# Immunocompromised Pneumonia

# 24

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## Abbreviations

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|---|---|
| AIDS | Acquired Immunodeficiency Syndrome |
| BAL | Bronchoalveolar lavage |
| CMV | Cytomegalovirus |
| HIV | Human Immunodeficiency Virus |
| ICU | Intensive care unit |
| NIPPV | Noninvasive positive pressure ventilation |
| PCR | Polymerase chain reaction |

## Case Presentation

**Case Scenario**: A 67 year-old man with no recent hospitalizations presents to the Emergency Department with shortness of breath. He has a history of ulcerative colitis and is currently treated with cyclosporine and prednisone 10 mg/day. He denies fevers, chills or sputum production. Pulse oximetry is 82% on room air. Initial chest X-ray and high-resolution CT scan of the chest are shown (Figs. 24.1 and 24.2). Over the next 24 h, he experiences progressive hypoxemia and respiratory distress despite supplemental oxygen and empiric antibiotic therapy for community-acquired pneumonia (ceftriaxone and azithromycin). The patient undergoes endotracheal intubation and mechanical ventilation is initiated.

### Question

Should the patient's antimicrobial regimen be changed? What diagnostic test should be performed?

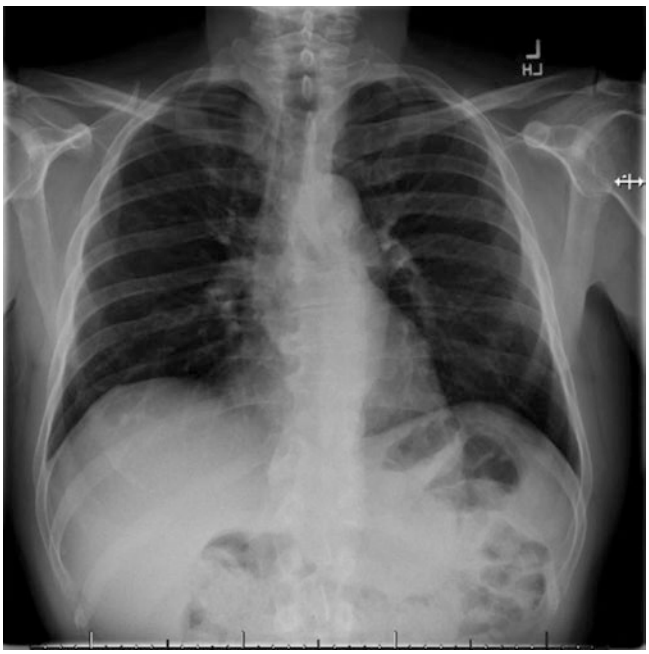

**Fig. 24.1** Chest X-ray

**Answer** The patient's antimicrobial regimen should be expanded empirically to cover *Pneumocystis jirovecii* (e.g. trimethoprim-sulfamethoxazole) given (1) his risk factors (cyclosporine and corticosteroids), (2) his consistent CT scan (interstitial infiltrate with cystic changes), (3) his hypoxemia disproportionate to radiographic infiltrate, (4) his lack of clinical response to an empiric regimen adequate for community-acquired pneumonia, and (5) the fact that empiric therapy does not compromise the diagnostic yield of subsequent bronchoscopy in the diagnosis of *Pneumocystis* pneumonia [1]. A lower respiratory tract specimen should be acquired, via bronchoscopy or mini-BAL; lavage fluid should be tested for gram stain and culture, respiratory virus PCR, fungal culture, galactomannan, acid-fast stain and culture, and *Pneumocystis* PCR. A serum β-D-glucan should be checked in order to delineate colonization from acute infection.

