation therapy with fluconazole for an additional 8–10 weeks and
  - Maintenance fluconazole therapy for 6–12 months.

Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244.
Fisher JF et al. Open Forum Infect Dis 2016. 1-12

Histoplasmosis

Introduction

- It is the most common among endemic mycosis, and is caused by a soil-dwelling dimorphic fungus, *Histoplasma capsulatum*.
- It is endemic in many states in India.
- The portal of entry is respiratory tract, with severity of disease depending on the infecting dose.
- The spectrum of disease varies from mild pulmonary disease, severe pulmonary disease, chronic pulmonary disease and disseminated histoplasmosis.

Wheat LJ et al. Infect Dis Clin North Am. 2016 Mar;30(1):207-27
Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244

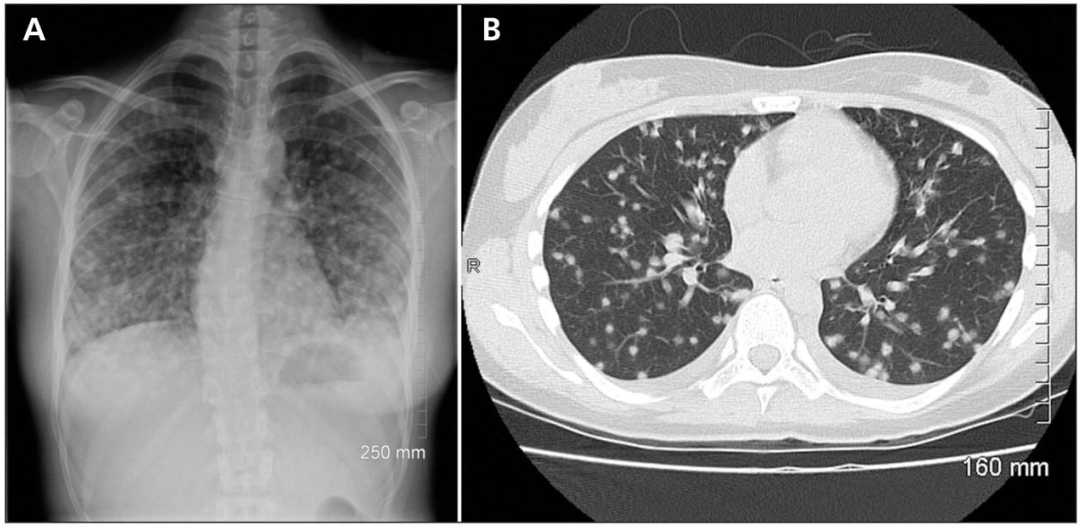
Clinical Features

- The extent of disease is determined both by the number of conidia inhaled and the immune response of the host.
- A small inoculum can cause severe infection in markedly immunosuppressed hosts.
- Conversely, healthy individuals, who most commonly have asymptomatic pulmonary infection, can develop life-threatening pneumonia if they inhale a large quantity of conidia.
- Pulmonary infection with *H. capsulatum can be* manifested as an acute self-limited pneumonia characterized by fever, dry cough, mild chest discomfort and fatigue.

Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244

Diagnosis

- Positive travel history to the endemic area.
- Demonstration of Histoplasma antigen in urine, blood or bronchoalveolar lavage fluid of infected patients is diagnostic and rapid.
- The chest radiograph reveals a patchy infiltrate, and the CT scan frequently reveals small nodules; hilar lymphadenopathy may be present and is helpful in differentiating histoplamosis from bacterial pneumonias.



(A) Chest radiograph and (B) CT scan Both images show symmetrically distributed nodules consistent with acute histoplasmosis.

Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244

Management

- The treatment of severe and disseminated disease involves administration of amphotericin B.
- Both the conventional and the lipid formulations can be used. However, the lipid formulation is found to be less nephrotoxic.
- Following initial stabilization, oral itraconazole can be added twice daily for at least 12 months.
- Monitoring of itraconazole serum levels has to be done every 2 weeks with monitoring of liver and renal functions

Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244

Blastomycosis

Introduction

- *B. dermatitidis, the causative agent of blastomycosis,* is a dimorphic fungus that exists as a mould in the environment
- The incidence of blastomycosis is much less than that of histoplasmosis
- Endemicity exhibit almost similar pattern as of histoplasmosis.
- It is less common in HIV-infected patients, but, if present, produces widely disseminated disease often involving the meninges.
- Other sites of infections are skin, bones and genitourinary tract.

