OPPORTUNISTIC INFECTIONS OF THE LUNG

Present by:

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DEFINITION

- Immune defect ⇒⇒⇒ potential pathogens causing infection.
- Defining disease in immunocompromised hosts: CT scans ⇒ better than radiographs
- In selected patients; early bronchoscopy ⇒⇒⇒ ⇑ microbiological identification.
- Predispose to Pneumocystis jirovecii pneumonia (PJP):
  - Prolonged high-dose glucocorticoids (>20 mg/day for >21days) .
  - Calcineurin inhibitors.
- Biological agents ⇒⇒⇒ specific immune defects ⇒⇒⇒ ⇑ the risk of opportunistic lung infections:
  - Anti TNF-α ⇒ mycobacterial disease, endemic fungi & Legionella pneumophila.
  - Anti-CD20 drugs ⇒ mycobacterial disease, cytomegalovirus pneumonitis & PJP.

INTRODUCTION

- Opportunistic infections:
  - Loss of innate or adaptive immune responses
  - An organism normally weakly virulent
  - Infection
- Commonly Infections ⇒⇒⇒ in healthy individuals ⇒⇒⇒ in immunocompromised hosts.
- Opportunistic lung infections ⇒⇒⇒ major cause of morbidity and mortality:
  - HIV infection
  - Haematological malignancy
  - Aplastic anemia
  - Chemotherapy treatment
  - Recipients of solid organ
  - Stem cell transplants
- Opportunistic infections ⇒⇒⇒ complicate treatment with the new biological therapies for inflammatory conditions.
- For a positive outcome: 1. Expert clinical assessment 2. Early diagnosis 3. Aggressive treatment
- Identifies the most likely pathogens:
  - CT / CXR
  - Immune status (loss of T-cell- or antibody-mediated immunity, or defects in neutrophil-mediated immunity)

Type of immune defect according to disease/treatment and range of pathogens commonly associated with infections in patients with this type of immune defect

Immune disorder	Causes	Typical microorganisms
Neutrophil disorders		
Neutropenia	**Drugs (chemotherapy, azathioprine, methotrexate, carbimazole, sulfonamides)** **Leukaemia** **AIDS** **Felty's syndrome** **Aplastic anaemia** **Early HSCT**	**Gram-positive bacilli (Staphylococcus aureus, streptococci)** **Gram-negative bacilli** **Fungi (Aspergillus spp., Candida spp., non- Aspergillus filamentous fungi)**
Neutrophil chemotaxis	**Diabetes mellitus** **Cirrhosis** **Sarcoidosis** **Drugs (glucocorticoids, amphotericin B)**	**Staph. aureus** **Streptococci** **Candida spp.** **Zygomycetes**
Neutrophil phagocytosis	**Chronic granulomatous disease** **Myeloproliferative disorders** **Inherited phagocyte defects**	**Staph. aureus** **Nocardia spp.** **Gram-negative bacilli** **Fungi (Aspergillus spp., Candida spp., non-Aspergillus filamentous fungi)**

Type of immune defect according to disease/treatment and range of pathogens commonly associated with infections in patients with this type of immune defect (continue)

Immune disorder	Causes	Typical microorganisms
T-cell-mediated immunity	**AIDS** **Lymphoma** **HSCT** **Solid organ transplantation** **Drugs (T-cell-depleting antibodies, glucocorticoids, ciclosporin, tacrolimus)**	**Herpesviruses** **Respiratory viruses** **Pneumocystis jirovecii** **Endemic mycoses, e.g. H. capsulatum, Cryptococcus** **Parasites (Strongyloides, Toxoplasma)** **Mycobacteria** **Nocardia** **Legionella pneumophila**
B-cell-mediated/antibody deficiency	**Multiple myeloma** **Plasmaphaeresis** **Drugs (anti-B-cell therapies)** **HSCT** **Chronic lymphocytic leukaemia** **Lymphoma** **Multiple myeloma**	**Encapsulated bacteria (e.g. Streptococcus pneumoniae, Haemophilus influenzae)** **Herpesviruses**
Complement deficiency	**Congenital Acquired (systemic lupus erythematosus, anorexia nervosa)**	**Encapsulated bacteria (e.g. Strep. pneumoniae, H. influenzae)** **Staph. aureus**
Asplenia	**Splenectomy** **Sickle cell disease**	**Encapsulated bacteria (S. pneumoniae, H.influenzae)** **Staph. aureus**