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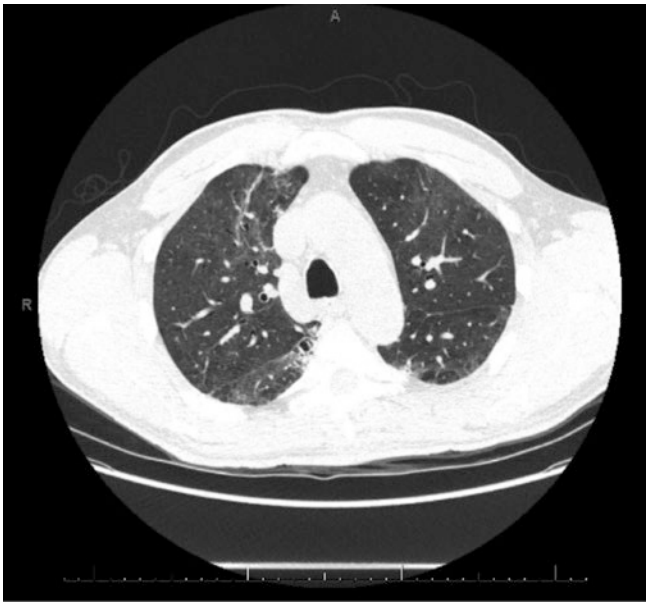

**Fig. 24.2** High-resolution CT scan

The patient underwent flexible bronchoscopy, and a positive *Pneumocystis* PCR assay confirmed the diagnosis. The patient received intravenous trimethoprim-sulfamethoxazole, and oxygenation gradually improved over the next 5 days. The patient was ultimately extubated and recovered full lung function. After 21 days of treatment, the patient's trimethoprim-sulfamethoxazole was changed to the prophylactic dose (1 double-strength tablet [160/800] once daily) for the duration of his immunosuppression.

## Principles of Management

### Presentation

The number of immunosuppressed patients is increasing because of both greater life expectancy among immunosuppressed adults due to improvements in medical management, new indications for immunosuppressive treatments, and novel immunosuppressive therapies [1]. Pulmonary infection remains the most common form of tissue-invasive infection in the immunocompromised patient [2, 3]. In particular, the incidence of pulmonary fungal infection is increasing in immunocompromised individuals despite advances in antifungal prophylaxis and therapy [4–7]. The presentation of pneumonia among immunosuppressed patients is often more subtle, indolent and atypical than among immunocompetent patients [8, 9]; the same immune deficits that permit microbial reproduction in the lower respiratory tract can decrease the intensity of fever, sputum production, or radiographic infiltrates. Immunosuppressed patients are often vulnerable to competing or concurrent non-infectious lung processes such as cardiogenic edema (e.g. among patients receiving cardiotoxic chemotherapy or aggressive hydration with chemotherapeutic regimens), medication toxicity (e.g. among patients receiving bleomycin or methotrexate), radiation pneumonitis, or malignancy (e.g. Kaposi's Sarcoma among patients with HIV/AIDS) [10, 11].

### Etiology

The presence and persistence of microbes in the respiratory tract are determined by the balance of microbial immigration, elimination and local microbial growth conditions [2, 3], all of which are altered in immunosuppressed patients. The microbiota of the upper respiratory tract (the primary source community for migration of microbes to the lungs [3, 4]) are altered by systemic immunosuppression, whether by underlying disease (e.g. HIV/AIDS) [5] or immune-suppressing medications [6]. Impairment of innate and adaptive immunity decreases the elimination rate of transient microbes, increasing the likelihood of persistent reproduction, and makes the microbial growth conditions of the lung environment more hospitable to dysregulated reproduction [2]. Each patient's specific constellation of immune deficits predisposes him/her to a select number of opportunistic pathogens (Table 24.1). Patient exposures influence the pattern of pulmonary infection and historical features are often useful in making a preliminary diagnosis and in selecting the initial empiric antimicrobial regimen The spectrum of infection and antimicrobial resistance may be altered by antimicrobial prophylaxis. (Table 24.2) Consideration of each patient's candidate pathogen profile is critical to the appropriate selection of empiric antimicrobial therapy. The most common culprits remain the bacteria and viruses responsible for community-acquired pneumonia (e.g. *Streptococcus pneumoniae*) [7], which should be covered by any empiric regimen, but mixed infections with typical pathogens and opportunistic pathogens are common [12–14]. Isolation of typical pathogens does not obviate the need for further diagnostic evaluation in those patients at risk for opportunistic infection. Coverage for atypical organisms (*Mycoplasma* spp., *L. pneumophila* and *C. pneumoniae*) is warranted in community-dwelling patients until a specific pathogen is identified; these are rare pathogens in hospitalized patients.