Castillo CG et al. Infect Dis Clin North Am. 2016 Mar;30(1):247-64

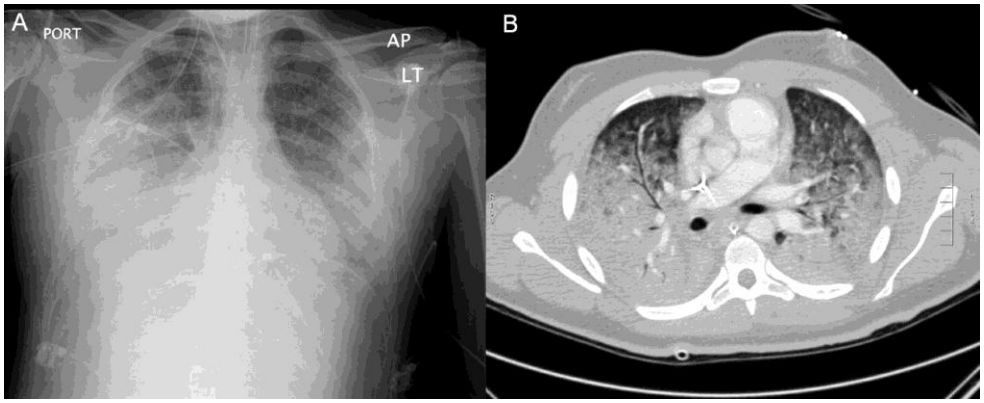
Clinical Features

- Chronic forms of pulmonary blastomycosis can present as mass-like lesions that resemble lung cancer or as upper lobe cavitary lesions that resemble tuberculosis or histoplasmosis.
- Fever, night sweats, weight loss, fatigue, dyspnoea and cough with purulent sputum and haemoptysis, are usually present for weeks.
- Hilar and mediastinal lymphadenopathy are seen less commonly than in histoplasmosis.
- Cutaneous lesions are the most common manifestation of disseminated extra-pulmonary blastomycosis; usually well circumscribed and can be verrucous or ulcerated

Castillo CG et al. Infect Dis Clin North Am. 2016 Mar;30(1):247-64
Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244

Diagnosis

- Histopathological examination of tissues, cytological examination of body fluids, such as sputum or BAL and antigen detection.
- The organisms are larger than most yeasts (8–10 mm), thick-walled and have a single broad based bud.
- EIA performed on urine or serum, detects a cell wall galactomannan antigen found in *B. dermatitidis*
- A real-time PCR assay for *B. dermatitidis has* 99% *s*pecificity and sensitivity of 86% when compared with culture results.



A: CXR with diffuse bilateral nodular airspace disease. B: Diffuse bilateral reticulonodular infiltrates are present on the chest CT

Castillo CG et al. Infect Dis Clin North Am. 2016 Mar;30(1):247-64
Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244

Management

- The treatment for the severe infection causing respiratory distress is by Amphotericin B (both conventional and liposomal).
- Followed by oral itraconazole twice daily for 12 months after initial stabilization.
- The meningitis usually responds to Amphotericin B with concurrent or sequential itraconazole or fluconazole.

Castillo CG et al. Infect Dis Clin North Am. 2016 Mar;30(1):247-64
Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244

Coccidioidomycosis

Introduction

- Caused by the soil-dwelling dimorphic fungus *Coccidiodes immitis.*
- The portal of entry is by respiratory tract and the usual presentation is community-acquired pneumonia.
- The most dreaded complication is meningitis, which may or may not be preceded by an acute illness.
- Disseminated infection occurs in less than 1% of patients with symptomatic coccidioidomycosis and may be present concomitantly with pulmonary involvement.
- Occasionally, it may present as stroke syndrome due to vasculitis of cerebral vessel

Galgiani JN et al. Clin Infect Dis. 2016 Sep 15;63(6):e112-46.