BACTERIA

CONVENTIONAL BACTERIAL PATHOGENS

- Conventional bacterial pathogens:
  - fever
  - focal consolidation
  - respiratory symptoms
  - rapid rises in inflammatory markers.
- Common post-viral illness.
- Major risk factors:
  1. neutropenia
  2. antibody deficiencies
  3. high-dose corticosteroids.
- More diverse & more likely to be resistant to first-line antibiotics.
- These include:
  - Gram-positive (Streptococcus pneumoniae, Staphylococcus aureus)
  - Gram-negative (Pseudomonas aeruginosa, Proteus species, Escherichia coli, other enteric pathogens).
  - Reactivation of latent tuberculosis.
- TB cultures & PCR (in respiratory samples) from immunocompromised individuals
  - with pulmonary infiltrates, particularly in high-prevalence areas

NOCARDIOSIS

- ✓ Uncommon Gram-positive bacterial infection
- ✓ High mortality in disseminated disease.
- ✓ >80 Nocardia species,
  - ✓ but Nocardia asteroides complex (human disease).
- ✓ Found in soil, decaying vegetable matter and stagnant water.
- ✓ The most common route of entry ⇒ Inhalation
  - ✓ pneumonia ⇒ most common infection.
- ✓ The main risk factors:
  - ✓ T-cell-mediated immunity defects (e.g. after transplantation), prolonged glucocorticoid therapy, malignancy, graft-versus-host disease (GVHD), diabetes mellitus, chronic granulomatous disease & alveolar proteinosis.
- ✓ Nocardia pneumonia ⇒ develops over weeks with cough, haemoptysis, weight loss, fever and night sweats, but can be more acute.

NOCARDIOSIS

- ✓ Common radiological features:
  - ✓ Patches of dense consolidation or macronodules, frequently pleurally based.
  - ✓ Cavitation and pleural effusions are common.
  - ✓ Can be mistaken for metastasis.
- ✓ Local spread to the pericardium and mediastinum.
- ✓ Haematogenous spread to brain, joints and soft tissue, occur in about half of patients.
- ✓ Diagnosis: characteristic beaded, branching Gram-positive and weakly acid-fast filaments on microscopy.
- ✓ Blood and sputum cultures: prolonged aerobic culture positive.
- ✓ PCR: Sensitive; Difficult to interpret; particularly in respiratory tract samples ⇒ colonization.
- ✓ Treatment with two or three intravenous antibiotics may initially be necessary in immunocompromised cases.
- ✓ Trimethoprim-sulfamethoxazole is first-line therapy, with carbapenems, amikacin, third-generation cephalosporins, tetracyclines or amoxicilline clavulanate as alternatives.
- ✓ Duration of treatment is prolonged up to 12 months in immunocompromised patients and central nervous system (CNS) disease.

VIRAL INFECTIONS

RESPIRATORY VIRUSES

- Defects in T-cell mediated immunity ⇒ Lower respiratory tract infections.
- Respiratory viruses:
  - respiratory syncytial virus, parainfluenza, influenza, adenovirus, metapneumovirus, coronavirus, rhinovirus.
- Bronchiolitis with coryzal symptoms, cough, fever and dyspnea.
- Characteristic squeaks or wheeze in auscultation (minority of patients).
- The chest radiograph is often normal or non-specific.
- Chest CT:
  - Classically diffuse 'tree-in-bud' ⇒ suggestive of small airways inflammation.
  - Ground-glass infiltrates.
- Diagnosis: rapidly confirmed by nasopharyngeal aspirate samples for viral antigen immunofluorescence or PCR (Favored in immunocompromised). {Bronchoalveolar lavage fluid (BALF) has higher sensitivity}.
- In the absence of pneumonia, mortality is relatively low, although infection can persist for several weeks.
- Treatment is supportive, but specific antiviral treatment is recommended in immunocompromised hosts and combination with intravenous immunoglobulin for severe infection.

