pneumonia in the immunocompromised patient

general

- The number of immunocompromised patients has increased over the past decade.
- Improvements in solid-organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) techniques, the expanded use of chemotherapeutic treatments and glucocorticoids, and the appearance of new immunomodulatory therapies are among the main reasons for this increase.
- Pulmonary infections continue to be the most frequent complications in these patients and are associated with high mortality, especially when intubation and mechanical ventilation are required.

causes of infiltrates in immuno-compromised patients

Causes of focal infiltrates:	Gram negative rods
	Staph. aureus
	Aspergillus
	Malignancy
	Non-specific interstitial pneumonitis
	Cryptococcus
	Nocardia
	Mucormycosis
	Pneumocystis carinii (uncommon)
	Tuberculosis
	Legionella or legionella-like organisms
	Radiation pneumonitis.

Causes of diffuse infiltrates:	CMV and other herpes viruses
	Pneumocystis carinii
	Drug reaction
	Non-specific interstitial pneumonitis
	Bacteria (uncommon)
	Aspergillus (advanced)
	Cryptococcus (uncommon)
	Radiation pneumonitis (uncommon)
	Malignancy
	Leucoagglutinin reaction

respiratory pathogens associated with immunodeficiency

Immunodeficiency state	Defence mechanism affected	Important pathogens
AIDS, immunosuppressive therapy, severe combined immunodeficiency	T cells (cell-mediated immunity)	• *Pneumocystis jiroveci (carinii)* • *Streptococcus pneumoniae* • *Legionella* species • *Mycobacterium tuberculosis* • *Nocardia* species • *Cryptococcus neoformans* • herpes viruses (eg cytomegalovirus, varicella-zoster) • *Strongyloides stercoralis* • respiratory syncytial virus
nephrotic syndrome, myeloma, chronic lymphocytic leukaemia, immunosuppressive therapy, AIDS, common variable immunodeficiency, X-linked agammaglobulinaemia	B cells (immunoglobulin production)	• *Streptococcus pneumoniae* • *Haemophilus influenzae* • *Neisseria meningitidis*
neutropenia (especially after chemotherapy/transplantation for haematological and other malignancies), chronic granulomatous disease	neutrophils (neutropenia or neutrophil dysfunction)	• Gram-negative bacilli (including *Pseudomonas* species) • *Staphylococcus aureus* • viridans streptococci (if bacteraemia) • fungi (*Aspergillus* and *Candida* species)

timeline of infections associated with transplant

First 30 Days after Transplant
Bacterial and fungal infections
Herpesvirus, respiratory viruses
Noninfectious complications: pulmonary edema, diffuse alveolar hemorrhage
2 to 6 Months after Transplant
Bacterial and fungal infections
Immunomodulatory viruses: cytomegalovirus, Epstein-Barr virus
Opportunistic infections: *Pneumocystis carinii, Listeria monocytogenes*
More than 6 Months after Transplant
Community-acquired respiratory viruses and bacteria
In patients with poor allograft function: consider opportunistic infections.

diagnostic approach

- Sputum cultures have a low sensitivity but are certainly indicated because organisms isolated in the upper respiratory tract are likely to be the cause of the pneumonia.
- Because immunocompromised patients with pulmonary infection are at risk for rapid dissemination of the disease with accompanying acute respiratory failure, fiberoptic bronchoscopy needs to be considered early after the appearance of the pulmonary infiltrates.
- The early use of fiberoptic bronchoscopy may add to the prompt identification of the specific etiologic agent, facilitating an etiology-guided treatment and avoiding unnecessary and potentially harmful additional treatment.
- The use of fiberoptic bronchoscopy in immunocompromised patients provides a specific diagnosis in 50% to 80% of the cases.
- Bronchoalveolar lavage (BAL) is a very reliable technique for detecting opportunistic infections such as P. carinii, CMV, and fungi but also bacteria, mycobacteria, and other pathogens.
- Bronchoscopy also provides material to diagnose alternative noninfectious causes, such as diffuse alveolar hemorrhage or alveolar proteinosis, which often afflict immunocompromised patients.
- Very rarely, an open lung biopsy will be needed for diagnostic purposes. Although its diagnostic yield is high, and often leads to changes in therapy, the indications and proper moment must be selected carefully owing to potential morbidity and mortality.
- Thoracic computed tomography (CT) is an important diagnostic tool in invasive pulmonary aspergillosis. The halo sign (hemorrhagic pulmonary nodule) and air-crescent sign (cavitation) are early radiologic signs typical of invasive pulmonary aspergillosis.
- This technique is also quite valuable in detecting pneumonic infiltrates in febrile neutropenic patients, particularly in transplant recipients, because it very often detects pulmonary infiltrates when a chest radiograph is normal.