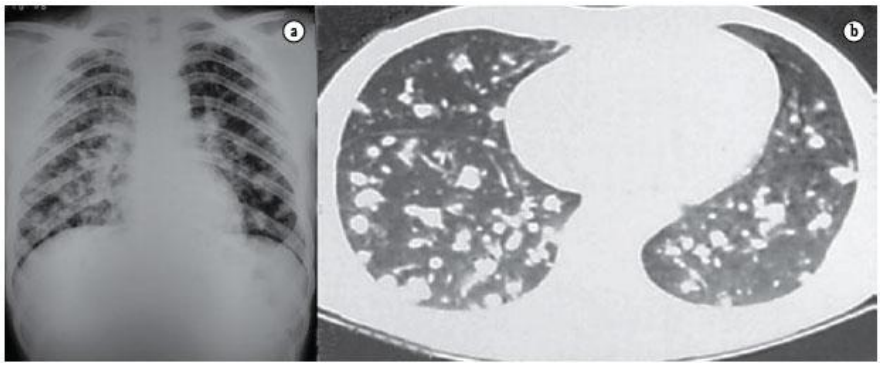
Clinical Features

- Most persons infected with *Coccidioides species* have no symptoms or symptoms suggesting mild community-acquired pneumonia.
- Fever, fatigue, dry cough, anterior chest pain, weight loss, purulent sputum, haemoptysis and dyspnoea are common symptoms.
- Diffuse infiltrates with hypoxemia are uncommon and are usually seen in immunosupppressed patients.
- Complications following acute pneumonia occur in 5–10% of patients and include solitary thin-walled cavities, chronic progressive cavitary pneumonia and fibrosis

Galgiani JN et al. Clin Infect Dis. 2016 Sep 15;63(6):e112-46.

Diagnosis

- *Coccidioides* species grow as a mould within a few days on most standard media.
- The large spherules are readily identified in tissues and with the aid of potassium hydroxide or calcofluor white, can be identified in sputum or BAL fluid.
- Chest radiographs usually show nodular or patchy infiltrates, and hilar lymphadenopathy may be present.
- The serologic tests are usually used to establish the diagnosis.
- The cerebrospinal fluid analysis in meningeal disease shows predominantly lymphocytic pleocytosis with occasional eosinophils



Chest X-ray and CT scan of Patient. revealing bilateral diffuse nodular opacities.

Galgiani JN et al. Clin Infect Dis. 2016 Sep 15;63(6):e112-46.

Management

- The treatment is often difficult as it is less susceptible to antifungal drugs as compared with histoplasmosis or blastomycosis.
- In severe and disseminated disease, amphotericin B (liposomal or conventional) is still used; however, oral fluconazole or itraconazole is considered the main drug for less-severe disease.
- There is, however, no consensus for treatment duration.
- Invasive and disseminated disease in immunocompromised patients is treated with Amphotericin B till clinical improvement, followed by itraconazole or fluconazole for at least 1 year.

Galgiani JN et al. Clin Infect Dis. 2016 Sep 15;63(6):e112-46.

Candidiasis

Introduction

- Invasive fungal infections with Candida spp. are the most common systemic fungal infections.
- The most common species are *C. albicans.*
- The incidence of nonalbicans Candida (NAC) has also risen dramatically.
- In India also, the isolates of NAC range from 52 to 96%, but the predominant species are *C. tropicalis*.

Badiee P et al. Indian J Med Res .2014 February; 139: 195-204

Risk Factors

Definite risk factors Broad-spectrum antibiotic use	Definite risk factors
Immunosuppression	Broad-spectrum antibiotic use Immunosuppression
Neutropenia	Neutropenia
Major abdominal surgery	Major abdominal surgery
Major trauma	Major trauma
Total parenteral nutrition	Total parenteral nutrition
Central venous cannulation	Central venous cannulation
Hemodialysis	Hemodialysis
Diabetes melllitus	Diabetes melllitus
Renal failure	Renal failure
Prolonged ICU stay	Prolonged ICU stay
Multiple blood transfusion	Multiple blood transfusion
Multi-site candida colonization	Multi-site candida colonization

Pappas PG et al. Clin Infect Dis. 2016 Feb 15;62(4):409-17

Diagnostic Methodologies

- The use of risk-factor-based prediction of invasive candidial infection is being used in routine clinical practice.

- Low risk or high risk depending on the presence or absence of four independent risk factors, namely
  - total parenteral nutrition (1 point),
  - multifocal colonisation sites (1 point),
  - severe sepsis (2 points) and
  - surgery (1 point).

- "*Candida Score*" of ≥3 predicts invasive candidial disease with a sensitivity of 81% and a specificity of 74%.

Pappas PG et al. Clin Infect Dis. 2016 Feb 15;62(4):409-17

Laboratory Tests

Beta-D-Glucan assay:

- It detects β-D-glucan, an important constituent of the cell wall of pathogenic fungi.

Polymerase chain reaction (PCR):

- It detects fungal nucleic acid and has been found to have a sensitivity of 90.9% with 100% specificity.