Antiviral treatments for respiratory viruses

Virus	Treatment
Influenza	Neuraminidase inhibitors (zanamivir, oseltamivir) a Amantadine
Parainfluenza	Ribavarin b,c IVIG b
Respiratory syncytial virus	Ribavarin c Palivizumab
Human metapneumovirus	Ribavarin b,c IVIG b
Adenovirus	Ribavarin b,c Cidofovir b Brincidofovir d

IVIG, Intravenous immunoglobulin.
a Effective at reducing disease severity and duration.
b In vitro activity present but no recommendations on treatment are currently available owing to lack of data.
c Can be administered orally, intravenously or nebulized.
d In Phase III clinical trials.

RESPIRATORY VIRUSES

- Viral infection; influenza(H1N1) ⇒ lung host defenses and predisposes to secondary bacterial infection.
- In immunocompromised hosts (chronic glucocorticoid use, chemotherapy for cancer and haemopoietic stem cell transplant (HSCT) recipients) ⇒ more severe illness.
- Clinically: ↳ relapse of fever ↳ respiratory symptoms ↳ new radiographic evidence of infiltrates.
- Antibiotic treatment for secondary bacterial infection ⇒ Strep. pneumoniae, Staph. aureus and Haemophilus influenzae. (most commonly encountered after influenza).
- Novel viruses: Middle Eastern Respiratory Syndrome coronavirus (MERS) and avian influenza A strain H7N9 (a low rate of transmission but a high mortality).
- Treatment of these infections is generally supportive.
- Adenovirus infections after allogeneic HSCT ⇒ first-line treatment generally being cidofovir until a defined reduction in viral load (success ≈70%).
- Brincidofovir, an orally bioavailable conjugate of cidofovir, in cidofovir-resistant cases (UK not licensed).

CYTOMEGALOVIRUS (CMV) & OTHER HERPESVIRUSES

- Lung infection of herpesvirus CMV ⇒ impaired T-cell-mediated immunity.
- CMV infection is defined: active CMV replication regardless of symptoms/signs.
- CMV disease is infection associated with evidence of organ-specific disease.
- Immunocompromised CMV infection:
  - reactivation of latent CMV acquired in early life;
  - primary infection in previously uninfected individuals (often more severe).
- Pneumonitis {important complication}:
  - insidious onset of fever
  - malaise
  - cough
  - dyspnea
  - hypoxia
- Classic CT: symmetrical peribronchovascular and alveolar infiltrates predominantly affecting the lower lobes, but asymmetrical changes, consolidation and effusions are not uncommon.

CYTOMEGALOVIRUS (CMV) & OTHER HERPESVIRUSES

- **Diagnosis of CMV infection/disease: viral load by PCR or CMV pp65 antigen testing of blood or BALF.**
- **Culture of urine, throat and BALF specimens.**
- **CMV reactivation does not always mean that concurrent lung disease is caused by CMV and, conversely, CMV viraemia is occasionally absent in patients with CMV pneumonitis.**
- **CMV pneumonitis is more likely with high-level viraemia, especially if the viral load increased rapidly. Furthermore, high CMV DNA loads (>500 IU/ml) in BALF from HSCT recipients are associated with poor outcome.**
- **CMV pneumonitis can also be confirmed by finding inclusion bodies in BALF cells or transbronchial or video assisted thoracic surgery (VATS) biopsy samples.**

CYTOMEGALOVIRUS (CMV) & OTHER HERPESVIRUSES

- **CMV pneumonitis treatment:**
  - **First-line: intravenous ganciclovir or oral valganciclovir.**
  - **Second-line: foscarnet, cidofovir and maribavir.**
  - **Letermovir: prevent CMV reactivation in allogeneic HSCT; difficult-to-treat CMV infection and disease.**
  - **CMV immunoglobulin: adjunct to therapy in immunocompromised individuals.**
  - **Treatment efficacy monitorinh: measuring blood CMV viral load, treatment continued for at least 2 weeks after resolution of viraemia.**
- **Other herpesviruses; herpes simplex virus (HSV), varicella-zoster (VZV) and human herpesvirus 6 (HHV-6): rare causes of diffuse pneumonitis; characteristic rash.**
- **First-line treatment of HSV and VZV is with aciclovir, but valaciclovir, famciclovir, cidofovir and foscarnet can also be used.**
- **No drug has been specifically been approved for the treatment of HHV-6, but ganciclovir and foscarnet are recommend by experts to treat severe HHV-6 infection.**

FUNGAL INFECTIONS

PNEUMOCYSTIS JIROVECII (P. carinii)

⇒Most common AIDS-defining illness (CD4 <200 cells/mm3).