### Diagnosis

Chest X-rays are of notoriously poor sensitivity in identifying pneumonia among immunocompromised patients; in one large series, the majority of neutropenic patients with infiltrates on thin-sliced CT scans had no detectable abnormality on chest radiograph [8]. High-resolution CT scan is often

**Table 24.1** Correspondence of immunodeficiency and susceptibility to respiratory pathogens

| Immune defect | | Disease examples | Iatrogenic examples | Organisms to suspect |
|---|---|---|---|---|
| Innate immunity | Neutrophil abundance | Leukemia<br>Parvovirus Infection<br>Agranulocytosis | Chemotherapy<br>Methotrexate<br>Clozapine | Gram-negative bacilli<br>*Staphylococcus* spp.<br>Fungi (e.g. *Aspergillus* spp.) |
| | Neutrophil function | Chronic granulomatous disease<br>Cirrhosis<br>Uremia | Anti-TNF agents [26] | *Staphylococcus aureus*<br>Fungi (e.g. *Aspergillus* spp.) |
| Adaptive immunity | T-cell abundance and function | HIV/AIDS<br>Lymphoma<br>Primary immunodeficiency | Chemotherapy<br>Corticosteroids<br>Calcineurin inhibitors<br>Anti-T-cell antibodies | *Pneumocystis jirovecci*<br>*Cryptococcus* spp.<br>Intracellular bacteria (e.g. *Legionella* spp.)<br>*M. tuberculosis*<br>Viruses (*CMV, HSV, VZV*) |
| | B-cell abundance and function | Multiple myeloma<br>Primary immunodeficiency | Rituxumab | Encapsulated bacteria: *S. pneumoniae, H. influenzae* |

**Table 24.2** Historical clues

| | |
|---|---|
| Environmental exposures | Exposures to mycobacteria (contaminated water), endemic fungi (e.g., *H. capsulatum*, *Coccidioides* spp.), *Rhodococcus equi* (horse breeders), *Cryptococcus neoformans* (e.g., pigeon breeders), *Strongyloides stercoralis* (even quite distant in time), or exposure to soil (e.g., *Aspergillus* spp. or *Nocardia* spp. in landscapers and gardeners) |
| Prolonged neutropenia | Higher risk for gram-negative infections, *Aspergillus* spp., and *Fusarium* spp. |
| Past antimicrobial exposure | Increased risk for multi-drug resistant gram negative organisms with fluoroquinolone prophylaxis, increased risk of *Mucorales* spp. or resistant *Aspergillus* spp. with voriconazole prophylaxes |
| Prior cultures | Molds (*Aspergillus* spp., *Fusarium* spp.), *Pseudomonas* spp., or *Stenotrophomonas* spp. |
| Sinopulmonary infection | *Mucorales* spp., *Aspergillus* spp. |

**Table 24.3** Diagnostic testing in immunocompromised patients with suspected pneumonia

| Specimen | Diagnostic tests |
|---|---|
| Bronchoalveolar lavage fluid | Cell count and differential |
| | Gram stain and bacterial culture |
| | Fungal stain and culture |
| | Acid-fast bacteria stain and culture |
| | Respiratory virus PCR |
| | *Pneumocystis jirovecci* PCR |
| | CMV antigen |
| | Galactomannan |
| Serum | Bacterial culture |
| | Fungal culture |
| | Acid-fast bacteria culture |
| | *Cryptococcus* antigen |
| | Galactomannan |
| | β-D-glucan |
| Urine | *Streptococcus* antigen |
| | *Legionella* antigen |
| | *Histoplasmosis and Blastomycoses* antigen (with proper exposure history) |