Pappas PG et al. Clin Infect Dis. 2016 Feb 15;62(4):409-17

Management

Prophylactic treatment:

- The prophylactic use of fluconazole is recommended in patients receiving chemotherapy for hematologic malignancies who are expected to be neutropenic,
- In patients with solid organ transplantation and in patients undergoing bone marrow transplantation.
- This prophylaxis can also be used in nonneutropenic at risk intensive care patients.

Definitive treatment:

- In patients with a definitive diagnosis of candidiasis, all catheters, including the central venous catheter, should be removed and invasive candidiasis such as endophthalmitis should be excluded.

Pappas PG et al. Clin Infect Dis. 2016 Feb 15;62(4):409-17
Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244.

Management

- In clinically stable patients, fluconazole is used in a dose of 400 mg to a maximum of 1600 mg per day for at least 2 weeks after the last positive blood culture unless azole resistance is suspected.

- Echinocandins (caspofungin, micafungin, anidulafungin) should be preferred if NAC such as C. glabrata or C. krusei are suspected.

- In unstable and severely ill patients, amphotericin B (conventional or liposomal) alone or in combination with fluconazole, echinocandins (caspofungin, micafungin, anidulafungin), voriconazole or highdose fluconazole (800 mg per day) may be used.

Pappas PG et al. Clin Infect Dis. 2016 Feb 15;62(4):409-17
Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244.

Summary & Conclusion

Diagnosis of Pulmonary Fungal Infections

Fungal infection	Diagnostic methods	Comments
Aspergillosis	Culture	Easily grown in lab
	Histopathology	Septate hyphae, but not specific for *Aspergillus*
	CT finding of halo sign	Suspect angioinvasive mould, but not specific
	Galactomannan EIA in serum and BAL	Has become standard test for aspergillosis in serum and likely will become standard in BAL
	RT-PCR in blood and BAL (not standardized)	Likely to play an important role in future
Mucormycosis	Culture	Culture requires special techniques for growth
	Histopathology	Broad non-septate hyphae presumptive evidence for mucormycosis
	CT finding of reverse halo sign	Suggestive only, not specific
	RT-PCR (not standardized)	Perhaps will play a larger role in future
Fusariosis	Culture	Easily grown in lab
	Histopathology	Septate hyphae resemble *Aspergilllus*
	Characteristic skin lesions	Painful lesions with hyphae seen on biopsy
	PCR and *in situ* hybridization (not standardized)	Both perhaps will play a larger role in future
Scedosporiosis	Culture	Easily grown in lab
	Histopathology	Septate hyphae resemble *Aspergilllus*
	PCR and *in situ* hybridization (not standardized)	Both perhaps will play a larger role in future
Cryptococcosis	Culture	Easily grown in lab
	Histopathology	Yeast forms with clear surrounding area are suggestive; mucicarmine stain is specific
	Antigen latex agglutination assay in serum, CSF, body fluids	Highly sensitive and . . . specific; yield lower . . . yield lower with pulmonary infection than with disseminated and CNS infection

Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244.

Diagnosis of Pulmonary Fungal Infections

Fungal infection	Diagnostic methods	Comments
Blastomycosis	Culture	Takes 2–4 weeks to grow
	Histopathology	Characteristic yeast forms provide presumptive evidence of infection
	Antigen EIA in urine, serum and perhaps body fluids	Rapid, sensitive, cross-reacts with histoplasmosis
	RT-PCR (not standardized)	Might play a role in future
Histoplasmosis	Culture	Takes 4–6 weeks to grow
	Histopathology	Characteristic yeast forms provide presumptive evidence of infection
	Serology	Useful for acute and chronic pulmonary infection; poor in immunocompromised host
	Antigen EIA in urine, serum BAL, other body fluids	Rapid, sensitive, cross-reacts with blastomycosis
	RT-PCR (not standardized)	Might play a role in future
Coccidioidomycosis	Culture	Easily grown; dangerous for lab; must send to reference lab for identification for safety reasons
	Histopathology	Spherules large and specific; give presumptive diagnosis
	Serology	Very useful for all forms of pulmonary infection
	Antigen EIA in urine, serum	Not clear how sensitive or specific

BAL, bronchoalveolar lavage; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; EIA, enzyme immunoassay; RT-PCR, real-time polymerase chain reaction.

Bajwa SJ et al. Ann Med Health Sci Res. 2013 Apr-Jun; 3(2): 238–244.