⇒Defects in Tcell- mediated immunity.

⇒Prolonged high-dose systemic glucocorticoids.

⇒Calcineurin inhibitors.

⇒CD4 count <200 cells/mm3 as biomarker to identify at-risk individuals.

⇒Increased risk of PJP in CMV infection caused by inhibition of T cell function.

❖Clinical presentation:

- ⁂ Classically insidious
- ⁂ Slowly increasing dyspnea
- ⁂ Dry cough
- ⁂ Hypoxemia
- ⁂ Few physical or radiological findings.
- ⁂ But it can be fulminant.
- ⁂ *Exercise-induced oxygen desaturation ⇒ sensitive marker.*

PNEUMOCYSTIS JIROVECII

- Chest radiograph: Diffuse, bilateral interstitial infiltrates but X-rays can be normal.
- High-resolution CT:
  - Much more sensitive; extensive ground-glass opacities, apical distribution, peripheral sparing, Pneumatocoeles (not uncommon), bizarre-looking cystic changes (chronic infection).
- P. jirovecii cannot be cultured.
- Diagnosis: by microscopy with Giemsa and Grocott stains on induced sputum or BALF.
- Immunofluorescence and PCR techniques increase the diagnostic yield.
- False-positive PCR: lung colonization.
- P. jirovecii can be found in BALF for <u>48-72 hours after starting empirical treatment</u>.
- <u>Elevated serum levels of β-d-glucan</u> (a cell wall component of many fungi and Pneumocystis): in patients too sick to provide bronchoscopic samples, 95% sen & 85% spe.

PNEUMOCYSTIS JIROVECII

- First-line treatment: high-dose trimethoprim-sulfamethoxazole for 21 days.
- Corticosteroids: severe hypoxemia (PO2 <8 kPa/60mmhg); survival benefit in HIV patients; no survival benefit in non-HIV immunocompromised hosts.
- Second-line therapies: clindamycin plus primaquine, pentamidine, atovaquone, or trimethoprim plus dapsone.
- Prophylaxis: <u>trimethoprim-sulfamethoxazole or nebulized pentamidine</u>
  - HIV infection (CD4 count <200 cells/mm3),
  - transplant recipients (solid organ and HSCT)
  - prolonged high-dose glucocorticoids (>20 mg/day for 21 days).

INVASIVE ASPERGILLOSIS

- Inhaled by all humans.
- Infection: major defects in phagocyte function, severe & prolonged neutropenia (e.g. after HSCT or aplastic anaemia), high-dose glucocorticoids or have haematological malignancy or chronic granulomatous disease, Chronic GVHD, tyrosine kinase inhibitors.
- Chronic lung disease or milder forms of immunosuppression develop semi-invasive forms of aspergillosis.
- Aspergillus fumigatus: The most common infective species.
- The respiratory tract (including sinuses) ⇒ most often affected.
- Blood-borne spread to internal organs (especially the CNS) and skin.

INVASIVE ASPERGILLOSIS

- Invasive pulmonary aspergillosis (IPA) presentation: fever + chest pain + haemoptysis (classic presenting triad); various respiratory symptoms.
- Predilection for growing into blood vessels ⇒ fatal massive hemorrhage.
- Chest radiographs: patchy infiltrates or nodules that can cavitate.
- CT: macro nodules (single/multiple, ± cavitation) or patchy consolidation.
- Nodules can show the '**halo**' (surrounding ground-glass infiltrates caused by hemorrhage) or '**air crescent**' (cavitation around a fungal ball) signs.
- Tracheobronchitis: relentless cough.
  - Focal bronchial wall thickening & 'tree-in-bud' in CT.
  - Diagnosis: Bronchoscopy; highly inflamed mucosa with necrotic white slough, positive on culture and histology for Aspergillus.