helpful for confirming the presence of infection, guiding site selection for bronchoalveolar lavage, and directing empiric therapy based on imaging characteristics. The presence of cavitation is associated with *Mycobacterium* spp., *Nocardia* spp., *Aspergillus* spp. and *P. jirovecci*.; interstitial infiltrates suggest viral (e.g. CMV) pneumonia or *Pneumocystis;* dense consolidation implies either bacterial pathogens or *Aspergillus* spp.. Serologic tests are of decreased utility in immunocompromised patients, especially in patients with impaired T-cell and B-cell immunity (Table 24.1) whereas antigen-based testing (e.g. *Streptococcus* and *Legionella* urinary antigens, *Cryptococcus* serum antigen testing) can be useful. An aggressive approach to sampling the lower respiratory tract (via bronchoscopy or miniature bronchoalveolar lavage ["mini-BAL"]) is warranted, as the spectrum of potential pathogens usually exceeds any reasonable empiric antimicrobial regimen. Depending on the patient's degree and type of immunosuppression, lower respiratory tract specimens should be tested for gram stain and bacterial culture, fungal culture, acid fast stain and culture, respiratory viral PCR, CMV antigen, galactomannan, *Pneumocystis* PCR. Recommended diagnostic tests by specimen site are listed in Table 24.3.

## Empiric treatment

Antimicrobial therapy should be given promptly in patients with suspected pneumonia. Unless lower respiratory tract specimens can be acquired immediately, therapy should not be delayed for the sake of increasing diagnostic yield. Empiric treatment of *Pneumocystis* does not compromise the yield of lower respiratory tract testing [1]. No single empiric regimen exists for immunocompromised pneumonia given the diversity of immunocompromised conditions and associated infections (Table 24.1). A reasonable approach is to start

with a regimen for community-acquired or hospital-acquired pneumonia as appropriate [9, 10], then expand according to the patient's specific immune deficits, exposure history, antimicrobial prophylaxis and past microbiological data. In the patient with malignancy, empiric therapy for Pneumocystis, invasive molds, or herpes viruses should be started based on standardized guidelines [15] (Table 24.4). Empiric regimens should be routinely reassessed for effectiveness based on the patient's clinical response and the results of invasive microbiological testing. Empiric treatment of fungal pneumonia should be strongly considered in patients with clinical risk factors (e.g. prolonged neutropenia, HCT), consistent imaging (Fig. 24.3, a CT scan of a patient with aspergillosis) and lack of response to antibacterial therapy.

## Supportive care

Unless otherwise contraindicated, immunocompromised patients with hypoxemic respiratory failure should be given a trial of noninvasive positive pressure ventilation (NIPPV) or oxygen therapy via heated high-flow nasal canula [11–13]. Corticosteroids are indicated for patients with HIV/AIDS and *P. jirovecci* pneumonia with room air $PaO_2$ under 70 or A-a gradient over 30 [14, 15]. Adjunctive steroids are not beneficial in non–HIV-associated *P. jirovecci* pneumonia [16]. A large propensity matched retrospective cohort study of an immunocompromised population without HIV showed no difference in mortality or respiratory outcomes with adjunctive steroids in severe Pneumocystis pneumonia [17]. Competing non-infectious diagnoses should be explored and potentially treated empirically (e.g. diuresis for infiltrates suggestive of cardiogenic edema).

**Table 24.4** Settings to consider empiric coverage for PCP, fungal infections, and herpes viruses in patients with malignancy

| Organisms to suspect | Risk factors | Recommended empiric therapy |
|---|---|---|
| Fungal organisms | Allogenic Stem Cell Transplant<br>Autologous Stem Cell Transplant with neutropenia<br>T cell Depletion therapy (Alemtuzumab)<br>Acute Leukemia<br>Prolonged Neutropenia<br>Significant GVHD requiring steroid therapy | Voriconazole, echinocandins, or amphotericin B |
| Herpes viruses | Acute Leukemia<br>T cell Depletion therapy (Alemtuzumab)<br>Proteasome inhibitor<br>GVHD Requiring Steroid Therapy | Acyclovir, Valacylovir |
| Pneumocystis jiroveci (PCP) | Allogenic Stem Cell Transplant<br>T cell Depletion therapy (Alemtuzumab or purine analogs)<br>B cell depletion therapy (rituximab)<br>Prolonged use of steroids | TMP/SMX<br>Atovaqone, dapsone, pentamdine if intolerant of TMP/SMX |