Treatment regimens for pulmonary fungal infections

Fungal infection	Preferred treatment	Step-down and second-line treatment
Aspergillosis	Voriconazole, 4 mg/kg bid IV[†] until stable, then step-down therapy	Step-down: voriconazole, 200 mg bid oral, until lesions resolved Second-line: lipid AmB, 5 mg/kg/d IV, until stable, or posaconazole, 400 mg bid oral,[‡] until lesions resolved
Mucormycosis	Lipid AmB, 5 mg/kg/d IV, or higher doses until lesions resolved	Step-down: posaconazole, 400 mg bid oral,[‡] until lesions resolved Second-line: AmB-d, 1 mg/kg/d IV, until lesions resolved (possible addition of echinocandin to AmB formulation)
Fusariosis	Lipid AmB, 5 mg/kg/d IV, or voriconazole, 4 mg/kg bid IV,[†] or combination of lipid AmB, 5 mg/kg/d IV, plus voriconazole, 4 mg/kg bid IV,[†] until stable, then step-down therapy	Obtain susceptibilities because resistance is common Step-down: voriconazole, 200 mg bid oral, until lesions resolved Second-line: posaconazole, 400 mg bid oral,[‡] until lesions resolved
Scedosporiosis	Voriconazole, 4 mg/kg bid IV,[†] until stable, then step-down therapy	Obtain susceptibilities because resistance is common Step-down: voriconazole, 200 mg bid oral, until lesions resolved Second-line: posaconazole, 400 mg bid oral,[‡] until lesions resolved
Cryptococcosis	Severe or with dissemination: lipid AmB, 3–5 mg/kg/d IV + flucytosine, 25 mg/kg qid oral, for 2–4 weeks	Step-down: fluconazole, 400 mg qd oral, for 8–10 weeks, then fluconazole, 200 mg for 6–12 months Second-line: AmB-d, 0.7–1 mg/kg/d IV + flucytosine, 25 mg/kg qid oral, for 2–4 weeks, followed by same step-down therapy as above (For other second-line options and differences in different hosts, see Perfect *et al*.[65])

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Treatment regimens for pulmonary fungal infections

Fungal infection	Preferred treatment	Step-down and second-line treatment
	qd oral, for 6–12 months	oral,[¶] or posaconazole, 400 mg bid oral,[‡] for 6–12 months
Blastomycosis	Severe or immunocompromised: lipid AmB, 3–5 mg/kg/d IV, until stable, then step-down therapy	Add steroids for ARDS Step-down: itraconazole, 200 mg bid oral,[§] 6–12 months Second-line: AmB-d, 0.7–1 mg/kg/d, until stable, then itraconazole, 200 mg bid, oral,[§] for 6–12 months
	Mild to moderate infection: itraconazole, 200 mg bid oral,[§] for 6–12 months	Voriconazole, 200 mg bid oral,[¶] or fluconazole, 800 mg qd oral, for 6–12 months
Histoplasmosis	Severe or immunocompromised: lipid AmB, 3–5 mg/kg/d IV, until stable, then step-down therapy	Add steroids for ARDS Step-down: itraconazole, 200 mg bid oral,[§] 6–12 months Second-line: AmB-d, 0.7-1 mg/kg/d, IV until stable, then itraconazole, 200 mg bid oral,[§] for 6–12 months
	Mild to moderate infection: itraconazole, 200 mg bid oral,[§] for 6–12 months	Voriconazole, 200 mg bid oral,[¶] or fluconazole, 800 mg qd oral, for 6–12 months
Coccidioidomycosis	Severe or immunocompromised: lipid AmB, 3–5 mg/kg/d IV, until stable, then step-down therapy	Step-down: itraconazole, 200 mg bid oral,[§] or fluconazole, 400 mg qd oral, for 12 months Second-line: AmB-d, 0.7-1 mg/kg/d IV, until stable, then itraconazole, 200 mg bid oral,[§] or fluconazole, 400 mg qd oral, for 12 months
	Mild to moderate infection: itraconazole, 200 mg bid oral,[§] or fluconazole, 400 mg qd oral, for 6 months	Voriconazole, 200 mg bid oral,[¶] or posaconazole, 400 mg bid oral,[‡] for 6 months

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Conclusion

- The better approach to the optimal management of fungal infection is early detection and identification of the causal agent.
- Appropriate treatment can be initiated as soon as possible, especially in immunocompromised patients.
- Clinicians should be familiar with the use of diagnostic methods and suitable antifungal agents,
- With the advances in antifungal therapy, the mortality and morbidity in intensive care can be greatly reduced.


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