INVASIVE ASPERGILLOSIS

Subacute IPA or chronic necrotizing pulmonary aspergillosis (CNPA) or chronic cavitary pulmonary aspergillosis (CCPA)

- ✓ **more indolent forms**
- ✓ **mild immunosuppression**
- ✓ **chronic lung disease.**
- ✓ **Presentation: long history of cough, frequently, marked systemic symptoms, a slowly progressive patch of consolidation with or without cavitation (CNPA), or an expanding dry upper lobe cavity with a thickened wall (CCPA).**

INVASIVE ASPERGILLOSIS

- ✓ The European Organization for Research and Treatment of Cancer (EORTC) has set out international consensus criteria for invasive fungal disease.
- ✓ Detection of galactomannan (a relatively specific cell all component) or β-d-glucan antigen in blood or BALF is useful for detecting IPA.
  - ✓ False-positives: use of β-lactam antibiotics, ingestion of flavored frozen desserts containing sodium gluconate.
  - ✓ False negatives: use of antifungals.
  - ✓ A BALF galactomannan optical density index (ODI) >1.5 is a strong indicator of invasive aspergillosis.
- ✓ Definitive diagnosis of IPA: positive culture for Aspergillus and tissue invasion in histopathological biopsies on CT-guided or VATS biopsy specimens.
- ✓ Histology is highly sensitive, septate hyphae showing dichotomous branching on Gomori methenamine silver or periodic acideSchiff staining.
- ✓ Histology specimens are often unavailable, and culture is relatively insensitive, so diagnosis is frequently made on clinical grounds (suggestive CT appearances, high-risk patient, positive galactomannan test).
- ✓ Aspergillus antibodies have no role in the diagnosis of IPA but are positive in CCPA and sometimes CNPA.

EORTC criteria for the diagnosis of invasive fungal disease

Category	Criteria
Possible	**A. Risk factors (neutropenia for >10 days, allogeneic stem cell transplant, prednisolone 0.3 mg/kg for ≥ 3 weeks, T cell immunosuppressant, inherited severe immunodeficiency)** **B. CT signs (nodule ± halo, air crescent sign, cavity)**
Probable (one from A, B + C)	**A. Risk factors (neutropenia for >10 days, allogeneic stem cell transplant, prednisolone 0.3 mg/kg for ≥ 3 weeks, T cell immunosuppressant, inherited severe immunodeficiency)** **B. CT signs (nodule ± halo, air crescent sign, cavity)** **C. Culture in BALF or sputum, positive galactomannan in BALF or serum, or positive β-D-glucan in serum**
Definite	**Culture of fungus from normally sterile sites (not BALF), or demonstration of tissue invasion on biopsy.**

INVASIVE ASPERGILLOSIS

- Increase in azole resistance A. fumigatus.
- Combination of an azole with an echinocandin antifungal agent is recommended in immunocompromised hosts with severe IPA.
- Monitoring of therapeutic azole drug levels in blood should be undertaken to help ensure therapeutic doses and improve outcome.

NON-ASPERGILLUS FILAMENTOUS FUNGI

- Filamentous fungi: Fusarium, Zygomycetes, Scedosporium, Penicillium.
- Invasive pulmonary infections in immunocompromised patients.
- Clinical presentation similar to IPA.
- Diagnosis: culture from respiratory samples or lung biopsy.
- Some species are resistant to conventional antifungal agents{important}.
- Galactomannan and β-d-glucan: negative in Zygomycetes infections.
- Isavuconazole and liposomal amphotericin B.
- Mortality is high.