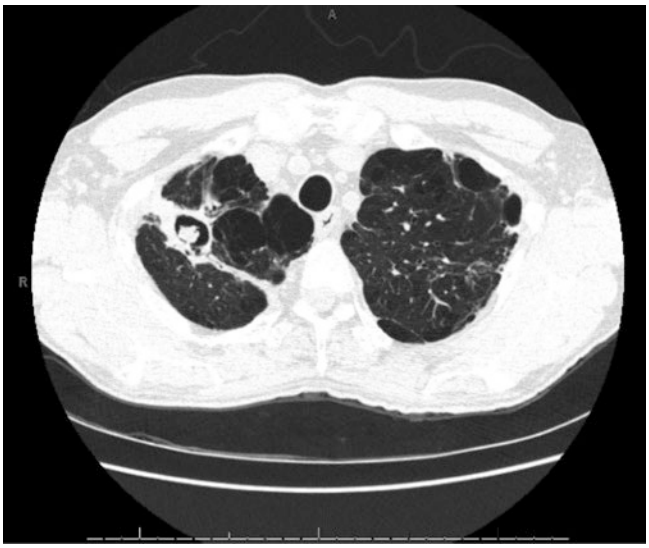

**Fig. 24.3** CT scan—Aspergillosis

## Evidence Contour

### Utility of invasive testing

Invasive sampling of the lower respiratory tract (by bronchoscopy with and without transbronchial biopsy, mini-BAL or open lung biopsy) is common in the diagnosis of pneumonia in immunocompromised patients, and wide practice variation exists among modalities used. Among intubated patients, mini-BAL performs comparably to flexible bronchoscopy with lavage [16]. Transbronchial biopsy increases the yield of bronchoalveolar lavage, generally by distinguishing invasive fungal disease from colonization [17, 18]. Transbronchial biopsy is associated with elevated rates of pneumothorax when performed on mechanically ventilated patients (14–24%) [19, 20], though this risk must be weighed against those of alternative diagnostic maneuvers (e.g. open lung biopsy). BAL galactomannan has excellent sensitivity and specificity in the diagnosis of invasive aspergillosis [21], and it is undetermined what effect its adoption has had on the marginal yield of transbronchial biopsy. In one series of patients with hematologic malignancies and pulmonary infiltrates, open lung biopsy identified a diagnosis in 62% of cases and changed management in 57% of cases [22], though only 55% of these patients had previously undergone bronchoscopy and only 13% had undergone transbronchial biopsy.

## Serum indices of infection

Serum tests for pneumonia in immunocompromised patients are an attractive arena for investigation, but no consensus exists regarding their utility, and in practice they rarely preclude invasive lung sampling. A serum galactomannan test is relatively specific (89%) for invasive aspergillosis among immunocompromised patients but has poor sensitivity (71%) [21]; a negative result does not exclude the diagnosis. (1,3)-beta-D-Glucan (BG) represents a major structural component of the cell walls of most fungi. A commercially available beta-D-glucan assay is sensitive for a wider variety of fungal infections in the immunocompromised host than serum galactomannan but less specific [23]. A serum procalcitonin level below 0.5 ng/mL effectively excludes the presence of a bacterial infection in critically ill immunocompromised patients [24].

## Noninvasive ventilation

Though NIPPV is infrequently indicated for immunocompetent patients with pneumonia given the difficulty of managing secretions and the lack of rapid reversibility, two randomized controlled trials have demonstrated a clinical benefit to its use among immunocompromised patients. In a large (238 patient) study of patients immunosuppressed for solid organ transplantation with acute respiratory failure, patients who received NIPPV (as compared to standard treatment with supplemental oxygen) were less frequently intubated and experienced lower ICU mortality [11]. In second study of more broadly immunosuppressed patients with respiratory failure and clinical evidence of pneumonia, treatment with NIPPV resulted in less frequent endotracheal intubation and lower ICU mortality and overall mortality [13]. This benefit was not observed in a large subsequent trial [25], potentially reflecting the evolution of treatment in the control arm: nearly half of the patients in the non-NIPPV arm received respiratory support via high flow nasal cannula, a modality that was not available at the time of earlier trials.

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