bacterial infections

- Bacteria are the most frequent cause of pulmonary infections in the different groups of immunocompromised patients.
- Encapsulated organisms such as Streptococcus pneumoniae and Haemophilus influenzae are particularly prevalent in patients with immunoglobulin defects, such as those suffering from multiple myeloma.
- In HIV-infected patients, bacteria are the most common cause of pulmonary infection, with the most common microorganisms being S. pneumoniae, H. influenzae, and Staphylococcus aureus.
- Many other bacteria must also be considered in ICU patients, particularly Staph aureus (including methicillin-resistant [MRSA]) and multiresistant gram-negative bacilli (Pseudomonas aeruginosa, Acinetobacter species, and Stenotrophomonas maltophilia).
- Epidemiologic studies have shown that Legionella pneumonia is nine times more prevalent in the immunocompromised host, particularly among recipients of renal allografts.
- Occasionally, uncommon opportunistic bacteria such as Nocardia must be considered in the differential diagnosis, especially in organ transplant patients (most notably, renal).

mycobacterial infection

- Pulmonary tuberculosis has experienced a marked decrease in HIV-infected patients with the introduction of HAART
- A high level of suspicion is necessary to diagnose pulmonary tuberculosis in immunocompromised patients.
- Typical radiologic pattern is often replaced by diffuse, basal or miliary infiltrates as well as mediastinal lymph nodes. Although sputum is a good noninvasive test for Mycobacterium staining, most patients will undergo bronchoscopy with a diagnostic yield of more than 90%.
- Atypical mycobacterial infections, particularly M. avium complex, were common in HIV-infected patients with less than 50 CD4+ cells/mm3. With the introduction of HAART, the incidence of these infections has dropped significantly.
- With the exception of lung transplant patients, atypical mycobacterial infections are rare in SOT recipients.

CMV pneumonia

- Cytomegalovirus (CMV) is the most prevalent and lethal virus causing pneumonia in immunocompromised patients. The incidence of CMV infection will depend on several factors:
(1) type of transplant (highest in allogeneic HSCT recipients),
(2) degree of immunosuppression (highest when graft rejection is present and/or additional immunosuppressive treatment is required), and
(3) previous serologic status.
- The incidence of CMV infection is as high as 60% to 70% during the first 3 months after allogeneic HSCT when graft donor or patients are pre-transplantation CMV seropositive.
- The incidence of CMV disease among SOT patients ranges from 8% to 35% in kidney, heart, and liver transplant recipients but is considerably higher in pancreas (50%) and lung or heart-lung recipients (50% to 80%).
- By contrast, introduction of HAART has resulted in a drastic decrease in the number of cases of CMV disease in HIV-infected patients
- CMV antigenemia based on the detection of the pp65CMV antigen in peripheral blood leukocytes and quantitative PCR for early detection of viral DNA/RNA in serum have been implemented for early detection of active infection. Both assays have a sensitivity and specificity for the diagnosis of active infection of greater than 80% and diagnose active infection 1 to 3 weeks before conventional tools.
- As a rule, symptomatic infection will not develop before 2 to 3 weeks after transplantation, and the peak incidence occurs between 4 and 8 weeks after the transplant. Although late symptomatic cases are well described, more than 90% of cases occur in the first 4 months after transplantation.
- Occasionally, involvement of other organ systems with hepatitis, ulcerative gastroenteritis, hemorrhagic colitis, or retinitis may be a clue to the etiology of the pulmonary disease.

other viral pneumonia

- Recent developments in molecular-based diagnostic tools have shown that conventional respiratory viruses (influenza, parainfluenza, respiratory syncytial virus, adenoviruses, enteroviruses, and rhinoviruses) are frequent causes of respiratory illnesses and are associated with high rates of morbidity and mortality among immunocompromised patients

pneumocystis jiroveci (carinii) pneumonia

- A marked decrease in the incidence of P. carinii pneumonia has been observed owing to the use of P. carinii prophylaxis in patients at risk and the use of highly active antiretroviral therapy (HAART) in HIV-infected patients.
- A CD4+ count less than 200 cells/mm3 is associated with a markedly increased risk for P. carinii pneumonia.
- In SOT recipients, the risk for P. carinii is higher in the first 6 months after intense immunosuppression, particularly in heart-lung recipients but can appear later on in patients treated for rejection (HSCT patients with graft-versus-host disease).
- P. carinii pneumonia in patients with AIDS has a longer median duration of symptoms and a better outcome than in patients with SOT and HSCT.
- The chest radiograph can vary from normal to any type of infiltrates, although diffuse bilateral infiltrates is the most common presentation.
- An increase in serum lactate dehydrogenase and, particularly, the presence of pneumothorax raises the suspicion of P. carinii pneumonia.