CANDIDIASIS

- Frequently isolated from sputum.
- Direct pulmonary invasion by Candida species is rare even in immunocompromised patients.
- Pulmonary infection: neutropenic patients.
- Haematogenous spread: infected indwelling vascular catheters /infections related to transplant surgery.
- Lung nodules: often peripheral and sometimes very large.
- Candida albicans: most commonly identified species,
- Non-albicans Candida: C. parapsilosis, C. tropicalis, C. glabrata, C. krusei.
- β-d-glucan levels are elevated in serum; sen≈ 75% & spe≈ 80%. (not necessarily useful in isolation).
- Novel culture-independent test based on miniaturized magnetic resonance detection of pathogen nucleic acid: rapid detection of Candida in blood; high negative predictive value, positive results need confirmation by culture.

CRYPTOCOCCOSIS NEOFORMANS

- Almost always affects only immunocompromised patients.
- Presentation: dyspnea, cough and fever.
- HIV/AIDS (CD4 <200 cells/mm3) ⇒ the most common risk factor.
- Defects of T-cell-mediated immunity (especially after solid organ transplantation).
- Radiological: diffuse interstitial infiltrates, focal consolidation, discrete nodules and hilar lymphadenopathy.
- Disseminated infection (usually CNS) ⇒ neurological symptoms ⇒ LP & CSF culture.
- Diagnosis: by microscopic identification (Indian ink stain) or culture from respiratory tract samples.
- Lateral flow assay of Cryptococcal antigens: sensitive; low positive titers ⇒ false positives.

ENDEMIC FUNGI

- In specific geographical areas (History of travel or residence in a high-risk area).
- Primary infection by inhalation or inoculation of contaminated material (e.g. bat faeces).
- Reactivation of latent infection in immunocompromised, especially defects in T-cellmediated immunity.
- Pulmonary infections: Histoplasma capsulatum, Coccidioides (Candida immitis, Candida posadasii), Blastomyces dermatitidis and Sporothrix schenckii.
- Presentation varies but tends to mimic tuberculosis: cavitating pneumonias, pulmonary nodules, enlarged mediastinal and hilar lymph nodes, miliary pattern, Systemic dissemination (immunocompromised).
- Diagnosis: fungus identification in respiratory samples or biopsy material, bone marrow aspirates.
- Culture can take 6 weeks.
- H. capsulatum: rapidly detected with an antigen detection assay (cross-react with other endemic fungi).
- Serology: previous exposure for most fungi, (not reliable in immunocompromised).
- Mortality is high without timely appropriate treatment.

Antifungal treatment choices

Fungal pathogen	Treatment
Aspergillus species	**First-line:** ↳ Voriconazole ± caspofungin ↳ Lipid formulation of amphotericin **Second-line:** ↳ Posaconazolea ↳ Itraconazole ↳ Isavuconazole ↳ Caspofungin ↳ Anidulafungin
Pneumocystis jirovecii	**First line:** ↳ Trimethoprimesulfamethoxazole **Second-line:** ↳ Clindamycin ± primaquine ↳ Atovaquone ↳ Pentamidine ↳ Trimethoprim ± dapsone

Antifungal treatment choices (continue)

Fungal pathogen	Treatment
Cryptococcus neoformans	**Induction therapy:** ↳ Liposomal amphotericin ± flucytosine **Consolidation and maintenance therapy:** ↳ Fluconazole **Second line:** ↳ Posaconazole ↳ Voriconazole
Candida species	**First line:** ↳ Fluconazole (C. albicans) ↳ Caspofungin (C. glabrata and C. krusei) **Second line:** ↳ Voriconazole ↳ Itraconazole ↳ Posaconazolea ↳ Micafungin ↳ Amphotericin

Antifungal treatment choices (continue)

Fungal pathogen	Treatment
Non-Aspergillus filamentous fungi (e.g. Fusarium, Zygomycetes, Scedosporium, Penicillium)	**Consider surgical debridement** **First line:** **Liposomal amphotericin** **Isavuconazole** **Second line:** **Posaconazole**
Endemic fungi (Histoplasma, Coccidioides, Blastomyces, Sporothrix)	**First line:** **Mild disease, immunocompetent: no treatment (Histoplasma), itraconazole (others)** **Moderate disease: itraconazole** **Severe disease: amphotericin** **Second line:** **Posaconazole** **Voriconazole** **Fluconazole**

a Intravenous formulation not approved in the UK.


WITH THE BEST WISHES