1. Mild to moderate disease
- Parameters of mild to moderate Pneumocystis jiroveci (carinii) pneumonia are PaO2 >70 mm Hg on room air, alveolar-arterial (A-a) gradient <35 mm Hg, and oxygen saturation >94% on room air. Use:
trimethoprim+sulfamethoxazole 5+25 mg/kg to 7+35 mg/kg orally, 8-hourly for 21 days.
- If sulfamethoxazole is contraindicated, use:
dapsone 100 mg (child: 1 to 2 mg/kg up to 100 mg) orally, daily for 21 days
PLUS
trimethoprim 300 mg (child: 5 mg/kg up to 300 mg) orally, 8-hourly for 21 days.
- If hypersensitive to trimethoprim+sulfamethoxazole, desensitisation may be undertaken. Alternatively, use atovaquone 750 mg orally, 12-hourly for 21 days.
- Adherence with treatment is imperative for effective therapy.

Severe disease
- Parameters of severe disease are PaO2 <70 mm Hg on room air, A-a gradient >35 mm Hg, and oxygen saturation <94% on room air. Use:
trimethoprim+sulfamethoxazole 5+25 mg/kg orally or IV, 6-hourly for a total of 21 days.
- If hypersensitive to trimethoprim+sulfamethoxazole, undertake desensitisation.
- If unresponsive to trimethoprim+sulfamethoxazole, use:
pentamidine 4 mg/kg up to 300 mg IV, daily for 21 days.
- concomitant corticosteroids should be used in patients with HIV infection and significant hypoxaemia (PaO2 <70 mm Hg on room air):
prednis(ol)one 40 mg (child: 1 mg/kg up to 40 mg) orally, 12-hourly for 5 days,
then 40 mg (child: 1 mg/kg up to 40 mg) daily for 5 days, then 20 mg (child: 0.5 mg/kg up to 20 mg) daily for 11 days.

invasive pulmonary aspergillous

- Aspergillus species are among the most common microorganisms causing pneumonia in the immunocompromised patient.
- A high clinical suspicion and the prompt institution of specific therapy are the only chances to control dissemination of disease.
- Because neutrophils are the key cells in the defense against Aspergillus, the neutropenic patient (e.g., HSCT patient) is at a highest risk for dissemination.
- In these patients, periodical surveillance of serum galacto-mannan (a polysaccharide antigen of the wall of A. fumigatus) permits early detection of the infection.
- Invasive pulmonary aspergillosis occurs most often in prolonged severe neutropenia, is usually rapidly progressive, and requires systemic antifungal treatment. Use:
voriconazole 6 mg/kg IV, 12-hourly for 2 doses, followed by 4 mg/kg IV, 12-hourly for at least 7 days, followed by 4 mg/kg up to 200 mg orally, 12-hourly
OR
amphotericin B desoxycholate 1 mg/kg IV, daily (dosage to be adjusted according to tolerance).
- In non-neutropenic patients with milder disease, use:
voriconazole 200 mg orally, 12-hourly
OR
itraconazole 300 mg (child: 7.5 mg/kg up to 300 mg) orally as the capsule, 12-hourly for 3 days, then 200 mg (child: 5 mg/kg up to 200 mg) 12-hourly. Blood levels of itraconazole should be monitored. If levels appear to be inadequate, switch to oral solution and re-check levels.

Candida

- Candida species colonize the respiratory tract and are often recovered from pulmonary specimens in immunocompromised patients, but they are only considered as truly pathogenic if fungemia occurs or lung tissue invasion can be demonstrated.
- With the expanded use of new antifungal therapies, a higher incidence of infections due to C. krusei and C. glabrata has been reported.
- Caspofungin is a recently introduced drug with activity against both Candida and Aspergillus. It is registered for salvage treatment.

Cryptococcal pneumonia

- Cryptococcus neoformans may cause primary community-acquired pneumonia with single or multiple pulmonary nodules in the normal host and in patients with defects in cellular immunity. The serum cryptococcal antigen is usually positive and the organism can sometimes be cultured from respiratory tract specimens. Use:
amphotericin B desoxycholate 0.7 mg/kg IV, daily (dosage to be adjusted according to tolerance) for 2 to 4 weeks
WITH OR WITHOUT
flucytosine 25 mg/kg IV or orally, 6-hourly for 2 weeks (monitor plasma levels)
- Alternatively, or for continuation after amphotericin, use:
fluconazole 800 mg (child: 20 mg/kg up to 800 mg) orally or IV for the first dose, then
400 mg (child: 10 mg/kg up to 400 mg) orally, daily for at least 4 weeks of therapy.